International Journal of Medical Research Professionals

Original Article

Long-Term Prognosis of Idiopathic Membranous Nephropathy: An Outcome Analysis from Single Centre

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Article History
Received: 22 Dec 2015
Revised: 09 Jan 2016
Accepted: 28 Jan 2016

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ABSTRACT

Background: Membranous nephropathy (MGN) remains the most common cause of adult onset nephrotic syndrome, and within the primary glomerulonephritis group is a leading cause of renal failure. A complete remission (CR) confers an excellent long-term prognosis, but the quantitative benefits of partial remissions (PR) have not been defined.

Methods: This study evaluated the rate of renal function decline (slope), relapse, and renal survival in nephrotic MGN patients with CR, PR, or no remission (NR). Analysis included clinical and laboratory data at presentation and over follow-up, blood pressure control and agents employed, and immunosuppressive therapy.

Results: The study cohort consisted of 48 nephrotic MGN patients. Over a median follow-up of 12 months, 14 experienced a CR, 19 had a PR, and 15 had no remission. Compared to NR, partial remissions could only be predicted by a pre-remission lower MAP. When compared to CR, the PR group had a lower CrCl at onset and a higher follow-up MAP, despite receiving more antihypertensive drugs. When patients with no treatment were compared to those receiving dual therapy within each group, patients with PR and CR did not receive more dual therapy than NR (By limiting this analysis to high-risk of progression patients with sustained proteinuria > 6 g/day over 6 months, a benefit to immunosuppression with dual therapy was seen. Subjects with a PR also had better blood pressure control and more ACEi or ARB therapy than the spontaneous remitters.

Conclusion: This study has shown that partial remissions, as defined by both a 50% reduction in peak proteinuria and achieving a sub-nephrotic level, is a valid and important therapeutic goal for the clinician to target because its achievement is strongly correlated with both a reduction in the rate of renal disease progression, and ultimately, a better renal survival.

KEYWORDS: Membranous Nephropathy, Prognosis, Remission.

INTRODUCTION

Idiopathic membranous nephropathy (MGN) remains the most common cause of primary nephrotic syndrome in adults. The natural history of untreated MGN has been widely reported, with most series finding a complete remission rate of 20% to 30% and a 60% to 80% 10-year renal survival.[1–5] Severity of proteinuria at onset and during follow-up has been associated with outcome in most studies.[5–9] Although there is evidence that nephrotic patients who experience a CR have a favorable long-term prognosis.[10,11] The long-term outcome of those with only a reduction in proteinuria has not been reported. Despite the lack of specific evidence of the value of a reduction in proteinuria in MGN as a valid surrogate for renal failure, this outcome is frequently reported as a positive finding in randomized controlled trials.[12–15]

This study addresses the long-term outcome of a partial remission (PR) in nephrotic MGN patients. It compares the rate of renal function decline, relapse, renal failure, and treatment among patients with a PR, CR, and no remission (NR).

MATERIALS AND METHODS

All MGN patients' information at onset is compiled using a standard form, and a periodic prospective assessment of the patient's clinical status, medication, and laboratory results.[16] This study focuses on nephrotic

MGN patients older than 16 years at presentation with at least 12 months follow-up.

Demographics were age and body mass index (BMI) at onset, sex, and race. Parameters collected included both initial and follow-up information on systolic and diastolic blood pressure, weight, serum creatinine, and 24-hour urine protein and creatinine. Also recorded was exposure to immunosuppressive agents and antihypertensive medications, including the angiotensin-converting enzyme inhibitor (ACEi) and angiotensin receptor blocker (ARB) classes of drugs.

Creatinine clearance (CrCl) values were adjusted for age, sex, and weight using the Cockcroft-Gault method.[17] Nephrotic patients were identified by a proteinuria value≥ 3.5 g/day at any point during follow-up. ACR was defined by a proteinuria value ≤ 0.3 g/day. A PR was defined by a proteinuria value< 3.5 g/day plus a 50% reduction from its peak value.[15] A relapse was a proteinuria value ≥ 3.5 g/day after any remission. Subjects that had both a PR and a CR were only included in the CR group. Time to remission was calculated from the first clinical assessment suggestive of renal disease (abnormal proteinuria or serum creatinine). Renal failure was defined as a CrCl ≤ 15 mL/min at last follow-up, the start of dialysis, or a renal transplantation. Remissions in proteinuria were not ascribed if the CrCl was≤ 15 mL/min at that proteinuria time point. Mean arterial pressure (MAP) was defined as the diastolic plus a third of the pulse pressure. For each patient, an average MAP was determined for each six-month period of follow-up. Time-average MAP represents the average of every period's mean.

