Mycophenolate Mofetil and Cyclosporine Therapy in Membranous Nephropathy

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Idiopathic membranous nephropathy (IMN) remains one of the most common causes of the nephrotic syndrome (NS) in adults. Although the natural history is extremely variable, approximately two thirds of the patients will have persistent high-grade proteinuria and/or develop renal failure over a decade of observation. On the other hand, the remaining third of patients will remit spontaneously and potentially toxic therapy should be avoided in this group. Our capacity to predict which patient will progress at an early stage of the disease has improved substantially in the past 10 years. We present the data from studies of cyclosporine (CSA) and mycophenolate mofetil (MMF) treatment of IMN with their level of evidence in support of efficacy. In addition, based on data related to predicting prognosis, we assign a risk for progression category to the trial patients at entry into these studies. The data are presented in this format so the reader will be able to better discern the risk benefit of treatment within each category and the rationale for our subsequent grade of recommendation for the use of these agents in IMN. CSA has been shown in randomized controlled trials in both the medium and high risk of progression categories of IMN patients to improve proteinuria and preserve renal function at least in the short term in up to two thirds of patients. Other studies suggest prolonged therapy beyond 6 months to 1 year may reduce the high relapse rate after CSA treatment supporting more long-term, continuous, or combination therapy in IMN treatment. The data in favor of MMF treatment of this disease is much weaker and are derived from pilot studies. Only one report applied MMF specifically to IMN patients. In these medium to high risk of progression patients, approximately one-half had a 50% reduction in their baseline proteinuria without a significant alteration in their serum creatinine level. MMF's role as a single agent or as adjunctive therapy in the treatment of IMN needs more rigorous evaluation.
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THE NATURAL HISTORY of idiopathic membranous nephropathy (IMN) has been discussed in other articles in this issue. However, it is important to recognize and appreciate the variations in the natural history before examining the effectiveness of therapies because the patients' baseline characteristics will dictate the outcome of the comparison or control patients in these therapeutic trials testing cyclosporine (CSA) or mycophenolate mofetil (MMF). Many studies have indicated the wide variation in natural history. This was summarized recently in 2 reviews. In one, a summary of 11 reports of the natural history showed a 10-year renal survival within a relatively tight band of between 70% and 90%.[1] A more current pooled analysis of 32 studies estimated renal survival between 65% and 75% at 10 years and 60% at 15 years.[3] Some of even this small

range is probably the result of variations in diagnostic criteria, choice of end points, baseline characteristics, and statistical techniques used in the analysis.[3] This good prognosis is likely an underestimate of today's outcome given the introduction within the past decade of more potent antihypertension medications and lower targets for both systolic and diastolic blood pressure.

One unique feature of this primary glomerular disease compared with all others is a spontaneous remission rate of between 15% and 35%. We recently documented the only factors associated with both spontaneous remission and its durability were persistent, low-grade (ie, subnephrotic) proteinuria during the preremission phase and female gender.[4] Although the relapse rate from a complete remission is high, varying between 30% and 50%, the prognosis remains excellent with the great majority remaining subnephrotic and only 5% ever progressing to chronic renal insufficiency.[4,5] In the patients who do not spontaneously remit, 40% to 50% progress to renal failure and the others remain with variable degrees of proteinuria but stable function for many years. Approximately 10% of the total will die of nonrenal causes over this same time frame.[6]

Several factors have been indicated to be associated with a poor prognosis including male gender, older age at onset, higher levels of proteinuria,

Table 1. Levels of Evidence of Rating Studies of Treatment, Prevention, and Quality Assurance

