Treatment of Idiopathic Membranous Nephropathy

- Membranous nephropathy is among the most common causes of the nephrotic syndrome, accounting for up to one-third of biopsy diagnoses

- MN in adults is most often idiopathic (approximately 75 percent of cases)

Natural History

- Decision to initiate therapy is based upon an understanding of the natural history of untreated patients
- Spontaneous complete remission of proteinuria occurs in 5 to 30 percent at five years
- Spontaneous partial remission (≤2 g of proteinuria per day) occurs in 25 to 40 percent at five years
- The occurrence of ESRD in untreated patients is approximately 14 percent at five years, 35 percent at 10 years, and 41 percent at 15 years

Schieppati A, Mosconi L, Perna A, et al. Prognosis of untreated patients with idiopathic membranous nephropathy. N Engl J Med 1993; 329:85.

Risk Factors for Progressive MGN

- Clinical findings
- Higher risk of developing ESRD include older age (particularly greater than 50 years)
- Male sex
- Nephrotic range proteinuria (particularly if protein excretion exceeds 8 to 10 g/day)
- Increased serum creatinine

Histologic Findings

- Correlates more closely with the severity of the tubulointerstitial disease than with the degree of glomerular injury

- More marked tubulointerstitial disease is often associated with older age, higher mean arterial pressure, and lower creatinine clearance at presentation

Degrees of Risk for Progression

Low risk

- Proteinuria remains less than 4 g/day and cr clearance remains normal for a six-month follow-up period. Such patients have a less than 8 percent risk of developing chronic renal insufficiency over 5 years.

Moderate risk

- Proteinuria is between 4 and 8 g/day and persists for more than six months. Cr clearance is NL or near NL and remains stable over six months of observation. Chronic renal insufficiency develops over five years in approximately 50 percent .

- High risk
- Proteinuria is greater than 8 g/day and persists for three months and/or renal function that is either below normal or decreases during the observation period

- Approximately 75 percent of such patients are at risk of progression to chronic renal insufficiency over five years.

- A random urine protein-to-creatinine ratio should not be used for initial risk stratification since the relationship between the ratio and 24-hour protein excretion varies widely among patients

- Immunosuppressive Therapy

Low risk for progression

- Should not be treated with immunosuppressive therapy as long they have subnephrotic proteinuria
- Clinical assessment and measurement of urinary protein excretion and serum cr every 3 months for two years and twice yearly thereafter since the risk of developing progressive disease falls significantly after two years.

Moderate Risk for Progression

- For patients who remain at moderate risk for progression and do not continue to show a progressive decline in proteinuria at six months, we recommend the initiation of immunosuppressive therapy rather than continued observation

- For moderate-risk patients with a progressive decline in protein excretion over this period that remains above 4 g/day, we suggest immunosuppressive therapy rather than continued observation

Cytotoxic Therapy plus Glucocorticoids

- The patients receiving immunosuppressive therapy had significantly higher rates of complete or partial remission (88 percent) and a higher rate of surviving without ESRD (92 versus 60 percent)
- Partial remission was defined as a normal serum creatinine plus protein excretion less than 2 g/day or more than 50 percent less than baseline

Ponticelli C, Zucchelli P, Passerini P, et al. A 10-year follow-up of a randomized study with methylprednisolone and chlorambucil in membranous nephropathy. Kidney Int 1995; 48:1600.

- Cyclophosphamide and chlorambucil -based regimens are equally effective, as noted in a randomized head-to-head comparative trial that primarily enrolled moderate-risk patients

- However, since chlorambucil has more side effects, we prefer administering the cyclophosphamide-based regimen

- Jha V, Ganguli A, Saha TK, et al. A randomized, controlled trial of steroids and cyclophosphamide in adults with nephrotic syndrome caused by idiopathic membranous nephropathy. J Am Soc Nephrol 2007; 18:1899.

