Management of Lupus Nephritis

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Abstract
Management of lupus nephritis is relatively nonspecific and includes various immunosuppressive drugs, cytotoxic agents and other modalities directed against the aberrant immune response. Treatment decisions are influenced by the clinical features, histology, response to treatment, relapses, patient consent and tolerance to medications. Guidelines based on available evidence, as to how best to manage lupus nephritis and possible future interventions are discussed.

INTRODUCTION
Renal involvement occurs in the majority of cases of systemic lupus erythematosus (SLE). Though only 25%-50% of patients have initial renal manifestations, upto 60% of adults and 80% of children eventually develop renal involvement.1 Outcome of SLE is influenced by renal involvement with 10%-15% developing endstage renal disease despite treatment; the outcome could be worse in case of delayed or no treatment.2 Management of lupus nephritis is hampered by the fact that the exact pathogenesis of SLE is unclear and comparison of treatment schedules is difficult due to the variability of presentation and unpredictable outcome. In this review, based on available evidence, guidelines on management and possible future interventions are discussed.

PATHOGENESIS
Management of lupus nephritis is influenced by our understanding of its pathogenesis. It is known that there is alteration in regulation of cellular and humoral responses. B cell hyperactivity results in formation of autoantibodies. Broadly, two mechanisms have been postulated. One is immune complex (IC) deposition and second, direct binding of antibodies to glomerular antigens. Available evidence suggests that DNA anti-DNA immune complexes are the most important. Alternatively anti-DNA antibodies can bind to glomerular constituents heparin sulfate and laminin. There is complement activation which binds to glomerular basement membrane, resulting in activation of complement and recruitment of inflammatory cells). However, the exact deficits in the immune system are yet to be identified, so that management today is broadly directed against various steps in the immune system, resulting in an inadequate response. Further, therapy is associated with significant side effects. Future unraveling of precise defects may aid in targeted and less harmful therapy.

FACTORS INFLUENCING TREATMENT STRATEGIES
Decisions on the type of treatment modality in lupus nephritis are influenced by several factors.

1. Clinical Picture
Most patients with absent or trivial urinary abnormalities (proteinuria less than 500 mg in 24 hours or occasional red or white cells without casts) have a benign histological picture and specific treatment may be unnecessary. Though most patients with severe renal disease would have passed through a phase of minor urinary abnormalities,1 there is no literature data as to how many of such patients would eventually develop significant renal disease. It is not clear whether steroid treatment at this stage can prevent progression to more severe stages. Addition to cytotoxic drugs does not appear to be warranted. Those presenting acutely with fever, arthralgia, rash, haematuria, proteinuria and renal insufficiency have almost always proliferative nephritis on histology and warrant aggressive therapy with steroids and cytotoxic drugs.

Treatment is directed at rapidly decreasing lupus activity (induction treatment) and once the disease activity has subsided, maintenance treatment can be given. In the acute phase, high dose steroids have a definite role. Oral prednisolone (1 mg/kg/day) for 8-12 weeks is effective, though often associated with significant steroid side effects. Use of intravenous methylprednisolone in a dose of 500-1000 mg daily for three doses followed by lower dose of oral steroids (10-15 mg/day) is not only more acceptable cosmetically to young females, but also has a more rapid effect on the inflammatory and autoimmune response.
However, this is seldom long lasting. Addition to cytotoxic drug like cyclophosphamide and azathioprine has a more sustained remission inducing effect, allows lower dose and shorter duration of high dose steroids, and lesser occurrence of mortality and chronic renal failure. Cyclophosphamide has a more powerful inhibitory effect on B cells than azathioprine. Though daily oral cyclophosphamide in a dose of 2-2.5 mg/kg can be used, the intravenous route is preferred, as it is less toxic when used as monthly bolus of 0.5-1 gm/m². Azathioprine, however, has a better safety profile with lesser risk of infertility and is safe in pregnancy. Plasma exchange rapidly clears immune complexes, but without significant clinical benefit. Synchronising plasmapheresis with subsequent pulse cyclophosphamide has shown better results. Maintenance treatment can generally be given after 12 weeks of induction treatment (chronic phase). Corticosteroids are continued at a lower dosage of 5-15 mg daily or even alternate day to decrease toxicity. In case of flares, methyl prednisolone boluses can be repeated. Cyclophosphamide given monthly has definite long term benefit. However, the exact duration is not well defined and gonadal toxicity due to prolonged use limits its use. Six monthly boluses of cyclophosphamide followed by once in three months for 24 months along with oral steroids is the usual recommendation. Reducing the duration to six months boluses alone may be effective in milder forms of lupus, but may not be sufficient in severe lupus and has to be followed by oral azathioprine in a dose of 2-2.5 mg/kg/day. There are, however, no convincing reports of superiority of cyclophosphamide over azathioprine in the long term.

