Outcome of Idiopathic Membranous Nephropathy: A Retrospective Study

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ABSTRACT: **Background:** Idiopathic membranous nephropathy (IMN) is one of the most common causes of nephrotic syndrome (NS) in Caucasian adults. Most patients have good renal prognosis, but 30–40% may progress to end stage renal disease (ESRD).
Objectives: To evaluate the efficacy and safety of immunosuppressive treatment (IST) in high-risk patients.
Methods: All IMN patients diagnosed by kidney biopsy from 2004–2010 were included. Clinical and laboratory data were collected at each follow-up visit. Risk assessment for renal progression classified patients as high risk if: 24 hour protein excretion › 6 g/day, estimated glomerular filtration rate (eGFR) ‹ 60 ml/min/1.73 m2, and severe disabling or life-threatening clinical symptoms of NS were present.
Results: Among 290 biopsies, 37 patients (12.7%) were IMN. They were allocated to the high-risk IST group (n=16) or low-risk supportive treatment (ST) group (n=21) according to the likelihood of developing renal failure. Mean follow-up was 47 ± 17.3 months. Complete and partial remission rate was 68.7% for high-risk IST vs. 90.4% for low-risk ST. In the high-risk IST group, eGFR was significantly lower at 30 months (65.5 ± 28.6 vs. 85.3 ± 21.6 at baseline, $P < 0.05$). Four high-risk patients reached ESRD. In the low-risk ST group, eGFR remained stable at 30 and 60 months.
Conclusions: This study showed a high remission rate for IMN. IST with prednisolone and cyclophosphamide provided favorable renal outcomes in most high-risk patients. The very high remission rate obtained in the low-risk patients confirms the adequacy of supportive treatment in this group.

IMAJ 2018; 20: 186–189

KEY WORDS: idiopathic membranous nephropathy, kidney biopsy, proteinuria, remission, immunosuppression

Membranous nephropathy (MN) is one of the most common causes of nephrotic syndrome in Caucasian adults, and about 75% of these cases are idiopathic (IMN) [1,2]. Secondary causes of MN have been associated with autoimmune diseases, hepatitis C and B viruses, drugs, and malignancy [3]. The pathogenesis of IMN involves in situ formation of subepithelial deposits that produce glomerular injury by damaging and/or activating podocytes through complement activation [4]. In 2002 Debiec and co-authors [5] identified neutral endopeptidase (NEP) antibodies in a newborn male with nephrotic syndrome. A significant advance occurred in 2009 when Beck and colleagues [6] identified antibodies against a conformation-dependent epitope of the M-type phospholipase A2 receptor (PLRA2) in 75% of patients with IMN. Most patients with MN present with the nephrotic syndrome [7]. The natural course of IMN varies considerably, but the amount of proteinuria and renal function are two important factors that predict outcomes [8]. Overall, 60% to 70% of patients with IMN enter complete remission or partial remission and generally have a good renal prognosis [2]. About 30% to 40% of patients have sustained proteinuria and are at increased risk for developing end stage renal disease within 5 to 15 years [2]. Supportive therapy with angiotensin-converting-enzyme inhibitors (ACE inhibitors) or angiotensin-receptor blockers (ARBs), a diet low in salt and protein, and statins are initiated in all patients for 6 months [9]. Immunosuppressive therapy, including steroids with alkylating agents or calcineurin inhibitors, is indicated in patients with persistent nephrotic range proteinuria and decreased renal function [10]. The most frequent adverse effects reported with cytotoxic agents are life-threatening infections, bladder carcinoma, and myelodysplasia [9].

Considering the large variations in the clinical course of IMN, the aim of this retrospective, single center study was to evaluate the history and safety of immunosuppressive treatment in patients with IMN.

PATIENTS AND METHODS

All IMN patients diagnosed by kidney biopsy from 2004 through 2010 at the Meir Medical Center were included in this retrospective study. Data were collected from the biopsy registry of the Pathology Department at Meir. Subjects with suspected secondary MN and/or possible concomitant renal disease were excluded. All biopsy specimens were examined by a nephro-pathologist. Analysis included light microscopy, immunofluorescence, and electron microscopy.

