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Choosing to Treat Membranous Nephropathy: A 30-year Experience

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Abstract

Background: Membranous nephropathy (MN) is one of the most frequent causes of nephrotic syndrome in adults. The clinical course is variable, and its treatment is still a matter of controversies. The aim of this study was to establish when immunosuppressive (IMS) therapy should be indicated in our population with MN.

Methods: We evaluated retrospectively clinical and laboratorial data from 71 patients with primary MN, followed in the Glomerulopathy Section (UNIFESP), from 1976 to 2006.

Results: Ten of the 71 patients have not received any specific IMS treatment, while the remainders were submitted to several specific therapies. The final mean creatinine in the non-treated (2.0 ± 1.83 mg/di) was higher than that of the treated group (1.66 ± 1.54 mg/di) and there was a strong and significant difference between decreases of proteinuria levels in the group of treated patients when compared to the non treated group. The highest frequency of complete remission was observed in the treated patients (22.9% vs. 10% in non treated) and the highest index of non response in the non treated group (60% vs. 41% in treated), but these differences were not statistically significant. When we compared the patients who received oral corticosteroid, or intravenous (IV) methylprednisolone (MP) plus cyclophosphamide (Cyp), and non treated patients, we observed a favorable effect of the IMS treatment, especially of IV MP plus Cyp.

Conclusions: In a long term follow-up of MN patients IMS treatment was associated to better renal outcome, including more frequent remission, lower final proteinuria and serum creatinine.

Keywords: Immune suppression; Membranous nephropathy; Nephrotic syndrome; Proteinuria; Therapeutics

Background

Treating or not idiopathic Membranous Nephropathy (MN) has been a matter of controversy for decades. Some authors emphasize rates of spontaneous remission is considered high and argue against immunosuppressive (IMS) therapy [1], while others reinforce the high frequency of progression to chronic renal failure and are favorable to IMS [2]. In 1992, Cameron [3] defended the idea that identifying patients at risk to progress to renal failure could give a clue of whom should be treated. According to this tendency, as there are concerns about the usefulness of IMS, only patients with a bad outcome should be treated. Ponticelli et al. [2] assumed that IMS retards the treatment of nephrotic syndrome caused by MN until the renal function begins to deteriorate. For those authors, wait until installation of renal failure means that irreversible lesions will occur [4].

As genetic or ethnic factors could have a prognostic role [5] and eventually influence immunosuppressive (IMS) treatment response in idiopathic MN, our aim in the present study was to evaluate if Brazilian patients with nephrotic proteinuria due to MN should or not be submitted to IMS therapy and which regimen could be more adequate.

Methods

A retrospective analysis was performed based on the reports of 71 patients with idiopathic MN, with ages above 12 years-old, followed along at least six months in our service. Exclusion criteria were clinical, laboratorial or histological evidence of secondary nephropathy and insufficient information for the aims of this study. Ethics Committee approval was obtained.

Assistant physicians of the Glomerulopathy Section were responsible for the decision of treating or not each patient with IMS therapy, usually following the medical literature tendency by the time of each renal biopsy (1976-2006).

The definitions utilized in this study were: nephrotic proteinuria: proteinuria levels equal to or superior to 3.0 g/24h; nephrotic syndrome: coexistence of nephrotic level proteinuria, hypoalbuminemia (serum albumin inferior to 3.0 g/dl) and edema; complete remission: proteinuria equal to or inferior to 0.3g/24h, without increase of serum creatinine; partial remission: decrease of proteinuria to levels between 0.31 g/24h and 2.0 g/24h. Late remission corresponded to proteinuria lower than 2.0 g/day within six months after the end of IMS when different therapies were not added.

