

CHAPTER

11

# Glomerulonephritis: Evidence Based Management

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## Introduction

Glomerulonephritis is the second most common cause of end-stage renal disease (ESRD) worldwide, next only to diabetic nephropathy. Except for a few forms of glomerulonephritis, the therapy of these diseases remains a matter of much debate and controversy. However, there has been a spate of new information in recent years, regarding treatment options in these common disorders. In this article, the discussion is to common idiopathic forms of glomerulonephritis, namely minimal change disease (MCD), focal and segmental glomerulosclerosis (FSGS), membranous nephropathy (MN), IgA nephropathy (IgAN), membranoproliferative glomerulonephritis (MPGN); and secondary forms of glomerulonephritis such as lupus nephritis (LN) and renal vasculitis. The emphasis in discussion is given to the most recent information available in the literature. Minimal change disease and to a lesser extent focal segmental glomerulosclerosis are common in children and their management differs somewhat compared to adults with respect to the dose and duration of the drugs, but the principles of therapy remain the same. I will restrict my discussion to the management of these disorders to adults only.

Recommendations for management are given based on the level of evidence and is followed by

more detailed discussion of the studies based on which the recommendations are made.

The grading of evidence was done as follows:

**Grade A** = Very strong evidence based on large randomized controlled trial or trials (RCT).

**Grade B** = Strong evidence based on smaller RCTs or meta-analysis of smaller RCTs.

**Grade C** = Good evidence based on large uncontrolled studies.

**Grade D** = Weak evidence based on small uncontrolled studies or case reports.

## Minimal Change Disease (MCD)

MCD accounts for 15 to 20% of adults with nephritic syndrome who undergo renal biopsy. The incidence is significantly higher than this in young adult less than 30 years of age. Corticosteroids remain the treatment of choice in MCD, leading to complete remission in more than 90% of cases. Adults tend to respond more slowly than children. Relapses after initial response to corticosteroid are common in children, but less common in adults.

### A. First attack of MCD:

**Recommendation:** Oral prednisolone at 1 mg/kg/d for 6 weeks or less, if remission has occurred. If remission occurs, reduce and taper

off prednisolone over next 4-6 weeks. In case remission has not occurred at 6 weeks, it is recommended to continue prednisolone at the same dose, taken either on daily basis (1 mg/kg) or on alternate days (2 mg/kg) till the remission occurs or up to 16 weeks, provided there is perceptible decline in the degree of proteinuria over time. Once the remission occurs, the dose can be tapered and the drug stopped over 4-6 weeks (*Grade-A evidence*).

**Discussion:** Despite being a common disease, few RCTs have been done in MCD in adults. Since the response to steroids is generally excellent and the disease behaves largely in similar fashion in children and adults, most of the treatment strategies in adults are based on the experience in treating children.<sup>1</sup> The response to corticosteroid in adults appears to be less and slower, when compared to children. Children with MCD have remission in more than 90% at 8 weeks, whereas only 60% do so in adults. However by 12-16 weeks the response rates are much higher in adults at more than 80%. A recent report from China reported that adults respond to corticosteroid therapy in a similar fashion to children, with remission rates of 91% at 8 weeks and near 98% at 12 weeks.<sup>2</sup> Our experience in treating large number of adults with MCD is similar to this. This indicates that, there may be a racial difference in steroid responsiveness in MCD. Short versus longer courses of steroids were compared in children in an RCT and the likelihood of relapse, as well as frequency of relapses were significantly lower in patients who received longer course of steroids for first attack of MCD.<sup>3</sup> Even though the total dose of prednisolone taken to treat the first attack was more, steroid side effects were no more severe. The cumulative dose of steroid taken over longer period was actually lower, since the relapses were less. However such study has not been conducted in adults. Recently Waldman et al compared daily versus alternate

day steroid for treatment of first attack of MCD in adults and found similar response rates and time to relapse in two groups.<sup>4</sup>

## B. Relapse of MCD:

**Recommendation:** Oral prednisolone at 1 mg/kg/d till urine albumin becomes nil or a few days more, then reduce the dose and taper off over 4 to 6 weeks (*Grade-A evidence*).