Clinical and laboratory data were collected at each follow-up visit starting from the time of the kidney biopsy until the last

follow-up visit. At each visit, blood pressure, body weight, and physical examination for peripheral edema and/or deep venous thrombosis were performed. Serum creatinine, albumin, total cholesterol, and 24 hour urine collection for proteinuria and sodium were analyzed by standard, automated laboratory methods. Estimated glomerular filtration rate (eGFR) was calculated by the chronic kidney disease epidemiology collaboration (CKD-EPI) equation (ml/min/1.73 m^2) [11]. The use of ACE inhibitors, ARBs, statins, anti-aggregants, and anticoagulants were recorded. Patient clinical and laboratory data were collected and evaluated for risk of developing renal failure. A patient was classified as high-risk for renal failure if: 24 hour protein excretion > 6 g/day, eGFR < 60 ml/min/1.73 m^2, or severe disabling or life-threatening clinical symptoms associated with NS were present [12].

TREATMENT PROTOCOLS

Supportive treatment (ST) consisted of a low salt and low protein diet, diuretics, ACE inhibitors or ARBs, and statins. Recommendations for a low salt diet (6 grams NaCl per day) and relatively low protein intake (0.7 gram/kg/day) were provided to all patients by a dedicated dietician from the nephrology department. Adherence to the low salt diet was assessed by 24 hour urine collection of sodium. When a patient was considered to be at high risk for progression, immunosuppressive treatment (IST) was initiated according to the modified Ponticelli protocol [13]. Briefly, intravenous methyl prednisolone 1 gm/day was initiated over 3 consecutive days, followed by oral prednisone 0.5 mg/kg/day for 27 to 28 days during months 1, 3, and 5. Oral cyclophosphamide 2 mg/kg/day was given at the beginning of months 2, 4, and 6, continuing for 1 month.

FOLLOW-UP

Follow-up included a 24 hour quantitative protein excretion, serum albumin, and creatinine. Complete remission was defined as proteinuria < 0.3 g/24 h, serum albumin > 3.5 g/dl, and eGFR > 60 ml/min/1.73 m^2. Partial remission was defined as a decrease in proteinuria of at least 50% from baseline and quantitative protein excretion < 3 g/24 h. No response (NR) was defined when complete remission or partial remission was not achieved. Safety and effectiveness of the immunosuppressive and supportive treatment were recorded.

STATISTICAL ANALYSIS

Data are presented as numbers and percentage for nominal parameters and continuous variables as mean and standard deviation. Differences in non-metric parameters between two groups were analyzed by chi-square test or Fisher's exact test, each when appropriate. Differences in metric parameters between two groups were analyzed with *t*-test or Mann–Whitney non-parametric test according to data distribution. $P < 0.05$ was considered statistically significant.

RESULTS

A total of 290 kidney biopsies were performed in our department from July 2004 through December 2010. Of these, 52% were requested to confirm the diagnosis of nephrotic syndrome or nephrotic range proteinuria. Forty-three patients (14.8%) were diagnosed with MN. Two patients who had an underlying disease (systemic lupus erythematosus and hepatitis C virus) were excluded from the analysis. Four patients were lost to follow-up. The remaining 37 patients with IMN were included and allocated to the high-risk IST group (n=16) or the low-risk ST group (n=21), according to the probability of developing renal failure (high-risk) or (low-risk), respectively. The mean duration of follow-up was 47 ± 17.3 months. The baseline characteristics of the patients are shown in Table 1. The high-risk patients had significantly higher levels of proteinuria and lower serum albumin levels. No significant differences were found at baseline regarding age, blood pressure, serum creatinine and eGFR, use of statins and ACE inhibitors or ARBs, and co-morbid conditions.

RESPONSE TO TREATMENT

The overall remission rate (complete remission + partial remission) was 11/16 patients (68.7%) in the high-risk IST group and 19/21 patients (90.4%) in the low-risk ST group [Table 2]. Complete remission and partial remission were obtained respectively in 4 and 11 patients in the high-risk IST group vs. 10 and 9 patients in the low-risk ST group. Five patients did not respond to IST and two in the ST group had persistent proteinuria. Patients in the high-risk IST group who did not

Table 1. Baseline characteristics of the study population (all patients with IMN), results are expressed as mean ± standard deviation or as median when appropriate

Characteristic	High risk (n=16)	Low risk (n=21)	*P*-value
Gender (male/female)	11/5	9/12	NS
Age (years)	50 ± 9	45 ± 15	NS
Serum creatinine (mg/dl)	1.02 ± 0.4	0.86 ± 0.3	NS
eGFR (ml/min/1.73 m^2)	91.1 (39–116)	95.2 (31–131)	NS
Serum albumin (g/dl)	2.6 ± 0.5	3.3 ± 0.6	0.01
Proteinuria (mg/24 h)	6.4 (3–27)	2.5 (1–8)	< 0.05
Systolic blood pressure (mmHg)	135.6 ± 18	132.8 ± 13.5	NS
Diastolic blood pressure (mmHg)	88.1 ± 12	83.9 ± 6.3	NS
Diabetes mellitus (%)	3 (18.7%)	3 (14.3%)	NS
Cardiovascular disease (%)	3 (18.7%)	3 (14.3%)	NS
ACEI or ARB (%)	11 (68.8%)	14 (66.6%)	NS
Statins (%)	9 (56.2%)	10 (47.7%)	NS