2. Role of Renal Biopsy

There is still lack of consensus on the utility of renal biopsy in the management of lupus nephritis. This is because renal histology in SLE is highly variable in different areas of the kidney and from glomerulus to glomerulus. Transformation of grades of severity is also noted in serial biopsies following treatment. Nevertheless, the renal histology may be as, if not more, important than the clinical picture in influencing treatment. Since proteinuria is present in almost 100% of patients with significant lupus nephritis, it is our policy to follow up all patients with SLE who do not have initial renal involvement with periodic monitoring for proteinuria, microhaematuria and renal functions. We perform renal biopsies in patients who either present with proteinuria, haematuria (active urinary sediment) or renal insufficiency or who develop these abnormalities on follow up. However, those having a dramatic clinical presentation with acute renal failure, active urinary sediments and lupus activity will almost always show diffuse proliferation and renal biopsy may not alter therapeutic decisions in such patients. It is perhaps those with mild proteinuria or haematuria and those with a less florid presentation where a renal biopsy would be more helpful in deciding therapy as the histological pictures could be variable. Study of renal biopsies with immunofluorescence is useful in conditions where the diagnosis of SLE is in doubt, as a full house immunofluorescence staining for C1q, C3, IgG, IgA, IgM is characteristic of SLE. Renal biopsy may have to be repeated in cases of unexplained worsening to look for transformation to more severe grades warranting more aggressive therapy.

The WHO classification (Table 1) is commonly used in clinical practice. Class I (normal or minimal renal lesions) needs only symptomatic treatment, though steroids have been used. Class II lesions (mesangial proliferation) are usually associated with mild urinary findings. Steroids have been used, but it is not clear whether steroid use prevents progression to renal failure. Treatment guidelines are not very clear-cut in class III lesions (focal proliferative nephritis) as this includes anything less than 50% of glomerular involvement. In addition, it also depends on the site of biopsy and number of glomeruli obtained. This has prompted further grading of severity with less than 25% involvement and primary segmental lesions having a better prognosis and not requiring addition to cytotoxic drugs, while presence of crescents, necrosis and wire loop lesions have a more ominous prognosis and needing treatment for as class IV lupus nephritis. Class IV (diffuse proliferative disease) has a high risk of progressive renal failure. These patients benefit with early aggressive management, with steroids and cytotoxic agents, the occurrence of end-stage renal disease is reduced by 40%. Membranous lupus or class V lesions have a variable course. Those with mild proteinuria do well even without medication or with steroids alone. Addition of cytotoxic drugs may be needed in those with heavy proteinuria, hypertension, renal insufficiency or proliferative lesions on histology. Short term cyclophosphamide boluses are preferred. Chlorambucil with methylprednisolone

<table>
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<tr>
<th>Table 1: WHO classification of lupus nephritis (1995)</th>
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<tr>
<td>I. Normal glomeruli</td>
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<td>A) Normal by all techniques</td>
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<td>B) Normal on light microscopy but deposits on immunohistology and/or electron microscopy.</td>
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<tr>
<td>II. Pure mesangial alterations</td>
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<td>A) Mesangial widening and/or mild hypercellularity</td>
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<td>B) Mesangial cell proliferation</td>
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<tr>
<td>III. Focal segmental glomerulonephritis (associated with mild/moderate mesangial alterations, and/or segmental epimembranous deposits)</td>
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<tr>
<td>A) Active necrotizing lesions</td>
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<tr>
<td>B) Active and sclerosing lesions</td>
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<tr>
<td>C) Sclerosing lesions</td>
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<tr>
<td>IV. Diffuse glomerulonephritis (severe mesangial/mesangiocapillary with extensive subendothelial deposits, mesangial deposits always present, and frequently subepithelial deposits)</td>
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<tr>
<td>A) With segmental lesions</td>
</tr>
<tr>
<td>B) With active necrotising lesions</td>
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<tr>
<td>C) With active and sclerosing lesions</td>
</tr>
<tr>
<td>D) With sclerosing lesions</td>
</tr>
<tr>
<td>V. Diffuse membranous glomerulonephritis</td>
</tr>
<tr>
<td>A) Pure membranous glomerulonephritis</td>
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<tr>
<td>B) Associated with lesions of category II (a or b)</td>
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<td>VI. Advanced sclerosing glomerulonephritis</td>
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The rate of relapse is around 25% at five years.24 Serological creatinine or recent detection of red cell casts. The cumulative active urinary sediment, increasing proteinuria, rise in serum
titres or a fall in serum complement levels, which occur within 8-10 weeks.25 Therefore, these patients should be monitored carefully for the next three months to look for a relapse, management is by increasing dose of immunosuppression. Intravenous methylprednisolone in a dose of 500-1000 mg for three days is more effective than intravenous methylprednisolone, 500-1000 mg/day.