**Discussion:** Treatment of relapse with longer courses of steroids for relapse of MCD has no significant benefit over shorter courses in the long term and hence not recommended.<sup>1</sup>

## C. Frequent relapses and steroid dependent MCD:

A frequent relapser is a patient who responds to corticosteroid, but experience four or more relapses within a span of one year. Steroid dependency is defined as two consecutive relapses occurring during or within 14 days of completing steroid therapy.

**Recommendation 1:** Oral cyclophosphamide (CYC) at 2 mg/kg/d or chlorambucil (CLB) at 0.2 mg/kg/d for 8 weeks (*Grade-A evidence*).

**Recommendation 2:** In case of frequent relapses or steroid dependency, even after a course of CYC, Cyclosporine-A (CSA) may be given at 5-6 mg/kg/d for 9 mo, and then tapered to 1.5-2.5 mg/kg/d for 3 mo (*Grade-B evidence*).

**Discussion:** Thirty-one patients including adults and children, who were frequent relapsers or steroid dependent were randomized to receive oral CYC given at 1.5-2.5 mg/kg/d for 8 weeks or CSA at 5-6 mg/kg/d for 9 months, then tapered and stopped over next 3 mo.<sup>5</sup> 63% of patients who received CYC and 25% of who received CSA were relapse free at the end of 2 years. Levamisole has been used with some success in children with frequent relapses and steroid dependency, but few of these studies were either randomized or controlled. There are no reports of use of levamisole in adults with MCD.

#### D. Steroid resistant MCD:

In such a situation, one should reconsider the diagnosis and repeat renal biopsy may be indicated to rule out focal segmental glomerulosclerosis, which could have been missed on first biopsy due to sampling error, due to the focal nature of the lesion. Steroid resistant nephrotic syndrome is difficult to treat, since the disease itself may expose the patient to the untoward effects of the disease such as deep vein thrombosis, infections and malnutrition, as well as the potentially dangerous side effects of the exposure to immunosuppression, which are often given to these patient.<sup>1</sup>

**Recommendation:** Oral CYC at 2 mg/kg/d for 12 weeks or CSA at 5 mg/kg/d for up to 12 mo in case there is evidence of remission either partial or complete at the end of 4 mo of therapy. Alternatively, tacrolimus (TAC) at 0.05 mg/kg/d given for 12 to 18 mo, provided response to therapy is apparent at 4 mo (*Grade-D evidence*).

**Discussion:** There is a paucity of data regarding therapy of steroid resistant MCD both in adults and children, CYC and CSA have been used, but with not much success. Fortunately this group comprises a very small minority and are the most difficult to treat. Many of them progress to renal insufficiency.<sup>1</sup>

#### Primary Focal and Segmental Glomerulosclerosis (FSGS)

Primary FSGS is the second most common cause of nephrotic syndrome in adults. The incidence of FSGS appears to be increasing in western world and is the most common cause of nephrotic syndrome in blacks. FSGS is a pattern of injury defined by a segmental scar, which involves some but not all glomeruli. Over the last 20 years, in addition to the “classic” segmental scar, a number of histological lesions or variants have been included in the diagnosis of primary FSGS, most notably the cellular or collapsing lesion and the

tip lesion. In nephrotic adults fewer than 15% of patients entering a complete or partial remission progress to ESRD, whereas 50% of persistently nephrotic patients progress to ESRD over 5 years.<sup>6</sup>

#### A. First attack of nephrotic syndrome in adults

**Recommendation 1:** Oral prednisolone at 1 mg/kg/d for up to 8 weeks. If there is any indication of reduction of proteinuria, prednisolone should be continued at the same dose till remission occurs or up to 4 mo. The dose may be changed to alternate days to reduce the risk of steroid related complications and prevent suppression of endogenous corticosteroid production. Once the remission occurs the dose of steroid may be gradually tapered and stopped over 6-8 weeks. If no remission occurs by 4 mo, it is recommended to taper off steroids (*Grade-A evidence*).

**Recommendation 2:** In case of steroid resistant FSGS, or if steroids are contraindicated or poorly tolerated, Cyclosporine-A (CSA) at 5 mg/kg/d given in two divided doses may be given up to 3 mo. In case there is reduction of proteinuria, the drug may be continued up to 12-18 mo. The dose of CSA may be adjusted to keep the blood trough levels between 125-250 ng/ml. However once the remission is achieved, the dose may be gradually reduced to maintain blood trough levels of 75-150 ng/ml. Addition of a small dose of prednisolone, if feasible would enhance the response to CSA (*Grade-B evidence*).