Calcineurin Inhibitors

- Both CSA and tacrolimus have proven efficacy in patients with idiopathic MN
- Cyclosporine plus low-dose prednisone is effective in inducing remission
- The best data are from a randomized trial of 51 patients (mean pr excretion 9.3 g/day and mean serum cr 1.2 mg/dL .The patients were assigned to prednisone (0.15 mg/kg up to a maximum dose of 15 mg/day) plus either placebo or cyclosporine for 26 weeks.
- The cyclosporine -treated group had a significantly higher rate of complete or partial remission (75 versus 22 percent with placebo)
- One year after the cessation of therapy, relapse was common

Alexopoulos E, Papagianni A, Tsamelashvili M, et al. Induction and long-term treatment with cyclosporine in membranous nephropathy with the nephrotic syndrome. Nephrol Dial Transplant 2006; 21:3127.

- The preferred regimen for CSA is treatment for at least six months at a dose of 3 to 5 mg/kg per day in two divided doses to maintain whole blood trough levels of 120 to 200 mcg/L; some investigators would also initiate therapy with prednisone given every other day (maximum 10 mg every other day)

- More prolonged cyclosporine use may be associated with nephrotoxicity

Goumenos DS, Kalliakmani P, Tsakas S, et al. The remission of nephrotic syndrome with cyclosporin treatment does not attenuate the progression of idiopathic membranous nephropathy. Clin Nephrol 2004; 61:17.

- Subsequent therapy is based upon the initial response:

- Among those with a complete remission (protein excretion ≤300 mg/day), we gradually taper the cyclosporine dose with therapy being discontinued after at least two to four months

- Among those with a partial remission (protein excretion less than 3.5 g/day plus at least a 50 percent reduction from baseline), we start to reduce the cyclosporine dose to the minimally nephrotoxic range of 1.5 to 2.5 mg/kg per day, which is given for at least one to two years

Tacrolimus

- Tacrolimus is an alternative to cyclosporine since outcomes appear to be similar
- The efficacy of tacrolimus was demonstrated in a randomized trial of 48 patients with MN
- The rate of complete or partial remission was significantly higher with tacrolimus at both 12 months (82 versus 24 percent) and 18 months (94 versus 35 percent)

- Praga M, Barrio V, Juárez GF, et al. Tacrolimus monotherapy in membranous nephropathy: a randomized controlled trial. Kidney Int 2007; 71:924.

- If a tacrolimus -based approach is chosen for initial therapy, the preferred regimen is 0.05 mg/kg per day in two divided doses to maintain whole blood trough levels between 3 and 5 mcg/L

- The dose may be increased to achieve a higher trough level between 5 and 8 mcg/L if there is no reduction in proteinuria by 2 months

- Among patients who attain a complete or partial remission, tacrolimus should be continued for 12 months and then tapered over 6 months (reducing the dose by 25 percent every 2 months to zero)

- Cyclosporine or tacrolimus should be discontinued if no response occurs by four to six months

- In addition, patients who do not respond to one of these drugs are unlikely to respond to the other.

- The choice between these regimens can depend upon a variety of factors, including patient preference

- As an example, a woman of child-bearing age may want to avoid cyclophosphamide because of its fertility risk, while an older patient with hypertension may prefer to avoid the vascular side effects of cyclosporine or tacrolimus

- we suggest close monitoring without the administration of immunosuppressive medications for 6 months in patients at moderate risk for progression, providing renal function remains stable and edema is controlled with diuretics

- Do not initiate immunosuppressive therapy if pr excretion spontaneously or as a consequence of ACEI falls to less than 4 g/day

- Among patients who do not have a decline in 24-hour pr excretion to less than 4 g by six months, we suggest continuation of nonimmunosuppressive therapies and initiation of cyclophosphamide plus glucocorticoids, or either CNI plus glucocorticoids.