ACEI = angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker, eGFR = estimated glomerular filtration rate calculated by the CKD-EPI equation, IMN = idiopathic membranous nephropathy

Table 2. Baseline characteristics of patients according to response to treatment

[A] High risk patients who received immunosuppressive treatment

Baseline characteristics	Remission (CR+PR) (n=11)	No response (n=5)	*P*-value
Age + SD (years)	52 ± 10.6	46 ± 10	NS
Gender (male/female)	7/4	4/1	NS
Serum creatinine (mg/dl)	0.85 ± 0.1	1.3 ± 0.6	0.02
eGFR (ml/min/1.73 m²)	93.5 ± 13.7	73.7 ± 32.6	NS
Serum albumin (mg/dl)	2.5 ± 0.5	2.5 ± 0.4	NS
Proteinuria (mg/24 h)	7.47 ± 0.48	8.45 ± 2.09	NS

[B] Low risk patients who received supportive therapy

Baseline characteristics	Remission (CR+PR) (n=19)	No response (n=2)	*P*-value
Age + SD (years)	46 ± 16	36 ± 0	NS
Gender (male/female)	9/10	0/2	NS
Serum creatinine (mg/dl)	0.8 ± 0.18	1.4 ± 0.85	NS
eGFR (ml/min/1.73 m²)	98.9 ± 15	63.3 ± 45.11	NS
Serum albumin (mg/dl)	3.3 ± 0.61	3.45 ± 0.21	NS
Proteinuria (mg/24 h)	3.08 ± 2.06	3.54 ± 2.74	NS

CR = complete remission, eGFR = estimated glomerular filtration rate, NS = not significant, PR = partial remission, SD = standard deviation

Table 3. Clinical outcomes of patients according to follow up after 30 and 60 months

[A] High-risk patients who received immunosuppressive treatment

	High-risk patients (IST)					
Clinical outcomes	0 m (n=16)	30 m (n=15)	*P*-value	30 m (n=15)	60 m (n=9)	*P*-value
Serum creatinine (mg/dl)	1.02 ± 0.4	1.33 ± 0.67	NS	1.33 ± 0.67	1.76 ± 1.84	NS
eGFR (ml/min/1.73 m²)	85.3 ± 21.6	65.5 ± 28.6	0.026	65.5 ± 28.6	70.3 ± 36.1	NS
Serum albumin (g/dl)	2.6 ± 0.5	3.9 ± 0.55	< 0.05	3.9 ± 0.55	4 ± 0.5	NS
Proteinuria (g/24 h)	8.2 ± 5.9	2.09 ± 2.65	< 0.05	2.09 ± 2.65	2.47 ± 2.72	NS

[B] Low-risk patients who received supportive therapy

	Low-risk patients (ST)					
Clinical outcomes	0 m (n=21)	30 m (n=20)	*P*-value	30 m (n=20)	60 m (n=13)	*P*-value
Serum creatinine (mg/dl)	0.86 ± 0.3	0.85 ± 0.3	NS	0.85 ± 0.3	0.96 ± 0.43	NS
eGFR (ml/min/1.73 m²)	95.5 ± 20.5	94.45 ± 23.64	NS	94.45 ± 23.64	85.7 ± 23.6	NS
Serum albumin (g/dl)	3.3 ± 0.6	4.01 ± 0.37	< 0.05	4.01 ± 0.37	4.2 ± 0.28	NS
Proteinuria (g/24 h)	3.1 ± 2.0	0.7 ± 1.16	< 0.05	0.7 ± 1.16	1.23 ± 1.9	NS

eGFR = estimated glomerular filtration rate, IST = immunosuppressive treatment, NS = not significant, ST = supportive treatment

achieve remission had significantly higher serum creatinine at baseline as compared to patients who entered remission (1.3 ± 0.6 mg/dl vs. 0.85 ± 0.17 mg/dl, $P = 0.02$).

Leucopenia occurred in two patients in the high-risk IST group. One patient developed a psychotic disorder, which improved after withdrawal of steroids. No major infections or sepsis occurred during the follow-up period (mean 47 ± 17.3 months). Four patients reached end stage renal disease (ESRD) and two deaths unrelated to infectious diseases occurred in the high-risk IST group. There were no serious adverse events, deaths, or cases of ESRD in the low-risk ST group.