**Discussion:** Early studies with steroids in treating FSGS were disappointing with complete remission seen only in  $\leq 20\%$  following therapy for 8 weeks. However in the last 2 decades it has become apparent that prolonged course of prednisolone given for 4-9 mo can induce remission in  $\geq 40\%$ . Less than one third of patients who ultimately achieve remission do so by 8 weeks and median time of complete

remission is 3 mo.<sup>6</sup> Two randomized studies in adults with steroid resistant FSGS showed that > 60% showed complete or partial response following therapy with CSA.<sup>7,8</sup> However the relapse rates were very high at 60-75%, once the drug was discontinued. Nonetheless, at 50 mo of follow up, Cattran et al found that creatinine clearance was reduced by 50% in only 25% of CSA treated patients compared to 52% of patients on placebo, and the renal survival at 4 y was 72% in the CSA group compared to 49% in the placebo group.<sup>7</sup> Thus, continuation of CSA therapy is required to maintain remission in proteinuria, but even with relapse, a beneficial effect resulting in the preservation of renal function is observed in some patients. Whether prolonged use of low dose CSA, required to maintain a remission in some patients is less nephrotoxic is not known and needs clinical evaluation.

#### **B. Relapse of nephrotic syndrome in FSGS**

The risk of relapse after an initial response to steroids in adults is small (25%), compared to children (80%), and majority (75%) of patients who relapse respond to treatment. Occasionally patients may become steroid resistant or more commonly steroid dependent.<sup>6</sup>

**Recommendation 1:** Along with prednisolone as given for the first attack, oral cyclophosphamide (CYC) at 2 mg/kg/d or chlorambucil (CLB) at 0.2 mg/kg/d may be given for 8 weeks (*Grade-B evidence*).

**Recommendation 2:** In case of steroid resistance or dependence, CSA as described above may be used along with a small dose of steroid for up to 12 mo, provided response is evident at 3 mo (*Grade-B evidence*).

**Discussion:** Cytotoxic drugs such as CYC or CLB increase the chance of sustained remission (reduce the chance of relapse), but don't increase the chances of inducing remission in FSGS.<sup>9</sup>

#### **C. Steroid and cyclosporine-A resistant FSGS**

These patients are the most difficult to treat and most of them ultimately progress to ESRD. Aggressive anti-proteinuric measures using combination of ACE inhibitor (ACEI) and angiotensin receptor blocking agent (ARB) should be used in these patients in an effort to reduce the rate of decline in glomerular filtration rate (GFR). Several uncontrolled reports show variable benefit with tacrolimus, sirolimus and mycophenolate mofetil; however among these tacrolimus shows better promise and may be used as a last resort.<sup>6</sup>

#### **Idiopathic Membranous Nephropathy (IMN)**

The study of natural history of IMN shows that one third of patients undergo spontaneous remission and approximately 40% progress to renal failure, which would eventually lead to ESRD. The therapy of IMN is controversial and much debated. When therapy is so much debated, it is important to identify the group of patients with IMN who could benefit with therapeutic intervention. In this respect it is important to identify the risk factors very early in the course of the disease, which predict progression to renal insufficiency. The heavy proteinuria of > 8 gm/day persistent for more than 6 mo, persistent severe hypoalbuminemia (< 2.2 gm/dl), urinary  $\beta_2$  microglobulin excretion of > 0.5 mcg/min are considered as the risk factors which predict progression even before the renal insufficiency has appeared.<sup>10</sup>

##### **A. IMN with high risk of progression**

**Recommendation 1:** Alternating monthly steroids and cytotoxic agent either CYC or CLB for 6 mo, the protocol of which is described below (*Grade-A evidence*).

**Recommendation 2:** In case combination of steroid and cytotoxic therapy fails to induce remission in patients with heavy proteinuria and normal renal function, patients may be

given tacrolimus 0.05 mg/kg/d for 12 mo with 6 mo taper, provided there is evidence of improvement in proteinuria at 3 mo (*Grade-B evidence*).