- Patients treated with either a cyclophosphamide or a CNI are considered unresponsive if a substantial reduction in proteinuria (30 to 50 percent from peak levels) is not observed after 6 months of therapy

- In such patients, we consider the other regimen

- Among patients who do not respond to initial cyclophosphamide plus glucocorticoid therapy, we usually wait three to six months after the cessation of cytotoxic therapy before initiating a calcineurin inhibitor, unless the patient has severe symptoms

High risk

- One problem with estimating the GFR by cr clearance is that cr secretion is often markedly increased in patients with nephrotic syndrome compared with normal controls

- As a result, the serum cr will be lower than expected , and the cr clearance will overestimate the GFR by a greater degree than in nonnephrotic subjects

- In one study, the overestimate was 36 mL/min per 1.73 m 2 in nephrotic patients with a serum albumin < 2.6 g/dL, compared with 11 mL/min per 1.73 m 2 in normal controls

- Branten AJ, Vervoort G, Wetzels JF. Serum creatinine is a poor marker of GFR in nephrotic syndrome. Nephrol Dial Transplant 2005; 20:707

Choice of Therapy

- Our treatment preferences for high-risk patients differ according to the course of renal function during the observation period:

- For patients who are classified as high risk because of deterioration of GFR, combination therapy with glucocorticoids and a cytotoxic drug appears to provide the best protection

- For all other patients who have pr excretion > 8 g/day that persists for more than 3 months, combination therapy consisting of either glucocorticoids plus a cytotoxic drug or glucocorticoids plus CNI are equally acceptable treatment options.

- Patients who present with severe symptoms, marked hypoalbuminemia (<2.0 g/dL), or an elevated serum creatinine that does not represent preexisting disease may be treated with immunosuppressive therapy without delay

- Patients with advanced and chronic renal impairment (estimated GFR < 30 mL/min/1.73 m 2 for >3 months) are a possible exception since it is not clear that immunosuppressive therapy is beneficial in this subgroup

- Patients considered to be at high risk because of deteriorating renal function should be carefully assessed for other causes that may be additional to or independent of MN
- As an example, older patients or those with long-standing hypertension may have a reduced GFR independent of MN
- Patients who have no other apparent reasons for reduced renal function or who have progressive deterioration while under observation should be treated without delay

- If cyclosporine therapy is chosen, an acceptable regimen is 3.5 mg/kg per day for 12 months, starting at a lower dose and gradually increasing to achieve a trough CSA concentration of 110 to 170 mcg/L

- Given the risk of nephrotoxicity with cyclosporine, we attempt to maintain trough concentrations at the lower end of the target range and monitor the serum cr

Relapsing Disease

- Once therapy is discontinued, there is an appreciable relapse rate (25 to 30 percent) that may require a second course
- The relapse rate may be somewhat lower and more delayed with cytotoxic as compared with cyclosporine therapy
- The approach to retreatment is partially dependent upon the initial regimen. However, before immunosuppressive therapy is considered, a change in diet to a high salt and/or high protein intake should be excluded

Exclusion of High Salt Intake

- In patients with proteinuric CKD, the antiproteinuric effect of ACEI and non-dihydropyridine calcium channel blockers is enhanced with salt restriction and impaired by a high salt intake even when blood pressure control is appropriate

- Presumed mechanisms are that high salt intakes increase intraglomerular pressure and flow

Cytotoxic Therapy

- Among patients treated with cyclophosphamide -based therapy, relapse of proteinuria has been described in 25 to 30 percent
- Such patients may be treated with a CNI or with a second course of cytotoxic therapy using the same regimen
- We do not give more than two courses of cytotoxic therapy in patients who repeatedly relapse.
- The apparent benefits of cytotoxic therapy in this setting must be weighed against the adverse effects of a second course

Calcineurin Inhibitors

- Among patients treated with calcineurin inhibitor-based therapy, a higher rate of relapse has been reported than with cytotoxic therapy
- Relapse occurred in 43 percent cyclosporine -treated patients
- Relapses may occur more frequently when lower doses of cyclosporine (1.0 to 1.1 mg/kg per day) are used, when the trough levels are less than 100 mcg/L, or perhaps when cyclosporine is given without glucocorticoids, which we do not recommend

- Alexopoulos E, Papagianni A, Tsamelashvili M, et al. Induction and long-term treatment with cyclosporine in membranous nephropathy with the nephrotic syndrome. Nephrol Dial Transplant 2006; 21:3127.