1) RCT that showed a statistically significant difference in at least one important outcome (eg, survival or major illness).
OR
2) An RCT that does not meet the level 1 criteria
3) A nonrandomized trial with contemporaneous controls selected by some systematic method (ie, not selected by perceived suitability for one of the treatment options for individual patients)
OR
Subgroup analysis of a randomized trial
4) A before-after study or case series (of at least 10 patients) with historic controls or controls drawn from other studies
5) Case series (≥10 patients) without controls
6) Case reports (<10 patients)

abnormal creatinine clearance at presentation and on histology, tubular-interstitial changes, and amount of glomerulosclerosis. The problem in associating these factors with prognosis is their qualitative nature and poor specificity. An alternate approach based on dynamic changes in renal function does produce a semiquantitative risk for progression.[7] It uses the clinical parameters of proteinuria and creatinine clearance estimates over 6-month periods of time. In its simplest form it shows that the overall accuracy of predicting outcome when the minimum level of proteinuria over a 6-month period was persistently greater than 4 g/d was 71%, if greater than 6 g/d over 6 months it was 79%, and 8 g/d or greater for 6 months was 84%. If the patients' renal function was impaired at the beginning of these time frames and/or there was a significant deterioration in function over the 6 months of observations, the sensitivity and positive predictive value were even greater. This algorithm was subsequently validated in 2 independent databases, one from Finland and one from Italy.[8] The advantages of the algorithm are its reliance on very few factors, all of which are standard laboratory measurements of renal function and its dynamic nature that allows recalculation of the risk for progression over the course of the patient's disease. The issue of age, sex, degree of sclerosis on biopsy examination, and hypertension are important but are not required because they are not independent factors in the model and do not add to the predicted value of the algorithm.

The focus of this article is on the results of treatment of IMN using either CSA or MMF. The observations of the natural history of the disease and our ability to predict outcome are the background on which the effectiveness of these therapies in these clinical trials are assessed. We have examined the 6-month period around the entry point of the studies reviewed and segregated the patients entered into the trials into risk for progression categories. We then discuss the risk benefits of the CSA or MMF treatment results in the context of their pretrial prognostic categories.

Tables 1 and 2 outline the levels of evidence for rating studies of treatment, prevention, and quality assurance that are used in this review.[9]

RISK FOR PROGRESSION CATEGORIES FOR IMN PATIENTS

Low-risk patients are defined by normal creatinine and creatinine clearance values and peak proteinuria less than 4 g/d over 6 months of observation. Medium-risk patients are defined by normal or near-normal creatinine and creatinine clearance values and persistent proteinuria of 4 or greater but less than 8 g/d over 6 months of observation. High-risk patients are defined by creatinine and creatinine clearance values either abnormal or deteriorating and/or persistent proteinuria of 8 g/d or greater over 6 months of observation.

CYCLOSPORINE: MECHANISM OF ACTION

The precise mechanism of action of CSA in patients with IMN has been the subject of intense investigation for over 15 years. In vivo studies have used the Heymann's nephritis experimental model in which the disease is known to be mediated by autoantibodies directed against known antigens of the cell membrane of the glomerular epithelial podocyte. CSA does not appear to inhibit either immunoglobulin production by these cells or interfere with the activated complement system. It is thought that the T cells or the release of cyto-

Table 2. Grading System for Recommendations

A The recommendation was based on one or more studies at level 1
B The best level of evidence available was at level 2
C The best level of evidence available was at level 3
D The best level of evidence was lower than level 3 and included expert opinion

kines from activated T cells or both must be involved because CSA works in this model if given at the early stage of the disease process. In vivo work in humans using a model that tests glomerular permeability characteristics have indicated specific actions of CSA that extend beyond its known hemodynamic effects in that it restores the dextran sieving curve toward normal.[10,11]

CLINICAL TRIALS OF CYCLOSPORINE IN IMN PATIENTS

Low Risk for Progression Patients

There have been no clinical trials of CSA in low risk for progression IMN patients.

