Recent Advances in Lupus Nephritis

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Abstract: Kidney involvement in SLE is quite common and carries a poor prognosis. Proliferative lupus nephritis is of major concern as it can present with renal impairment and may progress to end-stage renal disease (ESRD). A major advance in lupus pathogenesis has been the discovery that the disease is at least, in part, the result of an autoantigen-driven immune response. β cells trap circulating DNA-binding proteins, such as nucleosomes, through their membrane-bound anti-DNA antibody. Anti-dsDNA antibodies have also been shown to directly bind to human mesangial cells in vitro. Autoantibodies against C1q, a complement component, have also been incriminated in lupus nephritis. With better understanding of the pathogenesis and concerns regarding cumulative toxicity of cyclophosphamide, newer drug protocols and agents have been evaluated. Low dose fortnightly pulses of cyclophosphamide have been shown to be equally effective but less toxic as induction therapy. Mycophenolate mofetil (MMF) has also been shown to be a promising drug for induction therapy, with fewer side effects. For maintenance therapy, azathioprine and MMF seem to be better alternatives to cyclophosphamide as they are equally effective but less toxic. Cyclosporine, intravenous immunoglobulins and rituximab can be considered as alternative therapies in patients who are resistant to cyclophosphamide. β cell tolerization (LJP-934) (abetimus sodium), anti-CD40 ligand monoclonal antibody, anti IL10 monoclonal antibody are currently under evaluation for the treatment of lupus nephritis.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease. Amongst the various organs affected the kidney involvement is quite common and carries a poor prognosis. Renal involvement has been reported in about 25-75% of SLE patients.1 The severity of lupus nephritis varies from mild lesions with subclinical disease to diffuse proliferative lupus nephritis (DPLN). Proliferative lupus nephritis is of major concern as it can present with renal impairment and may progress to end-stage renal disease (ESRD). There are a number of advances made in the understanding of pathogenesis of lupus nephritis and also to have a common uniform classification system. But the main thrust has been on finding new management strategies.

PATHOGENESIS—NEW CONCEPTS

A major advance in lupus research has been the discovery that the disease is at least in part the result of an autoantigen-driven immune response. β cells trap circulating DNA-binding proteins, such as nucleosomes, through their membrane-bound anti-DNA antibody. The complex is endocytosed, processed, and presented with MHC class II restriction to histone-specific T-helper cells. In the presence of optimal co-stimulation (through CD40-CD40L [CD154] and/or CD28-B7.1/B7.2 [CD80/CD86]), β cells become fully activated, in particular through the production of T cell-derived cytokines. Clearance of apoptotic bodies by phagocytes is impaired in SLE, and autoantigen-containing apoptotic material is processed by dendritic cells and presented to T-helper cells. IFN-α favors the maturation of circulating monocytes in dendritic cells.
The role of nucleosome/antinucleosome complexes has also been recently hypothesized. Thus, specific antinucleosomal antibodies (not reacting with dsDNA or with histones) are detected in the sera of LN patients, and their titers correlate with renal disease activity. Nucleosomal antigens have also been detected in the glomerular basement membrane (GBM) of LN patients. Among other hypotheses, the cationic histone part of the nucleosome/antinucleosome complexes could bind to the negatively charged heparan sulfate molecule expressed on the GBM. Such nucleosome-mediated binding of antibodies to the GBM could then initiate glomerulonephritis, through complement activation but also through complement-independent mechanisms. Anti-dsDNA antibodies have also been shown to directly bind to human mesangial cells in vitro. Some data also suggest that the presence of autoantibodies against C1q, a complement component, which may correlate with lupus nephritis. The mechanism of action may be initiated by the general deposition of immune complexes on the glomerular basement membrane, with C1q being fixed on these immune complexes. Subsequent binding of anti-C1q antibodies to C1q activates complement resulting in an influx of inflammatory cells.