**Discussion:** Ponticelli used IV methyl prednisolone 1 gm once daily for 3 days followed by oral prednisolone (0.5 mg/kg/d) for remaining 27 days on mo 1, 3 and 5 and cytotoxic agent for mo 2, 4 and 6. At 10 years follow up, treatment increased remission rate (63% versus 33%) and improved renal survival (92% versus 60%).<sup>11</sup> In a recent RCT (n=93) from India, Jha et al reported that patients treated with alternating steroid and oral CYC for 6 mo, 34/47 (complete 15, partial 19) had remission compared to 15/46 (5 complete, 11 partial) in patients treated with supportive therapy at 10 years.<sup>12</sup> The dialysis free survival in treated and control groups were 89% and 65% respectively (p = 0.016).

A meta-analysis published recently, based on the data derived from 18 RCTs failed to show benefit with steroid and cytotoxic therapy on renal or patient survival.<sup>13</sup> However this meta-analysis is not considered to be the last word on this matter, due to the lack of larger, higher quality RCTs included in the analysis. In a recent RCT, 48 patients with normal renal function and large proteinuria were studied.<sup>14</sup> Twenty-five patients received tacrolimus (0.05 mg/kg/d) over 12 mo with a 6 mo taper, whereas 23 patients were in the control group. The probability of remission in the treatment group was 58, 82, and 94% after 6, 12, and 18 mo, but only 10, 24, and 35% respectively in the control group. Six patients in the control group and only one in the treatment group reached the secondary end point of a 50% increase in their serum creatinine.

#### **B. IMN with low risk of progression:**

**Recommendation:** ACEI and or ARB to reduce proteinuria for up to 6-12 mo. In case

proteinuria is reduced or patient goes in to remission the same strategy may be continued (*Grade-D evidence*).

**Discussion:** Looking at the natural history of the disease, it is clear that not all patients of IMN should receive immediate immunosuppressive treatment. Adoption of such an approach would unnecessarily expose up to 40% of patients to toxic immunosuppressive agents.<sup>10</sup> However no RCT is conducted specifically in patients at low risk of progression.

#### **C. Relapse of nephrotic syndrome after an initial incomplete or complete remission:**

**Recommendation:** A second course of combination of steroid and cytotoxic therapy may be given (*Grade-D evidence*).

**Discussion:** 15 patients who had received a course of Ponticelli therapy for IMN, but developed nephrotic syndrome again, were given second course consisted of cyclophosphamide. The interval between the first and second course was 40 mo. 10/15 (66%) patients had complete or partial remission following the second course and renal survival at 10 years was 86%.<sup>15</sup>

### **IgA Nephropathy (IgAN)**

IgAN is the most common cause of idiopathic glomerulonephritis worldwide. It causes ESRD in 15-20% of cases within 10 years of apparent onset of the disease and is the most common cause of ESRD among all glomerulonephritis.<sup>16</sup> IgAN appears to be a heterogeneous disease with variable presentation and progression. Elevated serum creatinine, persistent proteinuria of > 1 gm/d, hypertension and chronic tubulo-interstitial changes, diffuse proliferation and crescent formation on histology are the strong predictors of progression to ESRD.<sup>17</sup>

#### **A. IgAN with mild to intermediate risk of progression:**

This group is defined as those having proteinuria less than 3 gm/d and estimated GFR of more than 60 ml/min.

**Recommendation:** ACEI or ARB or combination of both (*Grade-B evidence*).

**Discussion:** In a recent randomized, multicenter, double blind placebo controlled trial in young patients (median age of 20.5 y), ACEI benazepril given at 0.2 mg/kg/d was compared with placebo.<sup>18</sup> The composite end point of > 30% decrease of creatinine clearance or worsening of proteinuria until nephrotic range was reached by 1/32 (3%) patients in the ACEI group, and 9/34 (26.5%) in the placebo group at a median follow up period of 38 mo; the difference was significant ( $p = 0.035$ ). The multivariate Cox analysis showed that treatment with ACEI was an independent predictor of prognosis. In another double blind placebo controlled trial involving 109 patients, valsartan given at 80-160 mg/d showed significant decrease in mean rate of GFR decline in the valsartan group ( $-5.6 \pm 6.8$  mL/min/y) compared with the placebo group ( $-6.98 \pm 6.2$  mL/min/y) throughout the study period of 2 years, after adjustment for average blood pressure and proteinuria ( $P = 0.014$ ).<sup>19</sup> However in the short duration of 2 years follow up, there was no significant difference in the composite end-point of doubling of serum creatinine or ESRD. Praga et al prospectively randomly assigned 44 patients with IgAN to enalapril or conventional antihypertensive agents and demonstrated that ACE inhibition significantly lowered proteinuria by 55%.<sup>20</sup> Moreover after 4 years of ACEI therapy, 100% of patients in the treatment group had intact renal function, defined as < 50% rise in serum creatinine compared with only 70% among the control subjects.