The IMS treatment was divided in four groups: (1) oral prednisone, 1 mg/kg/day, for at least 2 months; (2) intravenous (IV) methylprednisolone (MP), 10-15 mg/kg/dose/month (three consecutive doses in the first month and only one in the next months), for 6 months, associated with oral prednisone 1mg/kg/day along all the treatment period; (3) other oral IMS agents: azathioprine (2 mg/kg/day) or cyclosporine (4-5 mg/kg/day) or cyclophosphamide (2 mg/kg/day) for at least 3 months, when response was evaluated and the two first medications were maintained for at least 6 months when there was a tendency to remission; (4) IV MP (10-15 mg/kg/dose/month) associated to cyclophosphamide (2 mg/kg/day) in the following scheme: MP in the months 1, 3, and 5 (three consecutive doses in the first month only) and cyclophosphamide in the months 2, 4 and 6),

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associated with oral prednisone 0.5 mg/kg/day) for 6 months. This late treatment was the most frequently used.

It is of note that only patients with nephrotic syndrome were submitted to IMS. In the 1970's and early 1980's there was a tendency in our service to not use IMS in patients with MN, but in the 1990's those presenting with nephrotic syndrome were always invited to receive IMS. As this is a retrospective study the non treated group is composed by those that refused IMS and some patients followed during the first decade of this study. Also as a consequence of this retrospective nature, certain treatment regimens that are not anymore prescribed for MN were administered. An observational period was not adopted before the onset of IMS, i.e. once nephrotic syndrome was diagnosed, treatment was prescribed.

Results

Demographical, clinical and laboratorial characteristics of all patients were analyzed and can be observed in Table 1.

Sixty-one (86%) patients received some type of IMS along this study follow-up; 62.2% of them received only a type of IMS regimen and the remainder more than one. General control and renoprotective measures were prescribed by the physicians, but they were not uniform as the study involved three decades of follow-up.

Regardless of being or not submitted to an IMS regimen, 43.6% of the patients had no remission, 21% presented complete remission, and 35.2% partial remission.

By the time of inclusion differences between treated and non treated groups were only related to proteinuria levels and clinical presentation syndromes (Table 1): median proteinuria in the IMS group was 6.4 g/24h, while in the non treated was 4.2 g/24h (p=0.055); 96.7% of treated group had at onset nephrotic proteinuria vs. 70% of non treated patients, and this difference of statistically (p=0.018).

In (Figure 1), there is a comparison of renal function based on initial and final serum creatinine levels (mean ± SE), 1.23 ± 0.66 and

Characteristics	Treated (n=61)	Non-treated (n=10)	p
Age (years)			0.905#
Mean ± SD	40 ± 15	39 ± 16	
Gender			0.718##
Male	42 (68.9%)	6 (60.0%)	
Female	19 (31.1%)	4 (40.0%)	
Etnia			0.149##
Caucasian	37 (63.8%)	9 (90.0%)	
Non Caucasian	21 (36.2%)	1 (10.0%)	
Weight (kg)			0.608#
Mean ± SD	71.6 ± 13.5	74.9 ± 19.1	
Time (months) since symptoms onset until renal biopsy			0.406###
Median (min – max)	6.5 (1 – 108)	4.0 (1 – 36)	
Comorbidities			>0.999####
Without coexisting diseases	52 (85.2%)	10 (100.0%)	
Schistosomiasis	2 (3.3%)	-	
Hypothiroidism	4 (6.6%)	-	
Diabetes mellitus	3 (4.9%)	-	
Hypertension			0.735##
Yes	31 (50.8%)	4 (40.0%)	
No	30 (49.2%)	6 (60.0%)	
Hematuria			>0.999##
Yes	47 (77.0%)	8 (80.0%)	
No	14 (23.0%)	2 (20.0%)	
Proteinuria			0.013##
Nephrotic	59 (96.7%)	6 (66.7%)	
Non nephrotic	2 (3.3%)	3 (33.3%)	
Presentation syndrome			0.034####
Nephrotic syndrome	52 (85.2%)	6 (66.7%)	
Nephrotic proteinuria	2 (3.3%)	-	
Non nephrotic proteinuria	2 (3.3%)	3 (33.3%)	
Initial proteinuria (g/24h)			0.055###
Median (min - max)	6.4 (1.9 – 53.0)	4.2 (0.6 – 11.0)	
Initial serum creatinine (mg/dl)			0.418###
Median (min - max)	1.1 (0.4 – 3.4)	0.9 (0.5 – 3.3)	
Initial serum albumin (mg/dl)			0.181###
Median (min - max)	2.2 (0.8 – 3.8)	2.5 (2.0 – 4.7)	
Time of follow-up (months)			0.649###
Median (min - max)	34.0 (6 – 355)	22.5 (9 – 223)	

SD: Standard deviation; # Student's t test; ## Fisher's exact test; ### Mann Whitney U test; #### Generalization of Fisher's exact test.

