

Lupus Nephritis - The Current Landscape

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Systemic Lupus Erythematosus (SLE) is a heterogeneous disease that can affect numerous organ systems. Lupus nephritis is arguably the most important complication of the illness since it is closely linked to morbidity and mortality and occurs in 25-75% of patients [1]. The current classification system divides lupus nephritis into six classes based on proliferative or membranous changes (although tubulointerstitial nephritis, thrombotic micro angiopathy or vascular disease may be significant contributors to disease in some patients) [2]. Given the complexity and heterogeneity of the illness optimal treatment is elusive. Most if not all studies focus on classes III and IV proliferative disease and class V membranous disease. Current opinion advises an induction phase of intensive immuno suppression followed by a maintenance phase of less intensive suppressive therapy. The purpose of treatment is to control and prevent flares and thus damage to the kidney such as fibrosis and sclerosis; avoid all cause mortality and avoid treatment side effects. There are numerous questions that remain to be answered: Which drugs to use for treatment; how long should induction and maintenance therapy be; what markers can be used for monitoring; when should renal biopsy be considered; should and when and if to re-biopsy; how important is it to induce a full remission for long term outcome? To help with a few of these questions preliminary guidelines have been formulated and presented at the American College of Rheumatology annual meeting in 2011 [3].

In patients with active class III and IV disease without cellular crescents, Mycophenolate Mofetil (MMF) at 2-3 g/day for 6 months is recommended as induction therapy with cyclophosphamide as an alternative option. The guidelines suggest that MMF is preferred for initial therapy in African Americans and Hispanics in North America and Latin America.

In patients who are given cyclophosphamide, there are two alternative approaches: Low dose cyclophosphamide at 500 mg intravenously every 2 weeks for 6 weeks, or high dose at 500-1,000 mg/m² of body surface area monthly for six months. This former recommendation is based on evidence from a single randomized controlled trial of Caucasians of European (Southern and Western) descent and thus may be limited to that group. Part of induction therapy for class III and IV patients without cellular crescents is a concomitant pulse of steroids for 3 days, then prednisone at a dose of 0.5-1.0 mg/kg to induce improvement, with tapering to the lowest effective dose after a few weeks and continuing for 6 months.

Patients with cellular crescents should receive the higher 1.0-mg/kg per day prednisone dose. Patients who do not respond to induction should be switched to the alternative option. Maintenance therapy for responders to either MMF or cyclophosphamide should include MMF at 1-2 g/day or azathioprine at 2 mg/kg per day plus low-dose daily glucocorticoids. If patients fail both the MMF and the cyclophosphamide protocols the guidelines suggest rituximab or calcineurin inhibitors.

Those with class V membranous lupus nephritis should start on MMF (2 to 3 g/day for 6 months) plus prednisone (0.5 mg/kg per day for 6 months). If they improve, they should receive maintenance therapy with MMF or azathioprine. If there is no improvement, initiation of cyclophosphamide (500 to 1000 mg/m² monthly for 6 months) plus a glucocorticoid pulse, followed by daily prednisone (0.5 to 1.0 mg/kg per day) should be undertaken.

Adjunctive therapies include 1) hydroxychloroquine (since retrospective data suggest it may reduce long-term kidney damage) 2) all patients with proteinuria of at least 0.5 g/day or an equivalent protein/creatinine ratio receive an angiotensin-converting-enzyme inhibitor or an angiotensin-receptor blocker.

Finally, all patients who present with clinical evidence of active lupus nephritis should be biopsied.

Given that many published studies are not of the highest quality, credit has to be given to the authors for having pointed out the drawbacks of the literature they had to work with. Thus, when published, recommendations will signify whether they are based on multiple randomized controlled trials, only one randomized controlled trial or based on expert opinion.

In addition, although lupus nephritis studies (as well as the above mentioned algorithm) commonly refer to induction and maintenance therapy (terminology borrowed from oncology) these terms have been brought into question by recent studies [4,5]. "Rates of remission at the end of induction therapy were low (8.6% with mycophenolate mofetil and 8.1% with cyclophosphamide)" in one trial [4]. However, during the "maintenance" study following the "induction" trial, complete remission was achieved in approximately 60% of both mycophenolate and azathioprine arms. Thus, as the authors point out, "the distinction between induction therapy and maintenance therapy in patients with lupus nephritis may be an artificial one" [5].

Despite improvement in overall survival in patients with lupus nephritis since the introduction of cyclophosphamide, the ten year death rate still approaches 30% [6]. The need for better, safer and alternative medications in combination with significant progress in understanding the etiopathogenesis of SLE has led to an explosion of studies of potential new medications. Among these include B cell depleting biologics such as the anti CD20 monoclonal antibodies rituximab and ocrelizumab and the anti CD22 antibody epratuzumab. Recently approved for SLE but not yet investigated for lupus nephritis is belimumab. This human monoclonal antibody influences B cells by inhibiting the B-cell survival factor B-lymphocyte-stimulator protein (BLyS). T-cells contribute to the initiation and perpetuation of autoimmunity in SLE and are therefore an alternative target [7]. T cell co-stimulation blockade with the soluble CD28 antagonist abatacept remains to be shown to be of use. Current studies have trial design problems that may undermine the potential understanding of its effectiveness and those of B cell depleters. Calcineurin inhibitors have exhibited some efficacy. Cyclosporine has been shown to have positive effects when studied in small numbers of patients as has tacrolimus [8].

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In summary, an initial attempt at therapeutic guidance for lupus nephritis has been presented in the form of an algorithm. The point to make is that the criteria set forth are just for guidance and not all are based on good data. With newer medications on the horizon and as studies near conclusion, the algorithm is bound to change. We are entering a new era of therapeutics for a formidable illness.

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