#### B. IgAN with high risk of progression:

This group is defined as those who have persistent GFR of less than 60 ml/min and proteinuria of more than 3 gm/d despite ACEI therapy.

**Recommendation:** Oral steroids for up to 24 mo, in combination with a cytotoxic agent

such as cyclophosphamide given for 3 to 6 mo (*Grade-B evidence*).

**Discussion:** Despite the lack of consensus regarding the prognostic significance of crescents and other proliferative lesions, many investigators have chosen to treat more aggressive forms of IgAN with steroids, cyclophosphamide, or other alkylating agents. There are a few studies published recently to support this line of therapy. Ballardie et al treated 38 patients who had progressive IgAN with 3 mo of oral CYC (2 mg/kg/day) in combination followed by azathioprine up to 2 years, with 2 years of low dose methylprednisolone.<sup>21</sup> A clear renal preservation was found among patients who received combination steroid and CYC at 5 years, compared to controls (72% versus 6%). Roccatello et al treated 12 patients who had florid, crescentic IgAN (60 to 80% crescents) with pulse Solu-Medrol and oral CYC (1.5 mg/kg/d) for 8 wk. At 5 years, patients who received steroids and CYC had a 91% renal survival compared with 37% among untreated control subjects.<sup>22</sup>

### Membranoproliferative Glomerulonephritis (MPGN)

MPGN is a uncommon disease, which in its idiopathic form commonly occurs between the age group of 8 to 30 years. Three histological patterns Type-I, II and III are described, of which the first is most common. The outcome in idiopathic MPGN is generally poor with 50-60% reaching ESRD over 10 years.<sup>23</sup> Nephrotic syndrome, renal insufficiency and chronic tubulo-interstitial changes on histology are the risk factor for ESRD. The incidence of idiopathic MPGN has declined significantly world wide in recent years and indeed currently hepatitis-C virus (HCV) related MPGN is the leading cause of MPGN.

**Recommendation 1:** Combination of aspirin (500 mg) and dipyridamole (75 mg) given for several years (*Grade-B evidence*).

**Recommendation 2:** High risk adult patients with idiopathic MPGN may be given oral prednisolone 2 mg/kg/d on alternate days (maximum of 120 mg) 12 to 16 weeks. In case there is a favorable response, the dose can be gradually tapered to 20-30 mg given on alternate days; this maintenance dose can be continued for several years (*Grade-D evidence*).

**Discussion:** Although there is much less reported data in type II and III MPGN, the clinical course and response to therapy may be similar; however there is some evidence that type III may be less responsive to corticosteroid therapy. There is no systematic evaluation of corticosteroid therapy in idiopathic MPGN in adults. The recommendation for corticosteroid therapy in adults is based on the studies in children, where in prolonged corticosteroid therapy had a significant benefit in preserving renal function.<sup>23</sup> The use of aspirin and dipyridamole in adults slowed the progression of MPGN in a couple of small RCTs.<sup>23</sup> However there are no recent trials focusing on the treatment of idiopathic MPGN, probably because of rarity of this disease in recent times.

### Lupus Nephritis (LN)

During the course of their disease, the kidney is a major target organ in up to 40-60% of patients with systemic lupus erythematosus (SLE), with 25-50% presenting with renal involvement already at the time of SLE diagnosis.<sup>24</sup> The presentation of lupus nephritis is highly variable, ranging from mild asymptomatic proteinuria to rapidly progressive glomerulonephritis. Features invariably include some degree of glomerular proteinuria, nephrotic in 45-65% of the cases. Since the correlation between clinical presentation and histological disease is poor, the renal biopsy is indicated if the renal involvement is substantial (proteinuria > 1 gm/d, microhematuria or renal insufficiency). Milder forms with normal renal function, mild proteinuria < 1 gm/d and mild or no microhematuria may be treated without renal biopsy in accordance with the degree of

immunosuppression needed to treat the systemic manifestations of SLE.<sup>24</sup>

#### A. Induction therapy

This involves higher immunosuppression aimed at achieving remission and is generally given over 6 mo or less.