**CLASSIFICATION**

Based upon clinicopathologic correlations, a new classification system of lupus nephritis developed by a group of renal pathologists, nephrologists, and rheumatologists was formulated and published in 2004. This system divides the glomerular disorders into six different patterns or classes, based on kidney biopsy findings.

**Minimal mesangial lupus nephritis (class I):** Immunofluorescence reveals mesangial immune deposits but the glomeruli are normal by light microscopy.

**Mesangial proliferative lupus nephritis (class II):** Light microscopy with class II disease reveals mesangial hypercellularity (of any degree) or mesangial matrix expansion.

**Focal lupus nephritis (class III):** is defined by less than 50 percent of glomeruli being affected on light microscopy, with active or inactive segmental or global endocapillary or extracapillary glomerulonephritis.

**Diffuse lupus nephritis (class IV):** with diffuse lupus nephritis or class IV disease, more than 50 percent of glomeruli display endocapillary or extracapillary glomerulonephritis. Segmental (IV-S) and global (IV-G) diffuse lupus nephritis are defined by more than 50 percent of the affected glomeruli having segmental and global lesions, respectively. Class III and IV are further categorized as A: active lesions, A/C: active and chronic lesions, and C: chronic lesions.

**Membranous lupus nephritis (class V) and advanced sclerosing lupus nephritis (class VI).**

**THERAPEUTIC ADVANCES**

**Therapeutic Goals in Lupus Nephritis: Why the need for newer protocols and drugs?**

Optimal management of proliferative LN remains a challenge because of the heterogeneity of the disease at presentation and its unpredictable course and outcomes. Therapeutic goals are (1) to achieve prompt renal remission; (2) to avoid renal flares; (3) to avoid chronic renal impairment; and (4) to fulfill these objectives with minimal toxicity. Although patient and renal survival rates have improved over the past decade, it should be stressed that current immunosuppressive regimens still achieve suboptimal results. First, the rate of renal remission after a first-line therapy is at best 81%. Second, renal relapses occur in one third of LN patients, even when patients are immunosuppressed. Third, between 5-20% of LN patients experience ESRD 5 to 10 years after the disease onset. Finally, treatment-related toxicity remains a major concern.
**Induction versus Maintenance Therapy**

An advance in the therapy of LN has been the understanding that cytotoxics should be used sequentially. The concept is to induce remission of LN by a short course (a few months) of vigorous immunosuppression and to maintain remission by long-term administration (a few years) of either the same cytotoxic drugs given less frequently or potentially safer immunosuppressant like azathioprine. However, one needs to remember certain points while planning for this form of therapy: (1) there is no unanimously accepted definition of remission for LN; (2) the time frame to achieve remission and thereby the length of the induction phase is set somewhere between 3 and 12 months; (3) 20% of LN patients will never reach renal remission. Though it is difficult to separate the two phases of the therapy, and also irrespective of the fact how remission is defined, the underlying aim is to achieve disease quiescence so that the immune-mediated inflammatory process can be brought to an end before it progressively destroys the renal parenchyma. To maximize patient and renal survival while minimizing complications or treatment related adverse effects present a unifying theme for both induction and maintenance treatment. Until recently treatment of LN rested on 3 drugs: corticosteroids, cyclophosphamide and azathioprine. Recently, newer protocols and newer drugs have been tried to have a better remission with less toxicity in the long run.

**Induction Treatment Regimens—Whats New?**

A series of clinical trials from investigators at the National Institutes of Health USA (NIH) showed that induction treatment with intravenous cyclophosphamide pulses of 0.75-1 g/m² given monthly for six months followed by quarterly pulses was more effective than corticosteroid alone, and it was associated with fewer side-effects compared with prolonged (often exceeding one year) daily oral cyclophosphamide treatment. Extending the duration of intravenous cyclophosphamide treatment with quarterly pulses of two years reduced the relapse rate but increased the risk of ovarian failure, compared with treatment that included only the initial six monthly pulses. Combination therapy of intravenous methylprednisolone and intravenous cyclophosphamide was shown to achieve a higher rate of remission (Pulse Plus Study). Pulse cyclophosphamide had become the mainstay of lupus nephritis therapy though it is effective but has been associated with a number of adverse effects, which include leucopenia, infections, gonadal toxicity, hemorrhagic cystitis and potential predisposition towards malignancies. To reduce the toxicity of cyclophosphamide low dose pulse was tried.