Medium Risk for Progression Patients

A randomized controlled trial in steroid-resistant nephrotic patients with IMN compared CSA with placebo.[12] These patients would be classified as being in the medium-risk category for progression because they had nephrotic range proteinuria for the 6-month observation period before trial entry despite good blood pressure control and a restricted dietary protein intake of 0.8 g/kg/d. As well, these patients must have failed to achieve remission of their proteinuria despite a minimum of 8 weeks of prednisone therapy at 1 mg/kg/d. Approximately 50% of the patients were hypertensive and those on an angiotensin-converting enzyme inhibitors or angiotensin 2 receptor blockers were allowed to remain on this therapy during the study. Adjustments in the CSA doses were made to maintain a whole-blood trough level as measured by monoclonal assay between 125 and 225 ng/mL. The mean dose in the treatment group was 3.7 ± 2 mg/kg/d and the trough level at 26 weeks was 148 ± 29 ng/mL. There were no significant differences in supine, sitting, or mean arterial pressure between the 2 groups during the active medication or during the postmedication period.

There were 51 patients entered into the study (placebo n = 23, CSA n = 28). All patients received prednisone at 0.15 mg/kg/d up to a maximum of 15 mg/d during the 6 months of active treatment/placebo therapy. Complete remission was defined as less than 0.3 g/d proteinuria plus stable renal function, partial remission as a 50% reduction in initial proteinuria and less than 3.5 g/d plus stable renal function. At the end of the 6 months of treatment, 75% of the treated versus 22% of the control group had a remission in proteinuria ($P = .003$). This response in proteinuria was maintained for up to 1 year post–test medication in 48% of the CSA group and only 13% of the placebo group ($P = .007$). Renal insufficiency, defined by doubling of baseline creatinine and/or a 50% reduction in baseline creatinine clearance was seen in 2 patients in each group. The overall rate of renal function deterioration defined by the slope of creatinine clearance was flat and the same in both patient groups over both the active treatment and the year of follow-up. The drug was well tolerated and no patients had to discontinue treatment because of adverse effects (level 1).

Another randomized study has been reported by Yao et al.[13] The study included 30 patients with IMN with 15 allocated to CSA and 15 to angiotensin-converting enzyme inhibitors (captopril therapy). No patients had received steroids or a cytotoxic agent for at least 6 months before enrollment and all had to be nephrotic at time of trial entry. CSA was given in an initial dose of 5 mg/kg/d but tapered over the first 3 months to 2 mg/kg/d for a total duration of therapy of 15 months. This group was compared with the captopril group given 37.5 mg/d over the same time frame. At the end of the high-dose period (3 mo), 8 of 15 in the CSA group had either a complete (6) or partial (2) remission compared with only 2 partial remissions in the captopril group. At the end of 15 months, 11 of 15 patients were either in a complete (7) or partial (4) remission compared with only 2 in partial remission in the captopril group. No differences were found in either group between the mean initial creatinine or final creatinine levels. No serious adverse effects were reported. At the last visit (an average follow-up time of 44 mo) in the CSA group, 2 of 7 complete remission patients had relapse and 1 of 7 had increased their proteinuria from complete to partial remission status. The investigators concluded that CSA is effective in inducing remission of nephrotic syndrome in adults with IMN with a response rate of 80% (level 1).

A relatively high relapse rate (50%) was observed within 2 years of withdrawal. This was similar to the earlier study in which a relapse occurred in 43% of the CSA group by 52 weeks of follow-up. However, this fraction of the total population in remission remained almost unchanged and significantly different from the placebo group

until the end of the follow-up period (CSA 39%, placebo 12%, $P = .007$).

High Risk for Progression Patients

There has been one randomized controlled trial in patients with clearly documented progressive IMN before CSA therapy.[14] All patients in the initial (conservative treatment period) were followed-up for between 4 and 12 months and during this observation period they had to show an absolute decline in creatinine clearance of 8 mL/min or greater as well as have persistent proteinuria of 3.5 g/d or greater. This defines the group as being at high risk for progression. The patients had been on a restricted protein diet and had their blood pressure controlled to 140/90 mm Hg or less. Sixty-four patients entered the conservative part of the study but only 17 had the deterioration in function required by the entry criteria for part 2, and were eligible to participate in the randomized medication section of the study. The patients were treated with either a year of CSA or placebo. In this study, the drug was used as the only agent. CSA trough level target was between 110 and 170 ng/mL. The test medication was stopped if the creatinine level increased to greater than 30% above entry values despite a 50% reduction in test medication. The average slope of the creatinine clearance in mL/min/mo significantly improved in the CSA group from -2.4 mL/min/mo to -0.7 mL/min/mo versus no change in the placebo group (ie, -2.2 mL/min/mo to -2.1 mL/min/mo; $P \leq .02$). Proteinuria also decreased in the treatment group by an average of 4.5 g/d compared with a mean increase in the placebo group 0.7 g/d ($P = .02$). This improvement was maintained for up to 2 years postmedication (level 1).