- Relapses can occur during tapering or after cessation of cyclosporine therapy
- In either case, we treat with cyclosporine at a dose of 3 to 5 mg/kg and continue to monitor renal function and whole blood trough levels
- An alternative, particularly in patients who did not tolerate the initial cyclosporine regimen, is cyclophosphamide -based therapy

- Limited data suggest similar results with tacrolimus
- In one trial, relapse occurred in 9 of 19 (47 percent) patients who attained complete or partial remission

Resistant disease

- The optimal approach to moderate- or high-risk patients with stable renal function who fail treatment with both cyclophosphamide and CNI regimens is not known
- Studies in patients with idiopathic resistant MN have reported outcomes following the administration of rituximab :

- In a large single-center study, 100 patients with idiopathic MN and persistent proteinuria 4 weekly infusions of rituximab (375 mg/m 2)

- Ruggenenti P, Cravedi P, Chianca A, et al. Rituximab in idiopathic membranous nephropathy. J Am Soc Nephrol 2012; 23:1416.

- the mean age was 52 years, mean serum creatinine was 1.2 mg/dL
- and mean proteinuria was 9.1 g/day
- Patients were followed for a minimum of six months (mean follow-up, 29 Mo)
- Complete remission was achieved in 27 patients
- partial remission was achieved in 38 patients
- The remaining 35 patients did not achieve remission
- The proportion of patients having a complete or partial remission did not differ according to prior therapy
- Rituximab therapy was generally well tolerated: 28 patients had infusion reactions that were considered minor, and 11 patients had serious adverse events, none of which were considered related to therapy.

- In another study, rituximab (1 g given two weeks apart) was given to 15 severely nephrotic patients (6.1 to 23 g/day)
- seven had failed previous immunosuppressive therapy and eight had a creatinine clearance below 80 mL/min per 1.73 m 2

- At 12 months, 2 and 6 patients had achieved complete or partial remission, respectively; 7 of these eight patients had a baseline cr clearance above 80 mL/min per 1.73 m 2
- The likelihood of remission was not related to previous treatment
- Adverse effects were minor and primarily consisted of infusion reactions

Fervenza FC, Cosio FG, Erickson SB, et al. Rituximab treatment of idiopathic membranous nephropathy. Kidney Int 2008; 73:117.

- An observational study in which 20 patients with MN, pr excretion greater than 5.0 g/day, and cr clearance greater than 30 mL/min
- four weekly doses of rituximab 375 mg/m 2 with retreatment at six months
- At 12 months, complete or partial remission had occurred in 10 patients, and, at 24 months, among 18 patients who completed the study, 16 achieved either a complete (4) or partial (12) remission.
- four weekly doses of rituximab (375 mg/m 2) appear to have the same effect on proteinuria reduction as a regimen of 1 g every two weeks
- Patients who continue to have significant proteinuria may have this dose repeated at 6 months

Fervenza FC, Abraham RS, Erickson SB, et al. Rituximab therapy in idiopathic membranous nephropathy: a 2-year study. Clin J Am Soc Nephrol 2010; 5:2188.

- A decline in anti-phospholipase A2 receptor antibodies may predict the clinical response to rituximab treatment
- PLA2R is a transmembrane receptor that is highly expressed in glomerular podocytes and has been identified as a major antigen in idiopathic MN

- Anti-PLA2R antibodies were measured in serum samples from 35 patients with MN who were treated with rituximab
- Twenty-five patients (71 percent) had PLA2R antibodies at baseline
- PLA2R antibodies declined or disappeared in 17 (68 percent) weeks or months prior to any observed change in proteinuria.