*Euro lupus trial:* This trial showed that low-dose intravenous cyclophosphamide pulses of 500 mg fortnightly for six doses followed by azathioprine maintenance was as effective as high-dose cyclophosphamide given intravenously on a monthly basis for six doses followed by two quarterly pulses, over a median follow-up of 41 months, and there was a trend for fewer infections in the low dose cyclophosphamide group. At a median follow-up of 73 months, the two treatment groups showed comparable rates of ESRD or doubling of baseline creatinine.

**Mycophenolate Mofetil (MMF) as Induction Therapy**

Although cyclophosphamide has been used widely as induction agent, recent studies testing MMF have shown promising results. In a 6 month randomized trial comparing MMF with monthly intravenous cyclophosphamide, significantly higher remissions were achieved in the MMF group than the cyclophosphamide group (22.5% vs 5.8%). However, the selected patients had preserved renal function at presentation. The efficacy of MMF was confirmed by another randomized trial in which patients were randomized to oral cyclophosphamide and prednisolone for 6 months followed by 6 months of azathioprine and prednisolone or to prednisolone and...
MMF at a dose of 2 g/d for 12 months. The number of remissions was similar in the two arms of the study, but the cumulative number of side effects was significantly lower in the MMF arm. The incidence of hospitalization, amenorrhea, infections, nausea, and vomiting was significantly lower in the MMF and azathioprine groups than in the cyclophosphamide group. Thus MMF appears to be a promising drug but it needs to be tested in patients with severe illness and results need to be followed up for a longer duration before conclusions can be drawn.

**Maintenance Therapy: Azathioprine and MMF Replacing Cyclophosphamide**

Since prolonged usage of cyclophosphamide is associated with serious adverse events, less toxic agents are being considered for long term maintenance without compromising the efficacy. Contreas, et al treated 59 patients of proliferative lupus nephritis with induction therapy using monthly cyclophosphamide pulse. Subsequently, patients were randomized to one of the three maintenance therapies: quarterly cyclophosphamide pulses, oral azathioprine or MMF for 1-3 years. The 72 month event free survival rate for composite end point of death or chronic renal failure was significantly higher in azathioprine and MMF groups than in cyclophosphamide group. The incidence of hospitalization, infections, amenorrhea was also lower in MMF and azathioprine group. In a study of Chinese patients of DPGN on low dose prednisolone and azathioprine as maintenance therapy, long term stability of renal function was observed in the majority of patients. To sum up, azathioprine and MMF seem to be better alternatives to cyclophosphamide in maintenance immunosuppression as they are equally effective but less toxic.

**Alternative/Newer Therapies**

With improved understanding of the immunopathogenesis of SLE, novel immunological targeted therapies are being described and delivered. These include both β and T cell directed therapies, anticytokine therapies, complement directed treatments as well as immunoblatative chemotherapy with hematopoietic stem cell rescue.

**Cyclosporine**

Clinical and histologic improvement with cyclosporine has been reported in proliferative lupus nephritis both when the drug was given in patients resistant to intravenous cyclophosphamide or when given for maintenance. In a randomized controlled trial of proliferative lupus nephritis, Moroni et al, showed equivalence between cyclosporine and azathioprine for maintenance therapy, up to four years.