A earlier study by Rostoker et al[15] was performed in 15 patients given CSA in an open-label study. They were at high risk for progression in that they had documented deterioration in renal function over a median of 14 months before initiation of treatment. As well, at entry proteinuria was greater than 10 g/d in 12 of 15 patients. The dose of CSA was 4 to 5 mg/kg/d adjusted to achieve a 12-hour trough between 100 and 250 ng/mL by whole-blood monoclonal assay. If no response was seen within 4 months the drug was discontinued (4 of 15, 27%). In the 11 responsive patients (11 of 15, 73%), the drug was maintained for 6 months and then tapered over a further 6

months. In these 11 patients, 4 had a complete remission and 7 had a partial remission (daily proteinuria <2 g/d). At last follow-up evaluation, 2 of the patients were still on CSA and in remission and 9 had discontinued the drug. Relapse occurred in 3 of these 9 patients (33%), with remission re-established with reintroduction of the drug. Six of these 9 patients (66%) remained in remission after a mean of 40 months (range, 18-66 mo) of therapy. Adverse effects were modest: transient renal dysfunction (n = 5), hypertension (n = 3), and other minor effects (n = 4). One patient had a minor persistent deterioration of renal function with a creatinine increase from 130 to 167 umol/L. This value remained stable over the 18 months of follow-up (level 4).

The only other high risk for progression group using CSA was in a report of an open-label study of 41 IMN patients from Germany.[16] These were defined as high risk because their mean urinary protein loss at entry was 10.9 ± 5.7 g/d and entry creatinine was 116 ± 53 umol/L. The IMN patients were treated for a mean of a year with an average dose of CSA of 3.3 ± 1.1 mg/kg/d. Sixty-six percent of the MN patients also were given concomitant steroids averaging 27.5 ± 21 mg/d and 50% of the patients were on an angiotensin-converting enzyme inhibitor before starting CSA. Fourteen of the 41 patients (34%) had a complete remission during CSA treatment. The mean decrease in the proteinuria was 6 g/d. The median treatment time to complete remission was 225 days (quartiles 120 and 459 d). Adverse events were observed in 15 of the 41 patients, the most common ones were gingival hyperplasia, nausea, and muscle cramps. An increase in serum creatinine level from baseline to end of observation was a modest 26 ± 38 umol/L. Their conclusions were that CSA treatment was effective and that the duration of treatment seemed to be a crucial factor and they recommended a minimum of 1 year of treatment.

MMF: MECHANISM OF ACTION

MMF is a new immunosuppressive agent that preferentially inhibits purine synthesis in activated lymphocytes. Its active component mycophenolate acid reversibly inhibits the inosin monophosphate dehydrogenase pathway. This pathway is responsible for the de novo synthesis of guanosine essential for both B- and T-lymphocyte proliferation.

These cells therefore are particularly sensitive to inhibition by mycophenolate acid. There are further suggestions that mycophenolate acid inhibits components of the adhesion molecules, which in turn may suppress the influx of lymphocytes and monocytes into areas of inflammation. In experimental models MMF has been shown to inhibit mesangial cell proliferation in the anti-THY 1.1 nephritis model.[17]

CLINICAL TRIALS OF MMF IN IMN PATIENTS

Low Risk for Progression Patients

There have been no studies of MMF in low risk for progression in IMN patients.