Immunosuppressive treatment is reported as intent to treat regardless of the duration of therapy. Patients are categorized as having received no, mono-, or dual immunosuppressive therapy.[11] A minimum of 10 mg of prednisone plus at least 1.5 mg/kg of azathioprine or cyclosporine, or 1 mg/kg of cyclophosphamide or 0.15 mg/kg of chlorambucil or 1000 mg of mycophenolate mofetil defined this last group. Monotherapy was defined as exposure to any form of immunosuppressive treatment that did not satisfy the dual therapy definition (e.g., steroids alone). Therapy with ACEi or ARB is presented as any exposure.

Table 1: Baseline characteristics of patients with MGN

Age	**48 ± 15 years**
Sex	31% female; 69% male
MAP	103 ± 14 mm/Hg
CrCl	84 ± 33 ml/min
Proteinuria	6.3 (0.5-30.3) gm/day
Follow up	
Duration	12 (8-15 months)
MAP	101 ± 9 mm/Hg
Immunosuppression:	
None	39%
Mono	45%
Dual	16%
ACE #	39%
Outcomes	
Complete Remission	29%
Partial remission	39%
No remission	32%
Relapse	37%
Renal failure	12%

Table 2: Comparison between CR, PR and NR patients

	NR	PR	CR	P value
n	14	19	15	
AT ONSET				
Sex (% female)	23	30	41	0.01
Age years	46 ± 16	50 ± 15	48 ± 14	NS
MAP mm Hg	104 ±13	103 ± 13	102 ± 14	NS
CrCl mL/min	82 ± 37	79 ± 31	94 ± 31	0.004
Proteinuria g/d	7.5 (0.9-31.3)	6.6 (0.8-26.3)	75.3(0.5-27.4)	0.03
FOLLOW UP				
Duration (months)	11.4	14.1	5.7	0.001
MAP mm/Hg	104 ± 9	100 ± 98	97 ±8	0.001
Anti-HTN medicines (n)	0.8 (0-3.2)	0.6 (0-3.0)	0.3 (0-3.1)	0.003
IMMUNOSUPPRESSION (%)				
None	47	34	43	
Mono	44	53	39	NS
Dual	9	13	18	
ACE # %	31	32	23	NS
OUTCOME				
Renal failure	29	9	0	0.001

Table 3: Comparison of PR in those treated with dual vs no immunosuppression

	Dual treatment	No treatment	P
n	07	12	
AT ONSET			
Sex (% female)	39	28	NS
Age years	54 ± 14	51 ± 15	NS
CrCl mL/min	70 ± 36	85 ±28	NS
Proteinuria g/d	6.9 (2-22)	5.9 (1.1-15.5)	NS
MAP mm Hg	101 ± 13	103 ± 12	NS
AT START IMMUNOSUPPRESSION			
CrCl ml/min	59 ± 27	78 ± 32	0.04
MAP mm/Hg	94 ± 9	100 ± 08	0.02
ACE # (%)	61	29	0.02
OUTCOME			
Renal Failure (%)	6	4	NS

RESULTS

There were 48 patients with a diagnosis of MGN nephrotic at some time during their follow-up. The cohort's baseline characteristics, follow-up, and outcomes are summarized in Table 1. Overall, 19 patients had a PR, 14 at least one CR, and 15 had NR. Eighty percent of patients who satisfied the definition for PR had another consecutive proteinuria measurement to confirm this diagnosis. These patients had a rate of renal function decline identical to the remaining 20% with only one proteinuria.

Patients with PR were compared to CR and NR groups to identify predictors of this outcome. (Table 2) This analysis used only information up until remission for PR and CR. Compared to NR, partial remissions could only be predicted by a pre-remission lower MAP. When compared to CR, the PR group had a lower CrCl at onset and a higher follow-up MAP, despite receiving more antihypertensive drugs. Immunosuppressive therapy was not found predictive of remission in this retrolective study. When patients with no treatment were compared to those receiving dual therapy within each group, patients with PR and CR did not receive more dual therapy than NR (16% vs. 28% and 29% for NR, PR, and CR, respectively, N = 188, chi-square, P = NS). By limiting this analysis to high-risk of progression patients with sustained proteinuria > 6 g/day over 6 months[19], a benefit to immunosuppression with dual therapy was seen (30% vs. 55% and 65% exposed to dual therapy in NR, PR, and CR, respectively, chi-square, P = 0.02, NR compared to CR + PR). Subjects with a PR in the setting of dual immunosuppressive therapy had a similar slope and renal survival as spontaneous PR (Table 3). This group also had better blood pressure control and more ACEi or ARB therapy than the spontaneous remitters. The dual therapy group did have a significant improvement in their slope after remission in contrast to patients with a spontaneous PR (Table 3).

