Clinical Study

American Journal of Nephrology

Am J Nephrol 1999;19:474–479

Received: May 11, 1998
Accepted: August 24, 1998

Relapsing Membranous Nephropathy

Response to Therapy of Relapses Compared to That of the Original Disease

Wadi N. Suki Hernan Trimarchi J. Pedro Frommer

Renal Section, Department of Medicine, Baylor College of Medicine, and The Methodist Hospital, Houston, Tex., USA

Key Words

Relapsing membranous nephropathy · Nephrotic syndrome · Proteinuria · Prednisone · Cyclophosphamide · Azathioprine · Chlorambucil · End-stage renal disease

Abstract

Background: Although controversial, treatment of membranous nephropathy appears to yield a reduction in the degree of proteinuria and conservation of renal function. ***Methods:*** We report herein our experience with the treatment with steroids alone (group II, n = 13), or in combination with immunosuppressants (group III, n = 19) of patients with membranous nephropathy and the nephrotic syndrome, with a mean follow-up of 8.37 years. ***Results:*** All patients underwent a first remission, with 24-hour urine protein excretion falling to 0.63 ± 0.25 g in group II and 0.62 ± 0.26 g in group III (p = NS) after 12.69 ± 10.94 months of treatment in group II and 18.95 ± 13.17 months in group III (p = NS). Three patients from group II (23%) and seven patients from group III (36.8%) experienced four and eight relapses, respectively (proteinuria in 24 h 4.0 ± 0.80 g in group II relapsers and 4.4 ± 0.87 in group III relapsers; p = NS). On treatment, all relapses remitted (second remission) after 7 ± 6.93 months of therapy for group II and 8.6 ± 6.70 months of treatment for group III (p = NS). Thereafter, no patients from group II, but 3 patients from group III (33.3%) had a second relapse. After treatment, all relapses remitted (third remission) in 3.3 ± 1.53 months of therapy. ***Conclusions:*** These studies show that relapses, which occur in one-third of patients, respond favorably to treatment albeit remitting in approximately half the time, and that the duration of remission gets progressively longer in the later compared to the earlier remission.

Introduction

Membranous nephropathy has continued to attract considerable attention, both with respect to its natural history [1, 2] and treatment [3–5]. A number of reports on the course of untreated membranous nephropathy have been published, with the general agreement that complete spontaneous remissions (<1 g of proteinuria per day) occur in approximately 5–51% of cases, while partial remissions (<2 g of proteinuria per day) occur in 25–40% of cases [3, 6, 7]. The incidence of end-stage renal disease is about 14% at 5 years, 35% at 10 years, and 41% at 15 years [8], although Passerini et al. [7] found a 0% incidence of end-stage renal disease in their study, which consisted of approximately eleven years of follow-up [7]. Lit-

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Wadi N. Suki, MD
Renal Section, Baylor College of Medicine and The Methodist Hospital
6550 Fannin, Ste 1275
Houston, TX 77030 (USA)
Tel. +1 713 790 3275, Fax +1 713 790 5053

Table 1. Characteristics of patients with membranous nephropathy and the nephrotic syndrome

Group	Age range years	Mean years	Black	White	Female	Male	Proteinuria g/day
I	39–55	45.7 ± 8.3	1	2	1	2	4.4 ± 1.76
II	19–70	40.4 ± 16.83	–	13	4	9	8.02 ± 4.42
III	19–71	36.3 ± 17.26	–	19	7	12	11.5 ± 5.86

Group I = No treatment; group II = prednisone alone; group III = prednisone and immunosuppressant.

tle information is available in the literature, however, about recurrent membranous nephropathy.

The treatment of membranous nephropathy has also been the subject of considerable controversy. Many trials using prednisone alone in continuous or alternating doses [9–14], prednisone in combination with cyclophosphamide [4, 9, 10], azathioprine [9], chlorambucil [3, 9, 10], and cyclosporine [5], among others, have been used.

We have previously published an uncontrolled series of patients treated with prednisone, alone or with the addition of immunosuppressants, in whom we observed a remission rate of approximately 90% [9]. In these, and in subsequent patients given the same therapy with equally good results, we have observed after a prolonged period of follow-up that reached up to 27 years in one particular case, the interesting phenomenon of recurrent disease. We now report our experience with recurrent proteinuria in previously treated patients with membranous nephropathy, and compare the response to therapy of these recurrences to that of the original disease.