Medium Risk for Progression Patients

The only study with any substantial number of patients with IMN in this category was published recently by Choi et al.[18] There were 17 patients with IMN in a total of 46 patients with biopsy examination–proven primary nephropathy who received MMF for 3 months or greater as adjunctive or as stand-alone therapy. It was difficult to discern from the article the precise levels of proteinuria and/or if there had been any recent change in renal function in the IMN patients before entry. The indication for a trial of MMF included 2 steroid-dependent, 4 CSA-dependent, and 1 cytotoxic-dependent patient, with the remainder intolerant or resistant to one or another of the agents. Proteinuria was monitored by the urine protein to creatinine ratio rather than 24-hour urine estimates and changes in renal function by estimates of change in creatinine clearance values based on the modified diet in renal disease formula. On average, a urine protein to creatinine ratio of 3 or greater would indicate nephrotic range proteinuria. The median percent reduction in urine protein to creatinine was 61%, or to a urine protein to creatinine ratio of 1.5 by the end of MMF treatment ($P = .001$). In 15 patients with pretreatment nephrotic range proteinuria, the protein/creatinine ratio was reduced from 8.7 (3.6-18.5) to 2.3 (<0.1 to 14.3) ($P = .001$). Two patients (13.3%) achieved a complete remission, 8 (54%) achieved a partial remission, 3 (20%) achieved a 50% reduction in proteinuria, and 2 (13.3%) had no change. There was no change in median serum creatinine level or mean arterial pressure over the period of treatment. The average treatment time was 8 months but ranged from 4 to 25 months. Ninety percent of the patients were able to be withdrawn from prednisone and/or CSA while on the MMF treatment. Three patients had MMF discontinued early. One patient developed severe gastritis, 1 patient developed pneumonia, and 1 patient developed a squamous cell carcinoma. One other patient developed mild reversible leukopenia (level 5).

High Risk for Progression Patients

Sixteen patients treated with MMF in a study by Miller et al[19] were considered at high risk for progression because their mean proteinuria at the time of admission to the pilot study was over 9 g/d. As well, all of the patients failed to respond to a minimum of 6 months of corticosteroid therapy plus 6 patients also had failed cytotoxic therapy and 5 had failed CSA treatment. Thirteen of the 16 patients were on angiotensin-converting enzyme inhibitor therapy and despite this remained severely nephrotic. The majority of the patients also had some degree of chronic renal insufficiency in that 11 of the 16 patients had baseline creatinine levels greater than 135 umol/L. Partial remission was defined as a 50% reduction in baseline proteinuria and total proteinuria of less than 3 g/d with stable serum creatinine levels, complete remission was defined as proteinuria less than 0.3 g/d and a stable serum creatinine level. Target MMF dose was 2 g/d and this was achieved in 7 patients. The mean duration of MMF therapy was 8 months and all but 2 completed at least 6 months. There was no change in mean proteinuria by the end of the study (before: 9.2 g/d; after: 7.5 g/d). However, 6 of the 16 patients had a partial response. Two achieved a partial remission by 4 months and 4 others achieved a 50% reduction in their baseline proteinuria. The mean time to halving of the proteinuria was 3 months with a range between 1 and 6 months. There was no significant change in mean serum creatinine value by the end of treatment. Toxicity included 1 patient who discontinued MMF after 3 months because of severe diarrhea and 1 patient discontinued the medication owing to varicella-zoster infection. As well, there was transient leukopenia in 1 patient who responded to a dose reduction (level 5).

In summary, there is grade A evidence for the use of CSA in both medium and high risk for progression patients with IMN. In the medium-risk category there have been 2 randomized controlled

trials and in the high-risk group there has been 1 trial, although with small numbers. The major disadvantages to its use are its adverse effects and high relapse rates. This may indicate a more prolonged course, or perhaps continuous low-dose therapy may be a better approach to its use.