DISCUSSION

The long-term outcome in MGN nephropathy has been reported many times over the past 20 years. Outcome has classically been divided into three groups: complete remission, progression to renal failure, or continuing proteinuria.[20,21] The latter category includes those that never remitted, partial remitters, and those that have relapsed from complete or partial remission. The definition of a PR has varied, and none of them have definitively been tied to an improved prognosis, despite its use as a surrogate outcome. This analysis of MGN patients was undertaken to establish partial remission in proteinuria as a valid surrogate end point predictive of both survival from renal failure and the rate of progression of renal disease. This review included 48 patients with a median follow-up of 12 months. Prospective studies of this size and length are unlikely to be conducted, and the slow evolution of this disease does not allow conclusions to be drawn on definite end points, such as renal failure over shorter observation times. Hence, establishing additional standardized and valid early predictors of outcome in MGN are important and currently can only be made from large longitudinal population studies.

We found that in addition to a CR, achieving a PR independently slowed the rate of renal function decline and the risk of renal failure. As shown in previous studies, by univariate analysis, gender, CrCl and proteinuria at onset, blood pressure, ACEi or ARB therapy were associated with our main outcomes,[8,22–26] but the impact of PR dominated these by multivariate analysis. The definition of PR is an important one. The same definition was used in our previous trials[15,27] and in this analyses (i.e., both obtaining sub-nephrotic proteinuria levels and a 50% reduction in peak proteinuria). Different definitions are seen in the literature but overall they are similar to ours and are unlikely to alter the strength of the association with renal

survival found in this analysis.[12–14,28] The present study deliberately did not include stable creatinine in the definition of PR to avoid introducing a bias that would inevitably lead to a greater renal survival in that group because stable renal function and renal survival are clearly strongly associated.

However, we did exclude the diagnosis of PR once the CrCl permanently dropped below 15 mL/min because proteinuria is often reduced at low glomerular filtration rates. Our study did not find any clinical or laboratory variables either at onset or over time other than a lower follow-up blood pressure that could predict a PR. This was in contrast to patients who experienced a CR who were significantly different in regards to sex distribution (more females) and had a higher CrCl and lower proteinuria at presentation. It is possible that some NR did not have a sufficient observation period to reach a remission because they were followed for a shorter duration. Such misclassification could account in part for our inability to predict those who will have a PR, although part of this shorter follow-up is secondary to a rapid progression to the end point of renal failure. Certainly, the marked differences in slope and renal survival between NR and PR would suggest they are two distinct populations. Two other important issues, although not the main thrust of our study, are worthy of comment: the influence of immunosuppression, and the impact of ACEi or ARB therapy. The impact of specific immunosuppressive therapy was difficult to determine considering the multitude of regimens tested over the past three decades[29–31] and hence, it did not seem reasonable to classify patients solely by exposure to any immunosuppressive medication. The most recent and best evidence demonstrating the efficacy of immunosuppression comes from studies using dual therapies.[12–15] Even in these trials, different regimens and populations were studied. We therefore categorized patients, as have other authors, into those who received no, mono-, or dual immunosuppressive therapy.[11] The population treated could also introduce a bias. Most MGN patients at low risk of progression (i.e., those with low-level proteinuria, no edema, renal insufficiency, or hypertension) are not likely to be treated except for symptoms. These subjects perhaps should not be compared to those who receive the most intensive immunotherapy because they have a much better prognosis. This may explain some of the variance between conclusions drawn from meta-analysis studies and randomized controlled trials.[15,19,32–36] These issues may also explain why an association between remissions and dual treatment was only seen in a subset of our patients likely to have progressive nephropathy. Some additional support for a benefit to immunosuppression comes from a subgroup analysis of these patients. Those treated with dual immunosuppressive therapy had a significant improvement in their slope after remission in contrast to patient with spontaneous PR. Although this data suggests a direct therapeutic effect, given their disease course appears to have been significantly altered by the drugs, we are cautious about drawing these conclusions because of the issues related to selection bias, subgroup analyses, and other problems with retrolective studies. We have included the data primarily to emphasize the point that a PR, regardless how achieved, impacts on disease progression in MGN.

CONCLUSION

This study has shown that partial remissions, as defined by both a 50% reduction in peak proteinuria and achieving a sub-nephrotic level, is a valid and important therapeutic goal for the clinician to target because its achievement is strongly correlated with both a reduction in the rate of renal disease progression, and ultimately, a better renal survival.

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Cite this article as: Vikash Khandelia, Nilesh Jain, Umashankar Nama. Long-Term Prognosis of Idiopathic Membranous Nephropathy: An Outcome Analysis from Single Centre. Int J Med Res Prof. 2016, 2(1); 163-67.