Materials and Methods

The subjects of this report consist of 35 patients who were referred to us because they were suffering from nephrotic syndrome. The nephrotic syndrome is defined for the purposes of this report as the excretion in a 24-hour period of a quantity of protein equal to, or in excess of, 3 g. All patients had normal renal function, with a mean serum creatinine 1.13 mg/dl ± 0.30. All patients underwent a percutaneous needle biopsy of the kidney and were found to have membranous nephropathy, classified as class II or III, with absence of tubulointerstitial parenchymal damage. Two patients had adult-onset diabetes mellitus and 1 was positive for hepatitis B surface antigen with no evidence of hepatitis. Otherwise, these patients suffered from no systemic illness known to be associated with membranous nephropathy. Hypertension was defined as a supine blood pressure greater than 160/90 mm Hg on at least three different measurements.

All patients were offered therapy according to a protocol detailed below, and had the side effects and complications of this therapy explained to them. Three patients (8.6%) declined treatment and will be referred to hereinafter as group I (mean serum creatinine 1.1 ± 0.25 mg/dl). The remaining 32 patients underwent therapy: 13 (37.1%) with prednisone alone (group II) (mean serum creatinine 1.13 ± 0.36 mg/dl) and 19 (54.3%) with prednisone and immunosuppression (group III) (mean serum creatinine 1.3 ± 0.39 mg/dl). The characteristics of these three groups are depicted in table 1.

Treatment Protocol

Treatment in all patients consisted of prednisone 1 mg/kg a day orally for 2–3 weeks depending upon the tolerance of the patient. The dose of prednisone was then raised by 20% and given on alternate days thereafter. After 1 week of alternate-day therapy at this raised dose of prednisone, tapering of the dose was begun at the rate of 5 mg/week. At this rate of tapering, the alternate daily dose reached 30–40 mg/day after 3–4 months of therapy and was held at that level thereafter. In patients whose 24-hour protein excretion fell by 50%, or to less than 2 g, the dose of prednisone was gradually diminished to 10–20 mg/day, on alternate days. When the proteinuria became negative, steroids were gradually diminished and finally discontinued. In patients who did not meet these criteria, immunosuppressant medications (cyclophosphamide 2 mg/kg/day in 15 patients, azathioprine 2 mg/kg/day in 2 patients, and chlorambucil 0.1 mg/kg/day in 2 patients) were added, and the dose adjusted downward to maintain the leukocyte count above 3,000/mm^3, until the 24-hour protein excretion fell to below 2 g, at which point immunosuppressants were discontinued and the patients kept on prednisone, gradually tapering the dose as detailed above.

Remissions and Relapses

Patients whose protein excretion fell to below 2 g/day were considered to have undergone a remission (partial or complete). When protein excretion remained below 2 g/day throughout the follow-up period the patients (10 from group II and 12 from group III) were considered to be nonrelapsers and included in group A (table 2). Patients who developed a persistent increase in their protein excretion to over 2 g/day, after having had a remission at some point during their follow-up, were considered to have suffered a relapse (3 from group II and 7 from group III) and were included in group B (table 2). Patients in this latter group were subjected to another course of therapy in accordance with the above mentioned treatment protocol, and all underwent a second remission. Finally, in group B, after a prolonged follow-up, no patients from group II but 3 from group III suffered a second relapse. They in turn received another course of immunosuppressant therapy, to which they promptly responded undergoing a third remission.

Table 2. Classification of patients according to treatment modality and relapses

Group		A (no relapse)	B (relapse)	Total
II	Prednisone	10	3	13
III	Prednisone + immunosuppresant	12	7	19
Total		22	10	32