Table 1: Comparison of clinical, epidemiological and laboratorial characteristics of treated and non treated patients with idiopathic membranous nephropathy.

1.66 ± 1.54 mg/dL in treated and 1.19 ± 0.85 and 2.00 ± 1.83 mg/dL in non treated patients, respectively. A similar comparison involving initial and final 24-hour proteinuria is shown in Figure 2, where the values (mean ± SE) are 8.77 ± 7.62 g and 2.66 ± 3.08g in treated and 5.27 ± 3.81g and 2.75 ± 3.19 g in non treated patients, respectively.

Furthermore mean serum creatinine value variation between initial and final evaluation in the non treated group (0.8 mg/di) was higher than that observed between the treated patients (0.4 mg/di), but it was not statistically different.

Sixteen out of 71 patients (22.5% of total) presented loss of renal function at the end of the follow-up (defined as serum creatinine ≥ 2.0 mg/dl), with a median time of 6 years (minimum of 1 year and maximum of 20 years). Out of these 16, 21.0% were treated with IMS and 30% were not, and there was a higher but not statistically significant percentage of renal failure in the non treated one (Fisher's exact test, p=0.684), the same occurring as concerned to renal replacement therapy referral (p=0.108). Among those 16 patients, 9 were referred to dialysis in a median time of 5 years (and 2 lost follow-up). It is of note that among treated patients the median time to develop renal failure was 240 months while for non treated ones this time was 120 months.

When the patients were observed after 18 years (total period of follow-up of the non treated group), it was observed that 57.5% of the treated ones were free of renal failure vs. 37.5% of the non treated patients.
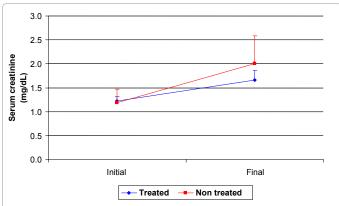

Figure 1: Initial and final serum creatinine (mean ± SE) of the patients with idiopathic membranous nephropathy according to the type of treatment.
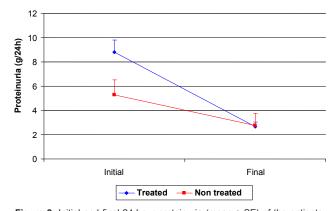

Figure 2: Initial and final 24-hour proteinuria (mean ± SE) of the patients with idiopathic membranous nephropathy according to the type of treatment.

In the treated group there was a significant decrease of 24-hour proteinuria from the initial to the final moment (mean difference ± standard error: 6.16 ± 1.01 g/24h, p<0.001), but not in the non treated group (2.52 ± 2.55, p=0.328).

Among the 57 patients that presented decrease of proteinuria along the follow-up, the median decrease was significantly higher (Mann-Whitney test, p=0.025) in the treated (N=50, 5.15 g/24h; 0.8-53.0 g/24h) than in the non treated group (N=7, 1.4 g/24h; 0.1-8.8 g/24h)

The highest frequency of complete remission was observed in the treated patients (22.9% vs. 10% in non treated) and the highest index of non response in the non treated group (60% vs. 41% in treated), but these differences were not statistically significant.

Considering each group of IMS agents, 72% of the patients that used oral prednisone, preceded or not by other IMS, were not responsive (final proteinuria > 2.0g/day). In this group edema improvement was reported by 40% of the patients. Late response was uncommon and relapse occurred in 32% of the cases. Only 20% used Angiotensin Converting Enzyme Inhibitor (ACEi) or Angiotensin Receptor Blocker (ARB), as most of them were treated in the first decade of study.

For the patients treated with cyclosporine A (CyA) there was a significant decrease in the median proteinuria from the initial to the final moment, with corresponding improvement of edemas. There was concurrently a significant increase in median serum creatinine that was higher than the increase observed with azathioprine or cyclophosphamide, but without statistical significance. In this group, 71.4% of those treated with CyA received also ACEi and/or ARB and 30% of those treated with azathioprine or cyclophosphamide.