##### **Class I (minimal change) and II (mesangial proliferative) LN**

**Recommendation:** No specific therapy is needed. If mild proteinuria is present ACEI or ARB may be used to control proteinuria. If proteinuria is significant (> 1 gm/d) oral prednisolone at 1 mg/kg/d up to 2-6 weeks (till proteinuria subsides), followed by slow taper over several weeks to a maintenance dose of 5 to 7.5 mg/d would suffice (*Grade-D evidence*).

**Discussion:** These histological lesions are associated with minimal or no proteinuria and hematuria and have normal renal function. There are no therapeutic RCTs designed specifically for these histological lesions. Generally these lesions are considered as benign and immunosuppression if at all needed is largely based on the non-renal manifestations of the disease. If there are no features to suggest systemic disease, these patients are treated with anti-proteinuric measures such as ACEI or ARB therapy.<sup>24</sup>

##### **Class III (Focal proliferative) and IV (Diffuse proliferative) LN**

**Recommendation 1:** Prednisolone combined with CYC either oral or monthly IV pulses, given up to 6 mo. This is the preferred combination therapy if renal insufficiency is present (*Grade-A evidence*).

**Recommendation 2:** If GFR is well preserved, combination of prednisolone and mycophenolate mofetil (MMF), 1.5-3 gm/d for up to 6 mo may be preferred especially in nulliparous women (*Grade-B evidence*).

**Discussion:** In case of renal insufficiency, IV methyl prednisolone given at 250 to 1000 mg

daily for 3-5 days, followed by oral prednisolone at 1 mg/kg/d for 2-6 weeks. Subsequently the dose of prednisolone may be tapered gradually to reach 0.5 mg/kg/d over 2-4 weeks, which may be continued till remission is achieved. Once the remission is obtained, the dose of prednisolone may be further tapered over several weeks to a maintenance dose of 5-7.5 mg/d. Oral CYC is given at 2 mg/kg/d (reduced in case of renal insufficiency to 1-1.5 mg/kg/d) till the remission is achieved (generally up to 3 mo).<sup>25</sup> Alternatively, IV pulses of CYC (500-1000 mg/m<sup>2</sup>) may be used depending on the severity of the disease and renal insufficiency (reduction in dose in case of severe renal failure). After an initial dose, the subsequent doses may be titrated to achieve a nadir WBC count of 3000-4000/c.mm. Houssian et al compared induction therapy of CYC, six monthly pulses at fixed dose of 500 mg with high dose pulse CYC in class IV-LN. At 3.5 years follow up, the remission rates and relapses were similar in both groups.<sup>26</sup>

A recently published meta-analysis of four RCTs comparing MMF with CYC for induction therapy in relatively well preserved renal function with biopsy proven proliferative lupus nephritis, MMF given in 2-3 gm/d had better chance of inducing remission (RR for failure to achieve remission with MMF compared to CYC was 0.7) and with less complications.<sup>27</sup>

### **Class-V (Membranous) LN**

**Recommendation:** Prednisolone and cytotoxic agent such as cyclophosphamide or chlorambucil (Ponticelli regimen) (*Grade-C evidence*).

**Discussion:** Immunosuppressive treatment of class-V LN is poorly standardized as a result of the lack of published controlled trials. Steroid alone appear to be inferior to combination therapy with either cytotoxic agent such as CYC, AZA or cyclosporine-A (CSA).<sup>28</sup>

### **B. Maintenance immunosuppressive therapy:**

This is aimed at maintaining remission with reduced intensity of immunosuppression and is generally continued for few years.

**Recommendations:** MMF initially given at 2 gm/d in two divided doses, which can be reduced to 1gm/d over few mo. Alternately azathioprine (AZA) may be given at 2 mg/kg/d, which can be tapered to 1 mg/kg/day over a few months (*Grade-A evidence*).

**Discussion:** In a recent RCT, the patients were given four to seven monthly IV CYC pulses before being assigned one of three different remission maintaining regimens: Quarterly IV CYC pulses (n = 20), AZA (n = 19; 1 to 3 mg/kg/d), or MMF (n = 20; 0.5 to 3.0 g/d) for 2 years.<sup>29</sup> Although the cumulative rate of renal survival did not differ statistically among the three groups, the most striking differences were (1) an increased mortality in patients who were given maintenance therapy with quarterly IV CYC pulses (versus those who were given AZA), (2) an increased drug-related morbidity in IV CYC patients (versus AZA and MMF patients), and (3) an increased relapse rate in IV CYC patients (versus MMF patients). No statistically significant differences were observed between AZA and MMF.