In the high-risk IST group, eGFR was significantly lower at 30 months (65.5 ± 28.6 vs. 85.3 ± 21.6 at baseline, $P < 0.05$). Serum albumin and the level of proteinuria significantly improved at 30 months (3.9 ± 0.55 g/dl vs. 2.6 ± 0.5 g/dl for albumin and 2.09 ± 2.6 vs. 8.2 ± 5.9 g/24-h for proteinuria, $P < 0.05$) [Table 3]. In the low-risk ST group, eGFR remained stable at 30 and 60 months and the improvement in serum albumin and level of proteinuria observed at 30 months persisted at 60 months [Table 3].

DISCUSSION

The results of this retrospective, observational study show favorable outcomes for patients with IMN. Overall, remission was achieved in 81% of participants. Four patients (10.8%) progressed to ESRD over a follow-up of 60 months. The selection criteria for allocating patients to the high-risk or low-risk group showed a very high remission rate in the low-risk ST group (91%), without progression to ESRD or disease relapse. According to the model developed by Cattran and colleagues [14], the severity and duration of proteinuria were correlated to the risk of progression to renal failure. After a slight modification of this model, as previously reported, we classified our patients into low-risk and high-risk groups according to the level of proteinuria, with a cut-off of 6 g/24 h [12]. Regarding the severity of renal failure, our patients entered the study with a mean GFR > 60 ml/min/1.73 m² without significant differences between groups.

A combination of steroids and cyclophosphamide was used, according to the modified Ponticelli protocol [13], where chlorambucil was replaced by cyclophosphamide. The efficacy of this treatment has been well-documented and represents one of the most widely used immunosuppressive regimens for IMN [8,10]. Most clinical studies do not recommend the use of steroids as monotherapy, with the exception of a few studies published in Japan [15]. Cyclosporin alone or combined with steroids has been suggested as an effective treatment for inducing remission in IMN [8,10]. The UK randomized, controlled trial found lower efficacy of cyclosporine when compared to steroids and chlorambucil, in the subset of patients with IMN and deteriorating renal function [16]. The KDIGO guideline for glomerulonephritis found low-to-moderate quality evidence to support a recommendation for cyclosporine therapy in IMN [17]. The 6 month therapy with cyclosporine was associated with a high relapse rate and the beneficial effect on proteinuria was obtained with a regimen of at least 6–12 months [18]. MMF has been suggested as an alternative to the classical steroid-alkylating regimen used

in IMN, but large, randomized, controlled studies and data on long-term renal survival are still lacking [19].

Rituximab for IMN has emerged as promising therapy for severe or resistant cases. A large study published by Ruggenenti and collaborators [20] enrolled 100 IMN patients with persistent nephrotic syndrome. During a median follow-up of 29 months after rituximab administration, 65 patients achieved complete or partial remission, four patients died and four progressed to ESRD. Patients whose serum anti-PLA2R decreased were more likely to achieve remission. No serious adverse events occurred during the study [20]. In a large cohort study of 376 patients with IMN, Cattran and co-authors [21] showed a positive correlation between the duration of remission and better renal outcomes and prognosis.

In our study, patients with IMN, who were treated with steroids and cyclophosphamide and who did not achieve remission, had significantly higher serum creatinine levels and lower eGFR. This finding confirms that decreased renal function is an important risk factor for progression to renal insufficiency. We classified our IMN patients as low-risk or high-risk for progression to renal insufficiency based primarily on the severity of proteinuria. At baseline, no significant differences were found in renal function. The high rate of spontaneous remission in the low-risk group confirmed the accuracy of this classification.

Our study has important limitations inherent to its retrospective design. The study population was small and from a single center. PLRA2 monitoring was not included due to its commercial unavailability at the beginning of the study. The study was not designed to compare different protocols of immunosuppressive treatments. However, the population was closely monitored and the homogeneity of the treatment modality strengthens the results obtained from the high-risk IST group.

CONCLUSIONS

This retrospective observational study both confirms the efficacy and safety of immunosuppressive treatment in patients at high risk of renal progression and justifies the choice of supportive treatment for low-risk patients.

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"The tools of conquest do not necessarily come with bombs, and explosions, and fallout. There are weapons that are simply thoughts, attitudes, prejudices, to be found only in the minds of men. For the record, prejudices can kill and suspicion can destroy; and a thoughtless, frightened search for a scapegoat has a fallout all of its own for the children, and the children yet unborn"

Rod Serling, (1924–1975), writer of the science fiction TV series *The Twilight Zone*