- Patients who had a decline in anti-PLA2R were more likely to achieve remission compared with those in whom the level of anti-PLA2 antibodies did not change (59 versus 0 percent, respectively at 12 months and 88 versus 33 percent, respectively at 24 months)
- One patient who relapsed had a return of anti-PLA2R antibodies prior to the onset of proteinuria
- The lag-time between disappearance of circulating anti-PLA2R antibodies and a remission of proteinuria may help to explain why only about 75 to 80 percent of patients with idiopathic MN are positive for anti-PLA2R antibody in cross-sectional studies
- The anti-PLA2R autoantibody-negative patients may be in the midst of a spontaneous or treatment induced remission.

- Suggests that monitoring serum anti-PLA2R antibodies may allow a more accurate assessment of the immunological response to rituximab (and possibly other therapies) than is provided by measurement of proteinuria alone

- Cravedi P, Ruggenenti P, Remuzzi G. Circulating anti-PLA2R autoantibodies to monitor immunological activity in membranous nephropathy. J Am Soc Nephrol 2011; 22:1400.

Immunosuppressive Agents in Older Patients

- In older patients, immunosuppressive therapy should be considered only for those who are at high risk for progression and after maximum conservative therapy has failed

- A careful examination to rule out an underlying malignancy is mandatory before considering immunosuppressive therapy in older patients with apparently idiopathic MN.

Alternative Agents

- mycophenolate mofetil
- synthetic adrenocorticotropic hormone (ACTH)
- intravenous immune globulin
- azathioprine

Mycophenolate Mofetil

First-line therapy:

- One randomized trial of 20 patients compared the effect of MMF (2.0 g/day) plus prednisolone (0.8 mg/kg daily tapering over six months) and Ponticelli
- All patients were of moderate risk and mean baseline cr of 1.07 mg/dL.
- There was no difference between the percentages of patients who achieved complete or partial remission; (64 percent of MMF group and 67 percent)
- At the end of follow-up (only nine months), there were no differences in patients with treatment resistance (four versus three) or relapse (two versus one)

Chan TM, Lin AW, Tang SC, et al. Prospective controlled study on mycophenolate mofetil and prednisolone in the treatment of membranous nephropathy with nephrotic syndrome. Nephrology (Carlton) 2007; 12:576.

Mycophenolate Mofetil

- In a randomized trial in 21 patients, MMF was as effective as cyclophosphamide
- Eleven patients received MMF (2.0 g/day for six months) and prednisone (0.5 mg/kg/day for 12 weeks); 10 patients received cyclophosphamide and glucocorticoids
- Remission rate was similar , and there were no relapses during a follow-up of 17 months

Senthil Nayagam L, Ganguli A, Rathi M, et al. Mycophenolate mofetil or standard therapy for membranous nephropathy and focal segmental glomerulosclerosis: a pilot study. Nephrol Dial Transplant 2008; 23:1926.

Mycophenolate Mofetil

- In a nonrandomized study of 64 patients with MGN and renal insufficiency [median baseline serum cr was 1.8 mg/dL]
- 32 patients were treated with MMF (2g for 12 months) and compared to 32 historic control who had received cyclophosphamide at a dose of 1.5 mg/kg. Both groups also received glucocorticoids
- The remission rate at 12 months was not significantly different (66 versus 72 percent), although treatment resistance was higher in the MMF group (five versus zero patients)
- During follow-up (median 23 months), the incidence of relapses was significantly higher with MMF (12 versus 4 patients)

Branten AJ, du Buf-Vereijken PW, Vervloet M. Mycophenolate mofetil in idiopathic membranous nephropathy. Am J Kidney Dis 2007; 50:248.