The data for MMF is much less secure. In the medium-risk category the best level of evidence is level 5, which currently would give it a grade D recommendation. In the high-risk patients again the best level of evidence is level 5 and a grade D recommendation. The limitation of its effectiveness currently, however, is the lack of studies rather than evidence against its usage. The early results would indicate a potential role for this agent in the management of the difficult patient with IMGN. Whether this should be as adjunctive therapy, perhaps in combination with CSA to reduce its' toxicity, and/or as a single agent perhaps as maintenance therapy after remission induction, needs to be addressed in larger and more rigorous trials.

REFERENCES

1. Cattran DC, Pei Y, Greenwood C: Predicting progression in membranous glomerulonephritis. Nephrol Dial Transplant 7:48-52, 1992 (suppl 1)

2. Hogan SL, Muller KE, Jennette JC, et al: A review of therapeutic studies of idiopathic membranous glomerulopathy. Am J Kidney Dis 25:862-875, 1995

3. Marx BE, Marx M: Prognosis of idiopathic membranous nephropathy: A methodologic meta-analysis. Kidney Int 51:873-879, 1997

4. Laluck BJ Jr, Cattran DC: Prognosis after a complete remission in adult patients with idiopathic membranous nephropathy. Am J Kidney Dis 33:1026-1032, 1999

5. Ponticelli C, Passerini P, Altieri P, et al: Remissions and relapses in idiopathic membranous nephropathy. Nephrol Dial Transplant 7:85-90, 1992 (suppl 1)

6. Heaf J, Lokkegaard H, Larsen S: The epidemiology and prognosis of glomerulonephritis in Denmark 1985-1997. Nephrol Dial Transplant 14:1889-1897, 1999

7. Pei Y, Cattran D, Greenwood C: Predicting chronic renal insufficiency in idiopathic membranous glomerulonephritis. Kidney Int 42:960-966, 1992

8. Cattran DC, Pei Y, Greenwood CM, et al: Validation of a predictive model of idiopathic membranous nephropathy: Its clinical and research implications. Kidney Int 51:901-907, 1997

9. Carruthers SG, Larochelle P, Haynes RB, et al: Report of the Canadian Hypertension Society Consensus Conference: 1. Introduction. CMAJ 149:289-293, 1993

10. Zietse R, Wenting GJ, Kramer P, et al: Contrasting response to cyclosporin in refractory nephrotic syndrome. Clin Nephrol 31:22-25, 1989

11. Ambalavanan S, Fauvel JP, Sibley RK, et al: Mechanism of the antiproteinuric effect of cyclosporine in membranous nephropathy. J Am Soc Nephrol 7:290-298, 1996

12. Cattran DC, Appel GB, Hebert LA, et al: Cyclosporine in patients with steroid-resistant membranous nephropathy: A randomized trial. Kidney Int 59:1484-1490, 2001

13. Yao X, Chen H, Wang Q, et al: Cyclosporin A treatment for idiopathic membranous nephropathy. Chin Med J (Engl) 114:1305-1308, 2001

14. Cattran DC, Greenwood C, Ritchie S, et al: A controlled trial of cyclosporine in patients with progressive membranous nephropathy. Canadian Glomerulonephritis Study Group. Kidney Int 47:1130-1135, 1995

15. Rostoker G, Belghiti D, Ben Maadi A, et al: Long-term cyclosporin A therapy for severe idiopathic membranous nephropathy. Nephron 63:335-341, 1993

16. Fritsche L, Budde K, Farber L, et al: Treatment of membranous glomerulopathy with cyclosporin A: How much patience is required? Nephrol Dial Transplant 14:1036-1038, 1999

17. Ziswiler R, Steinmann-Niggli K, Kappeler A, et al: Mycophenolic acid: A new approach to the therapy of experimental mesangial proliferative glomerulonephritis. J Am Soc Nephrol 9:2055-2066, 1998

18. Choi MJ, Eustace JA, Gimenez LF, et al: Mycophenolate mofetil treatment for primary glomerular diseases. Kidney Int 61:1098-1114, 2002

19. Miller G, Zimmerman R III, Radhakrishnan J, et al: Use of mycophenolate mofetil in resistant membranous nephropathy. Am J Kidney Dis 36:250-256, 2000