In the IV MP group, 66% of the patients presented partial or complete remission, including 50% of late response, and 50% of relapses. Fifty percent were also treated with ACEi and/or ARB.

In the group treated with IV MP associated to cyclophosphamide there was a significant decrease of median proteinuria and serum creatinine. In this group 63.6% of the patients used ACEi and/or ARB. They had a considerable rate of late response (30.2%) and less relapse (12.1%) than the group that used only IV MP.

Considering the number of patients in each group it was possible to compare only three groups among them: MP plus cyclophosphamide, oral prednisone and "non treatment". The first one had the higher mean initial serum creatinine (1.3mg/dl); in addition, this was the only group that had no significant worsening of serum creatinine levels (1.4mg/dl at the end) along the follow-up, while in the other two groups there was a considerable increase in serum creatinine levels that were significantly more elevated in the oral prednisone group (0.94 mg/dl initially and 1.78 mg/dl at the end). Serum creatinine of the non treated group increased along the follow-up reaching a mean final level of 2.0 mg/dl; but this increase was not statistically significant.

At the end, the lowest mean serum creatinine was seen in the MP plus cyclophosphamide, the worst mean was that of the non treated group, the worst variation was that of oral prednisone, and this last one was statistically significant.

Discussion

Treated or untreated patients with idiopathic MN with IMS agents are still a matter of controversy, as well as when they begin the treatment and which drugs they used. Interestingly it is possible to figure out how such discussion progress along the years by the titles of some papers

about MN: Cameron, in 1982, wrote about "Membranous nephropathy: the treatment dilemma" [6], and 10 years later he continued claiming "Membranous nephropathy - still a treatment dilemma" (3); after this, in 1995 and 2004, Glassock [7] and Stegeman et al. [8] questioned, respectively "The treatment of idiopathic membranous nephropathy: a dilemma or a conundrum" and "Treatment of idiopathic membranous nephropathy: the dilemma of who, when, and how", until more recently when Cattran argued, in 2005, "Management of membranous nephropathy: when and what for treatment" [9].

Certainly every physician that had to treat a patient with MN should ask himself the above questions, and it is possible that even having a well defined theoretical position about the best treatment option one still have doubts in some particular cases, regardless the variety of algorithms available to facilitate this choice.

Considering these concerns and the possibility that genetic and/or ethnic factors could have an influence on treatment response, we evaluated retrospectively idiopathic MN patients treated or not with IMS agents and followed for 6 months to 30 years in a Brazilian population, in which data on treatment responsiveness is still scarce.

It is important to make clear that the non treated group in the present study was substantially smaller than the treated one, thus it is possible that number of patients be at least in part responsible for the absence of significance in certain comparisons between treated and non treated groups, as well as among subsets of these groups in the present study. Non treatment here means only those patients who have not received immunosuppressive treatment. In all cases, physicians always had the intention to control hypertension and any symptoms as well as concurrent complications. It is also of note that the use of ACEi and/or ARB was not homogeneous in all subgroups, because at least in the first decade of study its use was not widely indicated as antiproteinuric as today.

At first in the analysis of our population we could say that loss of renal function was more commonly observed and faster (half the period of time) among patients that have not received IMS treatment that also progressed more frequently to end-stage renal disease. Consequently a higher percentage of patients (30%) in the non treated needed renal replacement therapy than in the treated group (21%). In addition the last one was followed for a longer period of time.

Previously others have described unfavorable outcomes when IMS was not prescribed to MN patients [10]. Torres et al. [11] reported free survival without dialysis after 5 years of 55% in the non treated vs. 90% in the treated group, as well as 20% and 90% after 7 years respectively. Zuchelli et al. [12] described a worse outcome in non treated patients after 10 years in comparison with those that received steroids and cytotoxic therapy; 44% of non treated progressed to chronic renal failure vs. 24.2% of the treated ones, in parallel with a complete and sustained remission of proteinuria of 14.3% and 39.1%, respectively.