**Intravenous Immunoglobulins (IVIg)**

IVIg have been used successfully to treat clinical manifestations of SLE, including refractory thrombocytopenia, pancytopenia, central nervous system involvement, secondary antiphospholipid syndrome, and nephritis. The beneficial effects of IVIg on overall disease activity are usually prompt with marked improvement within a few days, but of limited duration. In a review of 106 lupus nephritis patients treated with IVIg proteinuria, nephritic syndrome, and creatinine clearance showed improvement. But there is a serious concern expressed regarding nephrotoxicity of IVIg, particularly with the use of sucrose containing IVIg products. Thus, IVIg may give good results in some patients with lupus nephritis resistant to conventional therapy, but the exact success rate and clinical indications remain undetermined.

**Rituximab**

Rituximab is the antibody directed against CD20, a phosphoprotein expressed on almost all β cells but not on plasma cells. Therefore, through the elimination of β cells rituximab may prevent
the generation and expansion of antibody secreting autoreactive cells. Thatayatikom and White\textsuperscript{19} recently reviewed the published experience with rituximab in SLE. Most patients demonstrated complete β cell depletion within 1 to 3 months of treatment; these patients had clinical response with improvement of arthralgias, serositis, vasculitis, mucositis, and neurologic symptoms. The few patients without β cell depletion did not show clinical response. β cell depletion lasted for 3 to 12 months, but clinical benefits lasted longer. Less clear were the benefits on renal disease. When the response was assessed by serum creatinine and proteinuria, out of 20 cases 6 entered complete remission, 8 had partial remission and 6 failed to respond. These results are interesting, but a proper evaluation of the clinical efficacy of rituximab in lupus nephritis is yet to be done. Until then its use should be confined to cases resistant to standard induction therapy or to patients with contraindications to corticosteroids and immunosuppressive agents.

**Agents Under Evaluation**

**β Cell Tolerization (LJP-934)**

LJP-394 (abetimus sodium) is a construct of four dsDNA epitopes attached to a nonimmunogenic polyethylene glycol platform. It leads to β cell tolerance by cross-linking anti-dsDNA antibodies on the surface of β cells resulting in anergy or apoptosis. LJP-394 appears to be well tolerated. At present LJP-394 may be a useful adjunct to standard therapy in SLE.

**Anti-CD40 Ligand Monoclonal Antibody**

It interacts with CD40 ligand (CD40L) that is upregulated on active CD4 T-helper cells. The interaction between CD40 and CD40L results in proliferation and differentiation of β cells and is necessary for antibody and cytokine production. At present anti-CD40L monoclonal antibody therapy has thus far been relatively ineffective and/or associated with unacceptable risks.

**Anti-IL10 Monoclonal Antibody**

Inteleukin-10 (IL-10) levels are increased in active SLE and correlate with disease activity. Steroid resistant SLE treated with a murine IgG1 anti-IL-10 monoclonal antibody have shown improvement in cutaneous lesions, joint symptoms with need for lower prednisolone dose were decreased.\textsuperscript{20}

**Agents/Therapies in Pipeline**

**CTLA-4Ig**

The fusion protein CTLA-4Ig has shown to bind B7, blocks B7/CD28 interaction, and inhibits T cell activation. Studies of CTLA-4Ig in SLE are awaited

**Anti-C5b Monoclonal Antibody**

Eculizumab is a humanized monoclonal antibody that exerts its effect by blocking the generation of terminal complement components C5a and C5b-9. Results from clinical trials in lupus nephritis patients are awaited

**Autologous Hematopoietic Stem Cell Transplant**

The process of autologous Hematopoietic Stem Cell Transplantation (HSCT) involves removing patients hematopoietic stem cells before giving an aplasia inducing dose of cyclophosphamide; this is followed by rescuing the patient with an autologous HSCT. The potential of autologous HSCT as a treatment to induce lasting remission has not yet been borne out, however its use may lie in its ability to revert the progression of severe disease towards a more benign course that could be more amenable to conventional immunotherapy.\textsuperscript{21}
REFERENCES