Mycophenolate Mofetil

- Another randomized trial of 36 patients found that MMF monotherapy was ineffective
- All patients had normal kidney function and were of moderate risk
- All received the same conservative therapy and 19 patients received MMF in addition to conservative therapy
- At 12 months, there was no difference between the two groups in the frequency of complete or partial remission o (37 versus 41 percent with conservative therapy alone) or in renal function.

- Dussol B, Morange S, Burtey S, et al. Mycophenolate mofetil monotherapy in membranous nephropathy. Am J Kidney Dis 2008; 52:699.

Resistant disease

- No randomized controlled trials have been performed:
- Sixteen patients with idiopathic MN , were treated with MMF for approximately eight months
- MMF was given at 2000 mg/day. At six months, proteinuria decreased to one-half of initial levels in six patients, with partial remissions in another two
- Most patients had evidence of renal dysfunction, and with treatment there were no significant changes in the serum cr concentration

- Miller G, Zimmerman R 3rd, Radhakrishnan J, Appel G. Use of mycophenolate mofetil in resistant membranous nephropathy. Am J Kidney Dis 2000; 36:250.

- In a retrospective report, MMF was evaluated in 17 patients with MN who had dependence upon glucocorticoids; resistance or increasing renal dysfunction
- Treatment duration and follow-up were four months to two years.
- Ten patients received MMF 2 g/day, 11 of whom also received glucocorticoids
- Proteinuria significantly decreased. In addition, 14 of 15 patients with either glucocorticoid or cyclosporine dependence were able to successfully withdraw from either agent
- There were no significant changes in the median serum cr
- MMF-dependency was observed in four patient

Choi MJ, Eustace JA, Gimenez LF, et al. Mycophenolate mofetil treatment for primary glomerular diseases. Kidney Int 2002; 61:1098. s

- In summary, insufficient data support the use of MMF with glucocorticoids as initial therapy in idiopathic MN
- However, MMF may be a therapeutic option for some patients who have either relapsed , or are unable to tolerate
- There is also limited support for the use of MMF in patients who are resistant
- If MMF is used, we suggest a dose of 1 g twice daily combined with glucocorticoids for 6-12 months
- High rate of relapse

SYNTHETIC ACTH

- There are several uncontrolled reports of synthetic ACTH improving proteinuria in patients with MN, although the mechanism of action remains unknown
- This was examined in a randomized trial of 32 nephrotic patients with MN in whom one year of therapy with ACTH was associated with complete or partial remission in 87 percent (compared to 93 percent in the standard (chlorambucil) therapy)
- There are no data on long-term outcomes, nor data on its use in treatment-resistant MN.
- Mild cushingoid effects may be observed, about equivalent to those seen with a prednisone dose of 15 to 20 mg per day.
- Synthetic ACTH as a depot preparation is used at a starting dose of 1 mg/week, increasing to 1 mg twice weekly, with tapering after 6-9 months. Synthetic ACTH is not currently approved for therapeutic use in the United States.
- Berg AL, Arnadottir M. ACTH-induced improvement in the nephrotic syndrome in patients with a variety of diagnoses. Nephrol Dial Transplant 2004; 19:1305.

- INTRAVENOUS IMMUNE GLOBULIN

One small, uncontrolled study suggested that this modality also may be effective in MN, although other studies have shown little if any benefit

Acute renal failure after IVIG has been reported frequently, especially in formulations containing sucrose or maltose

Azathioprine

Some studies have suggested a limited benefit of azathioprine among patients with MN

Yokoyama H, Goshima S, Wada T, et al. The short- and long-term outcomes of membranous nephropathy treated with intravenous immune globulin therapy. Nephrol Dial Transplant 1999; 14:2379.

Goumenos DS, Ahuja M, Davlouros P, et al. Prednisolone and azathioprine in membranous nephropathy: a 10-year follow-up study. Clin Nephrol 2006; 65:317.