Results

The patient characteristics are tabulated in tables 1 and 2. The preponderance of men, previously noted in this disease, is evident. Of note is that all but one patient were white. Therapy resulted in a remission in all patients who were treated (n = 32). Of these, 22 patients (68.8%) never relapsed and constitute group A, while 10 patients (31.2%) had one or more relapses during follow-up (group B). In this group there were 3 patients from group II (23%) and 7 patients from group III (36.8%). There was no significant difference between the groups according to age, nor was there a difference in age between those who relapsed (40.0 ± 13.9 years) and those who did not (36.7 ± 17.26 years). Kidney biopsies showed the same histological findings in both groups. As pointed out earlier, initial renal function (as judged by the serum creatinine) was normal in the three groups; final serum creatinine levels were not significantly different between the three groups: group I 1.21 ± 0.25 mg/dl, group II 1.08 ± 0.25 mg/dl, and group III 1.26 ± 0.41 mg/dl. Patients who required immunosuppressant therapy (group III) had a higher, although nonsignificant, initial daily protein excretion (11.5 ± 5.86 g) than those who remitted with prednisone alone (8.02 ± 4.42 g) (group II). There was no significant difference in initial protein excretion between those who subsequently relapsed (9.9 ± 6.4 g/day) (group B), and the nonrelapsers (10.17 ± 5.05 g/day) (group A), while there was a lower initial proteinuria in the control group (4.4 ± 1.76 g/day) (p = NS).

Duration of Follow-Up

The mean duration of follow-up of these patients was 2.33 ± 0.58 years for group I, 6.36 ± 5.64 years for group II, and 10.68 ± 9.07 years for group III. Patients who never experienced a relapse (group A) were followed-up for a mean of 7.95 ± 7.63 years, while those who relapsed (group B) were followed for a mean of 11.21 ± 8.76 years. Noteworthy is that in group A, 6 patients (3 from group II and 3 from group III) are still being followed-up to the present time, with a mean follow-up of 12 ± 6.41 years and with protein excretions below 1 g a day since their first remission.

Duration of Treatment

Therapy with prednisone was continued for the duration of the period of follow-up in most patients, so that the total duration of treatment was 12.69 ± 10.94 months for group II (13 patients) and 18.95 ± 13.17 months for group III (19 patients) until they reached the first remission. The duration of treatment until the second remission was achieved was 7 ± 6.93 months for group II (3 patients) and 8.6 ± 6.70 months for group III (7 patients). Finally, the duration of treatment to the third remission was 3.3 ± 1.53 months, in 3 patients, all from group III (fig. 1, 2).

In patients from group III, immunosuppressant therapy was required for 13.7 ± 2.1 months before they experienced the first remission, 3.4 ± 1.2 months before their second remission, and 1.8 ± 0.9 months until their third remission. In group A, 12 of the 22 nonrelapsers (54.5%) had been treated with an immunosuppressant and the mean duration of therapy was 13.4 ± 2.1 months until they reached the first remission, while in group B, 7 of the 10 relapsers (70%) had received an immunosuppressant, the duration being 13.7 ± 2.1 months as depicted above.

Protein Excretion

After initial therapy, daily protein excretion fell in all patients to 0.63 ± 0.25 g/day in group II and to 0.62 ± 0.26 g/day in group III. The control group (group I) had a final protein excretion of 7.8 ± 8.39 g/day, which was higher than the initial value, and than both treated groups after treatment ($p < 0.0005$). Noteworthy, in the control group, is that initial and final serum creatinine levels were approximately the same, indicating that the degree of proteinuria evolves with time but does not synchronously correlate with renal dysfunction. The fact that in group I the proteinuria displays such a wide standard deviation is caused by the fact that 1 patient had a final protein excretion of 17 g/day, while another had had a spontaneous remission (as expected in some patients from the natural course of the disease) with a final protein excretion of 0.6 g/day.

Twelve episodes of relapse of nephrotic range proteinuria were observed in 10 patients (group B): 4 episodes in 3 patients from group II, and 8 episodes in 7 patients from group III. Mean peak proteinuria was 4.2 ± 0.80 g/day

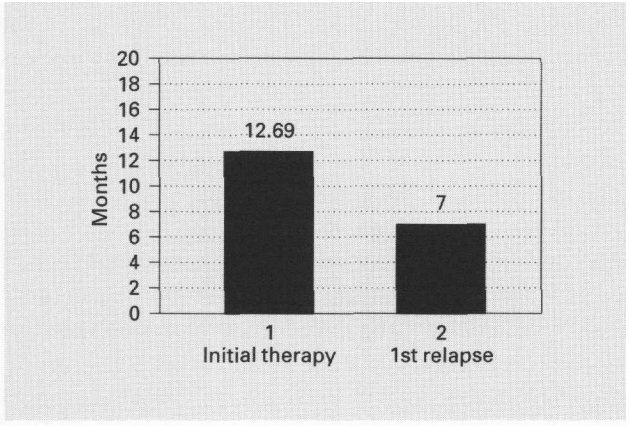

Fig. 1. Duration of therapy until remission in group II patients.