### **C. Resistant LN:**

The true resistance to induction therapy in LN is fortunately rare. It is characterized by immunological activity of the disease and not just proteinuria, since proteinuria may be related to secondary sclerosis.

**Recommendation:** If patient fails to respond to induction with MMF, pulse CYC should be instituted. If resistant to CYC, persistence with further doses of CYC or change to high dose MMF may be done (*Grade-D evidence*).

**Discussion:** There are no good trials addressing this issue. In case disease activity is very severe,



with severe systemic manifestations, alternate therapies such as plasma exchange, intravenous immunoglobulin (IVIG), autologous stem cell transplantation or rituximab may be considered.<sup>25</sup>

#### D. Discontinuation of immunosuppressors:

**Recommendation:** Discontinuation after a slow taper after 3-5 years from the onset of class-IV LN, provided remission is sustained (*Grade-D evidence*).

**Discussion:** It is difficult, based on current available data, to precisely define the criteria that allow the identification of patients in whom immunosuppression can be stopped safely. Duration of therapy (including induction) of at least 5 years seems warranted. Discontinuing maintenance therapy should only be attempted in patients with proliferative LN who have been treated for at least 5 years and who have had a long period of both clinically and serologically quiescent disease, by slowly tapering the drugs and under strict and frequent surveillance. Because of the limited data available, it is difficult to predict the success rate, but discontinuation is probably feasible in about one-third of the patients. Although data are limited, a permanent decrease of renal function may occur in another one-third of the patients. These facts need to be taken into account when counseling a patient on cessation of immunosuppressive therapy.<sup>30</sup>

### Renal Vasculitis

Wegener's granulomatosis (WG) and microscopic polyangiitis (MPA) are systemic diseases with renal involvement, but renal limited disease is well described. Antineutrophil cytoplasmic antibody (ANCA) is positive in majority of these patients. Vasculitis is a uncommon disease, with reported incidence of 24 per million, however the incidence appears to be increasing in recent years, especially in elderly population.<sup>31</sup> Renal involvement is

characterized by rapidly progressive renal failure and pauci-immune crescentic glomerulonephritis on histology. The key to a better outcome in this potentially devastating disease is an early diagnosis and aggressive induction therapy.

#### A. Induction therapy:

**Recommendations 1:** Oral prednisolone at 1 mg/kg/day to a maximum of 80 mg, with reducing doses over time to 12.5 to 15 mg by 3 mo and CYC (2 mg/kg/d adjusted for age, renal function, and the prevailing white cell count), in which CYC is maintained for 3 mo. Alternately CYC may be given as monthly intravenous pulse at 750-1000 mg/m<sup>2</sup> (adjusted for age and renal function) for 6 mo (*Grade-A evidence*).

**Recommendation 2:** In case baseline serum creatinine is more than 5.8 mg/dl, in addition to prednisolone and CYC, the patient may receive 7 sessions of one volume plasma exchange (PE) over a period of 2 weeks in ANCA positive patients (*Grade-A evidence*).

**Discussion:** A recent meta-analysis suggested that pulsed CYC is less toxic with fewer adverse effects than continuous oral CYC and that it is at least as potent an inducer of remission, but possibly at the expense of a slightly higher relapse rate.<sup>32</sup> Hence the choice of route of administration of CYC in vasculitis is one of convenience and safety, rather than efficacy. Combination therapy with prednisolone and CYC would induce remission in more than 90% of cases when given early in the course of the disease. In a multi-center RCT conducted by European Union vasculitis study group (EUVAS), 137 patients with a new diagnosis of ANCA-associated systemic vasculitis confirmed by renal biopsy and serum creatinine > 5.8 mg/dl were randomly assigned to receive seven PE or 3000 mg of intravenous methylprednisolone (MP).<sup>33</sup> At 3 mo, 49% of patients who received intravenous methylprednisolone compared with 69% of whom received PE were alive and independent of dialysis (p=0.02). As compared

with intravenous MP, PE was associated with a reduction in risk for progression to ESRD of 24% at 12 mo (from 43 to 19%). Patient survival and severe adverse event rates were similar in both groups.