Although glomerular filtration rate (here evaluated by measuring serum creatinine) had only a tendency to be worse among non treated patients, the proteinuria profile was statistically different between the groups. From the baseline to the final period proteinuria decreased in both groups, but this was more pronounced and statistically significant in the treated group; the proteinuria levels variation inside the non treated group was not significant. Even presenting more elevated initial mean proteinuria levels the treated group had at the end of follow-up lower levels of proteinuria than the non treated, reaching median non nephrotic levels and clinical improvement expressed overall as marked edema improvement.

We were able to compare statistically three treatment groups. All of them showed a decrease of mean proteinuria levels along the time, but only in the MP plus cyclophosphamide group it was statistically significant, and this was also clinically associated to symptoms improvement, especially edema. It is of note that MP plus cyclophosphamide group presented the highest initial proteinuria, and they had also the highest decrease along the follow-up, as well as the lowest final mean proteinuria and serum creatinine, in opposition to the highest serum creatinine in the non treated group.

Good response to IMS has been widely described with MP associated to alkylating agents, or using oral CyA. These were also the IMS agents that showed a better therapeutic performance in our study. Nevertheless as the CyA group used more frequently ACEi and/or ARB than the others, it was not possible to establish that CyA was the only responsible by the expressive decrease of proteinuria, neither by the more accentuated increase of serum creatinine levels observed in this group.

The group of patients with IV MP had better response indexes than the oral prednisone group, with a high frequency of proteinuria decrease associated to stable serum creatinine.

Our results reinforce previous reports that had already shown oral prednisone is ineffective to preserve renal function or to provide and maintain remission of nephrotic syndrome in patients with idiopathic MN, and should not be used alone in this disease treatment [13].

Azathioprine and cyclophosphamide used in isolation apparently were not adequate therapy options here, neither elsewhere [13], but the number of patients treated with these medications was very small in our study disabling any conclusion about this.

Undoubtedly IV MP plus cyclophosphamide presented good results in this group of patients, demonstrated by a significant decrease in proteinuria and serum creatinine, as well as 30% of late response. It is necessary to remember that late response is an important aspect in the analysis of MN but how long one should wait for this kind of response is not well defined.

In addition IV MP plus cyclophosphamide seemed to contribute to the decrease in relapses frequency that was 12.1% in comparison with 50% in the group that used only IV MP. As previously demonstrated by others [14] both regimens could be effective in MN treatment, but the combined regimen had a best profile. This combination of drugs is currently accepted worldwide as the first choice in treatment of MN by most authors [13]. It was initially proposed by Ponticelli et al. [10] utilizing chlorambucil instead of cyclophospamide, as used by us, and evaluated by themselves as similar [14].

Based on our findings it is reasonable to conclude MP plus cyclophosphamide had the best performance when compared to the other types of treatment as well as to non IMS treatment.

Conclusion

The present study provided an overview on the IMS responsiveness of Brazilian patients with MN, in a long term follow-up. The highest frequency of complete remission was observed in the treated patients

and of non responsiveness in the non treated group, although not significant these differences suggest a favorable effect of treatment, as previously shown by others [15]. Despite the limited number of patients, some subgroups of treatment were amenable to comparison, allowing establish that the MP plus cyclophosphamide regimen administered for six months presented the best response to treatment, and affected favorably the course of the disease.

In general there is no doubt in indicating IMS treatment to patients with MN at high risk to progress to CKD stage 5. But our data indicate that even for other nephrotic patients with idiopathic MN regardless the risk level a better outcome was observed among those treated, particularly when the association of MP and cyclophosphamide was used. Thus like others [16] we believe treatment decision should not be based only on prognostic factors that indicate the progression risk, but also and mainly on the possible extrarenal complications, that are imminent in the nephrotic state.

Competing Interests

There are no competing interests.

Authors' Contributions

Both authors have participated in all steps of the study and article elaboration.

Authors' Information

MCED is Nephrology Professor of the Santos University. GMK is Nephrology Adjunct Professor of the Federal University of Sao Paulo, Head of the Glomerulopathy Section of the Division of Nephrology (UNIFESP) and Head of the Brazilian Chronic Kidney Disease Prevention Campaign.

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