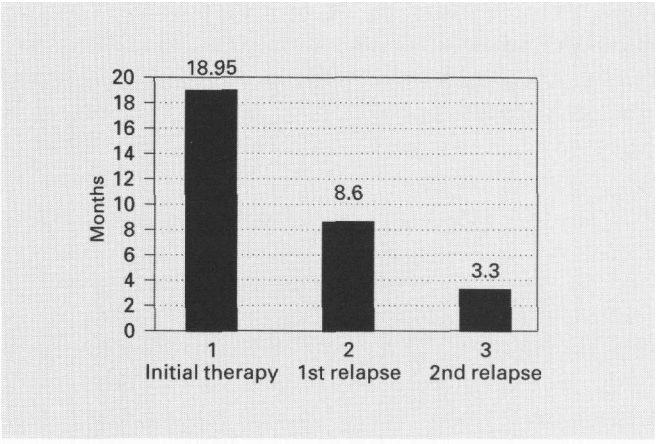

Fig. 2. Duration of therapy untilremission in group III patients.

for the whole group during the first relapse, with no significant difference between group II (4.0 ± 0.80 g/day) and group III (4.4 ± 0.87 g/day), respectively. After retreatment protein excretion fell to 0.36 ± 0.30 g/day for group II and 0.67 ± 0.19 g/day for group III. Finally, 3 patients from group III experienced a second relapse, with a mean protein excretion of 4.36 ± 2.11 g/day and falling to 0.6 ± 0.2 g/day after their third remission. All relapse episodes were treated in accordance with the treatment protocol.

Duration of Remissions

In group A, the first remission has lasted for 12 ± 6.08 years for group II patients and 12 ± 6.82 years for group III patients. In group B, the first remission lasted 38.3 ± 10.79 months (3.2 years) for group II patients, and 60.3 ± 57.79 months (5 years) for group III patients. The second remission has lasted for 80.3 ± 25.54 months (6.6 years) in group III patients. With respect to the 3 patients from group II, follow-up has lasted 2 years after the second remission, with the latest protein excretion being less than 1 g/day. Finally, the third remission has lasted for 100 months (8.3 years) for the 3 patients from group III who underwent a second relapse and third remission (followed-up until the present time).

Discussion

In the present report we confirm and extend our findings published 18 years earlier [9]. Briefly, in that study, a group of 27 patients with nephrotic syndrome secondary to membranous nephropathy, treated with prednisone alone (9 patients) or with prednisone plus immunosuppressants (18 patients), a remission of the proteinuria was achieved in all patients. In that report, a proteinuria <2 g a day was considered a remission. Although some authors tend to consider a complete remission when proteinuria is less than 500 mg/day, after 18 years it was observed by us that once it reached this value it invariably decreased to below 1 g/day and remained so unless an eventual relapse occurred [9]. This definition of remission is based on several observations in the literature. Williams et al. [15] found the rate of decline of renal function to be negligible when proteinuria was below 2 g a day. Similarly, Donadio et al. [2] observed that progression to end-stage renal disease rarely occurred in untreated patients with proteinuria less than 3.5 g/day.

In the present report, the initial protein excretion was higher although not statistically significant in the patients who required the addition of immunosuppressant medication compared to those who did well with prednisone alone, pointing out that the degree of proteinuria cannot foretell the response to one or another regimen nor the chances of having one or more relapses. Besides, at the initiation of the study the control group had the lowest degree of proteinuria compared to the other two groups and a normal renal function; by the end of the follow-up (2.33 ± 0.58 years) the protein excretion had increased to 7.8 ± 8.39 g/day while the serum creatinine had not changed from the initial value.

Prognostic factors have recently been reviewed by Reichert et al. [16]. They found that female sex, the absence of tubulointerstitial changes or focal sclerosis on kidney

biopsy, and the absence of nephrotic syndrome at presentation are indicative of a good outcome. Heavy proteinuria for over 6–12 months, and a steady increase in serum creatinine are good predictors of future development of end-stage renal disease [2, 16]. The predictive value of age, glomerular stage at biopsy, or systemic hypertension are too low to be of practical value [16]. Taking these prognostic indicators into consideration, in our study 11 women (34.4%) underwent therapy and tubulointerstitial abnormalities and glomerular sclerosis were absent in the biopsies. However, all patients had initial proteinuria of 3 g/day or greater. Whether the fact that one-third of our patients were women, renal function was essentially normal in all patients and the biopsies lacked predictors of progression, contributed to our outstanding results cannot be ascertained.