## B. Maintenance therapy:

**Recommendation 1:** CYC can be replaced with AZA (1.5-2 mg/kg/d) once remission is induced and can be continued for up to a year or longer depending on the disease activity (*Grade-A evidence*).

**Discussion:** In a recently published CYCAZAREM study, 144 patients of systemic vasculitis who entered remission with prednisolone and CYC were randomized to receive AZA (2 mg/kg/d) or continuation of CYC (1.5 mg/kg/d).<sup>34</sup> At 18 mo follow up the relapse rates in AZA and CYC groups were similar (15 versus 13%), as well as the severe side effects. The withdrawal of CYC and the substitution of AZA after remission did not increase the rate of relapse, thus, the duration of exposure to CYC may be safely reduced. More recently, MMF has been used as an alternative to AZA. However the results of an ongoing, large multicenter trial conducted by EUVAS comparing AZA and MMF are still awaited. Other drugs used successfully as maintenance therapy in vasculitis are methotrexate and cyclosporine-A, the evidence to support their efficacy is at best weak.<sup>31</sup>

## C. Rescue Therapy for Refractory and Relapsing renal vasculitis:

Standard induction therapy fails to induce remission in approximately 10% of patients. A further difficult patient group comprises those who frequently relapse, necessitating recurrent use of CYC. Both these groups have a high risk of side effects from CYC, due to the high cumulative dose of the drug that is accrued. There is a paucity of data concerning the optimal management of relapses or refractory renal vasculitis. The most common strategy

is the prolonged use of corticosteroids and CYC. Alternate strategies have involved the use of tumor necrosis factor (TNF) blockade such as etanercept or infliximab, polyclonal antithymocyte globulin (ATG), or monoclonal anti-T cell antibodies. However data regarding their efficacy and safety are lacking.<sup>31</sup>

## D. Discontinuation of immunosuppression:

Early discontinuation of immunosuppression is a risk factor for relapse. Generally relapses are more common in WG, whereas they are uncommon in MPA. No study has approached this issue in a prospective fashion; hence it is difficult to make recommendations regarding discontinuation of therapy. However discontinuation of therapy 12-24 mo after remission in WG and lesser period in MPA may be safe with less chance of relapse.

## Supportive Therapy

Along with an effort to induce remission, which may not be possible in many patients with different forms of glomerulonephritis, simultaneous attention must be paid to the supportive measures to prevent or retard the progression of nephropathy to renal insufficiency and ESRD and to prevent complications of nephrotic state such as coagulopathy and hyperlipidemia. The major factors which predict progression of nephropathy are proteinuria and hypertension. The target blood pressure in proteinuric patients should be 120/75 mm Hg or less. The use of ACEI and or ARB along with good blood pressure control should be part of the therapeutic approach for all patients with glomerulonephritis. In a recently published meta-analysis of 11 RCTs that enrolled 1860 patients of non-diabetic renal disease, efficacy of ACEI was assessed.<sup>35</sup> The relative risk of doubling of baseline serum creatinine and ESRD with ACEI compared to controls were 0.69 and 0.7 respectively. Additional analysis by the same group showed that renoprotective benefit was most prominent in patients with current protein excretion of 1-2 gm/d and

a current systolic pressure between 110-129 mm Hg.<sup>36</sup> Limited evidence suggests that combination of ACEI and ARB is superior to either of the drugs alone. This was best shown in a recent trial (COOPERATIVE trial) of 263 patients, in which combined ACEI and ARB significantly reduced proteinuria and decreased the incidence of doubling of serum creatinine, when compared to either of the drug alone.<sup>37</sup> Some patients may not tolerate maximum doses of ACEI or ARB or combination of both, due to development of hypotension, hyperkalemia or significant increase (> 30% above baseline) in azotemia. In patients who do not tolerate maximal doses of combination of these drugs, sub-maximal doses of combination therapy has a better anti-proteinuric effect, compared to higher doses of a single agent.<sup>37</sup> It appears that no level of GFR is a contraindication for therapy with ACEI or ARB; however caution should be entertained while using these agents in patients with advanced renal insufficiency.

## Conclusion

Several trials addressing the therapy of different forms of glomerulonephritis have been published in recent years. These studies though far from being conclusive, have greatly clarified immunosuppressive therapies in various forms of glomerulonephritis and significantly increased our knowledge of antiproteinuric strategies aimed at preserving renal function.

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