Table 2: Activity and chronicity indices in lupus nephritis

<table>
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<tr>
<th>Active lesions</th>
<th>Chronic lesions</th>
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<tr>
<td>A. Glomerular</td>
<td>A. Glomerular sclerosis</td>
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<tr>
<td>1. Cellular proliferation</td>
<td>1. Segmental</td>
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<tr>
<td>2. Disruption of capillary walls</td>
<td>2. Mesangial</td>
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<td>4. Hematoxylin bodies</td>
<td>B. Fibrous crescents</td>
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<td>5. Crescents, cellular, or fibrocellular</td>
<td>C. Tubular atrophy</td>
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<td>6. “Wire loops” (light microscopy)</td>
<td>D. Interstitial fibrosis</td>
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<tr>
<td>7. Hyaline “thrombi”</td>
<td>E. Vascular sclerosis</td>
</tr>
<tr>
<td>B. Vascular</td>
<td></td>
</tr>
<tr>
<td>1. Hyaline (immune complex) deposits</td>
<td></td>
</tr>
<tr>
<td>2. Necrotizing arteritis</td>
<td></td>
</tr>
<tr>
<td>C. Tubular degeneration and necrosis</td>
<td>D. Interstitial inflammation, active</td>
</tr>
<tr>
<td>D. Interstitial inflammation, active</td>
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Renal histology can often be predicted from the clinical picture. Those with no significant or mild urinary abnormalities are more likely to have class I or II lesions, whereas haematuria, telescopied urinary sediment, hypertension and renal failure are more likely with class III or class IV lesions. Occasionally, surprises do occur with severe proliferative lesions noted with seemingly minimal clinical renal involvement.28 Role of repeat renal biopsy has already been discussed.

3. Management of Relapse of Lupus Activity

Relapse manifests as renewal of activity as evidenced by active urinary sediment, increasing proteinuria, rise in serum creatinine or recent detection of red cell casts. The cumulative rate of relapse is around 25% at five years.24 Serological tests predicting a relapse are an elevation of anti-ds DNA titres or a fall in serum complement levels, which occur within 8-10 weeks.25 Therefore, these patients should be monitored carefully for the next three months to look for a relapse, management is by increasing dose of immunosuppression. Intravenous methylprednisolone in a dose of 500-1000 mg for three days is more effective than intravenous cyclophosphamide.

4. Treatment of Resistant Lupus Nephritis

Patients unresponsive to conventional treatment with prednisolone, cyclophosphamide or azathioprine can be termed resistant cases. Cyclosporine, mycophenolate mofetil, intravenous immunoglobulin, plasmapheresis etc have been tried in such situation. Cyclosporine has a powerful effect on helper T cell clonal expansion, and has theoretical benefits in SLE. In the maintenance phase, it has a steroid sparing effect, decreases proteinuria and stabilises renal function in class IV lupus.26 Initial dose is 5 mg/kg/day, which can be lowered to 2.5 mg/kg/day after 6 months. Its use in the acute phase has not been proved to be useful and its use alone has a high relapse rate.27 It does not reduce anti-ds DNA or complement levels. Mycophenolate Mofetil has been tried with beneficial effect on the degree of proteinuria and renal functions.28 It has been found to be as effective as prednisolone and cyclophosphamide in the maintenance phase of diffuse proliferative lupus nephritis.29 However, how long it should be given and whether relapses would occur on its withdrawal is not clear. Intravenous immunoglobulin can be used as monthly doses during the maintenance therapy phase for six months to one year. It diminishes immunologic activity by interacting with FC receptors of effector cells.30 However, an increase in disease activity due to enhanced immune complex production can occur.31 Plasmapheresis has been tried in resistant lupus nephritis without proven clinical benefit.32 Cladribine (2-chloro-2 deoxyadenosine) used in the management of B cell neoplasms may have a role in SLE. It decreases proteinuria, glomerular inflammation, is well tolerated. It is a promising agent.32 Total lymphoid irradiation may induce a remission with minimal need for immunosuppressive drugs subsequently.33 This has not been widely used and is not recommended in prepubertal and transpubertal subjects. Immunoabsorption can remove circulating antibodies and theoretical advantages but requires further studies.34 Other modalities include ancrord, a defibrinating agent35 and fish oil supplementation.36 Maximal cytotoxic or immunosuppressive therapy with or without autologous stem cell transusions has been tried.37