Several controlled observations have suggested that daily steroid therapy is helpful in this disease [14], while others failed to confirm such benefit [11]. Cameron et al. [12] and Bolton et al. [13] have proposed prolonged alternate-day steroids as another mode of therapy. In our report, daily and then alternate-day therapy with prednisone, as detailed under the treatment protocol above, has resulted in remission in approximately 40% of cases (group II), while the remaining 60% required the addition of immunosuppressant medication (group III). Only 3 patients in the prednisone group (23%) relapsed, and they promptly responded to repeat prednisone therapy and remain in remission until now. There were no short-term complications, while long-term side effects included cataracts, epidermal vascular fragility, hirsutism, overweight, and osteoporosis.

Regarding the treatment with prednisone plus immunosuppressants, many protocols have been developed with different degrees of success [3, 4]. Our results show that all patients who had not responded to prednisone went into remission when an immunosuppressant was added (group III), giving us a 100% response rate in the patients followed. Comparing group II and group III, all patients went into remission at approximately the same time, demonstrating that receiving immunosuppressant medication does not necessarily indicate a higher risk of unresponsiveness. The response to cyclophosphamide was not different from that achieved with azathioprine or chlorambucil. As also experienced by other groups [3] short-term complications of this therapy were few, and none of them serious. It is, therefore, our belief that immunosuppressive agents are indicated for the treatment of patients who do not respond to prednisone alone, and that patients with renal insufficiency may be candidates for prednisone plus oral immunosuppressant therapy right from the outset. No evidence has been advanced to show that intravenous cyclophosphamide [3, 10] is better than oral administration. Finally, there is clinical evidence that cyclophosphamide alone is less likely to be beneficial [4].

Interestingly, the duration of therapy until the first remission was reached was longer for both groups than was the duration of therapy until the second; and that in turn was longer than the duration of therapy till the third remission. Conversely, the duration of remission was longer in the third remission than in the second, and in the second than in the first, in both groups. These data also indicate that the frequency of relapses declines over time. Therefore, a prompt diagnosis of a proteinuria of >2 g/day, and a prolonged follow-up are mandatory to achieve good and quick results. As the follow-up in our study has been ample, whether with respect to number of patients or to duration of follow-up, we feel fairly confident that the above results are representative of the course of treated membranous nephropathy.

None of our patients developed end-stage renal disease. We were unable to discern any differences between those who developed a relapse and those who did not, nor could we discern any differences between those who relapsed whether belonging to group II or group III. All episodes of relapse were treated in accordance to the treatment used for the original episode of nephrotic syndrome, and all responded satisfactorily to it. Based on the above data, we believe it is essential to treat all patients with nephrotic range proteinuria despite normal renal function.

Hogan et al. [8] carried out a meta-analysis and concluded that prednisone or immunosuppressant therapy did not improve renal survival in idiopathic membranous nephropathy, although complete remission of the nephrotic syndrome was observed more frequently with alkylating agents. By contrast, in our protocol and that of others [17] the use of prednisone and immunosuppressants has proven to be beneficial to patients with this disease, as none of them progressed to end-stage renal disease and complete remission was reached.

Few authors have specifically commented on relapse of proteinuria after remission. Manos et al. [18] reported relapses in 8 of 15 patients who have undergone a remission. No distinguishing features nor an influence of relapse on overall prognosis could be identified. Tornroth et al. [19] reported a histologic study of 10 patients treated with prednisone and 3 with prednisone plus cyclophosphamide or azathioprine, who experienced a relapse 5.6

years after the onset of their disease. They observed during relapse the reappearance of stage I changes in the kidney biopsies on a background of persisting old parenchymal changes. Only 4 patients went into remission, while 3 developed end-stage renal disease. Our observation of 12 relapses in 10 patients, all of which culminated in remission and preservation of renal function after therapy, is unique and promising.

These results underscore the value of a prompt diagnosis and sustained follow-up of patients with membranous nephropathy, as well as the importance of prolonged treatment of this disease with a baseline dose of prednisone. This study further shows that relapses, possibly due to early detection, remit in approximately one-half the time necessary to achieve a remission on initial therapy.

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