5. Patient Factors Influencing Treatment

As SLE is common in young females, it is necessary to obtain an informed consent especially the risk of infertility/amenorrhoea following cyclophosphamide therapy. Patients who refuse cyclophosphamide therapy due to the above reasons should be informed about the potential risk of flares and progressive glomerular damage. Azathioprine can be used in such cases. As the steroid facies can be depressing to females of this age group, drug compliance could be a problem. Use of intravenous methyl prednisolone may have advantage.1 Cyclophosphamide should be avoided during pregnancy and six months prior to conception. Lupus nephritis in children is generally more severe than adults. Further, aggressive treatment, has the added risk of growth retardation, accelerated atherosclerosis and infection.38

6. Drug Toxicity Influencing Treatment

Steroid side effects may warrant use of cytotoxic drugs even in mild lupus nephritis, their steroid-sparing effect permitting lower dose of steroids. In patients developing amenorrhoea following cyclophosphamide, azathioprine can be substituted. Leucopenia may necessitate use of
cyclosporine or mycophenolate mofetil. Blood leucocyte counts should be monitored before giving cyclophosphamide and the latter avoided if counts are less than 4000/mm$^3$. Patients should be well hydrated and asked to avoid frequently if needed with a diuretic, to decrease the risk of haemorrhagic cystitis. Timing the bolus when a developing follicle is not present may theoretically limit gonadal damage.$^1$ Since the risk of malignancy and infertility are dose-dependent, limiting monthly pulses of cyclophosphamide to six followed by azathioprine has a better safety profile and can be used in selected patients with mild clinical disease.

**MONITORING RESPONSE**

Effective therapy is associated with a decrease in inflammatory manifestations evidenced clinically by relief of extra-renal symptoms, decrease in proteinuria, microhaematuria and stabilization of serum creatinine. Normalisation of serum complement and anti-ds DNA titres is also useful.$^9$ Clinical and biochemical data should be given more importance than complement and anti-ds DNA titres, with the latter being more important in the maintenance phase.$^1$

**When Can Treatment Be Stopped?**

Stable renal functions, lack of proteinuria and a decrease in anti-ds DNA titres are signs of successful treatment. Though it is often possible to stop treatment altogether after five years or more, even in those with severe lupus, an occasional person can relapse even up to 20 years after treatment was stopped.$^1$ Repeat renal biopsy may help in deciding whether treatment can be stopped. In those with chronic irreversible changes, there may not be any benefit of continuing immunosuppressive drugs and transplantation may be a better option.$^{40}$

**THE FUTURE**

Unfortunately, the present treatment directed against production and deposition of autoantibodies, complement activation and recruitment of inflammatory cells is associated with major complications like infection, infertility, osteoporosis, avascular necrosis and malignancies. Drugs precisely targeting specific B cell clones and blocking signal transduction pathways could have greater efficacy and lesser side effects.$^{41}$ Optimal treatment could also include reprogramming T and B cells to ignore nephritogenic antigens and thereby preventing release of inflammatory mediators. Modalities targeted against lymphocytes like high dose chemotherapy, with or without bone marrow transplantation, antibodies against T and B cell surface antigens, inducing antigen specific tolerance, decreasing IL-10 levels etc are under investigations.$^{42}$ Gene therapy is an attractive prospect, once lupus promoting genes are identified.$^{43}$ A better understanding of pathogenesis may result in better treatment modalities.

**INDIAN EXPERIENCE**

Renal involvement in SLE was noted in around 66% of Indian adults and 80% of children$^{44}$ which is comparable with western data$^1$ though an increased initial presentation of 62% as lupus nephritis was noted.$^{45}$ The spectrum of renal histological involvement is comparable with developed countries with 14.3% class II lesions, 22.8% class III, 17.2% class V, 2.8% class IV and the majority (42.8%) being class IV.$^{46}$ The course of lupus nephritis appears to be more severe amongst Indians, with around 50% having renal failure$^{45,47}$ and 25% of class IV lesions developing endstage renal disease.$^{48}$ No significant differences in outcome between cyclophosphamide and azathioprine treatment for class IV lesions was seen.$^{49}$ Indians thus seem to have a more severe form of SLE, which may be due to genetic or racial factors, which have been implicated in the pathogenesis.$^{50}$

**CONCLUSION**

Review of the literature thus reveals a variety of immunosuppressive drugs which are used in varying dosage and combinations in different clinical settings and histological grades. Some of the recommendations are confusing as they are diametrically opposite. Thus while active intervention is not recommended in Class I lesions, risk of progressive glomerular damage with delayed treatment is reported.$^{51}$ Most of the studies are from Western literature which appears to have a more favourable outcome and we cannot be sure whether the dosage and schedule are appropriate in the Indian setting. More studies on outcome and side effects of various treatment schedules in the Indian population need to be looked into before formulating a treatment protocol in the Indian scenario.

**REFERENCES**


45. Khanna UB, Bhaivandkar MG, Almeida AF, et al. Spectrum of


