

Corticosteroids, Cyclophosphamide, and Chlorambucil Therapy of Membranous Nephropathy

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Corticosteroids and cytotoxic agents have been studied widely in membranous nephropathy (MN). However, controlled studies with corticosteroids have not shown a clear benefit of these agents on the outcome of the disease. Some controlled trials reported that cytotoxic agents can reduce proteinuria significantly, but it was difficult to assess the efficacy of these drugs in protecting renal function because of the short follow-up period of the studies. Three randomized controlled trials showed that a 6-month treatment regimen based on corticosteroids and a cytotoxic agent, giving each for 1 month at a time in an alternating schedule, could favor remission of the nephrotic syndrome and protect renal function. Taken together, the results of these trials at the end of the follow-up period, 74% of the 174 treated patients were without nephrotic syndrome, 4 patients were on chronic dialysis, and 2 patients died. Good results with cytotoxic drugs, often associated with corticosteroids, also have been reported in progressive membranous nephropathy. However, in patients with renal insufficiency side effects were frequent and severe. Moreover, in most cases renal function improved but did not return to normal.

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WHETHER, HOW, AND WHEN to treat membranous nephropathy (MN) is still a matter of controversy. In this article we review the results with corticosteroids and cytotoxic drugs given alone or in combination.

For the sake of clarity, we use the following definitions: nephrotic syndrome (NS) was equivalent to proteinuria of 3.5 g/d or greater, partial remission was equivalent to proteinuria between 0.21 and 2.0 g/d with normal renal function, complete remission was equivalent to proteinuria less than 0.2 g/d with normal renal function.

CORTICOSTEROIDS

Four randomized trials with these agents have been published. In these studies, prednisone was administered either at low doses for 6 months, or at high doses for 8 weeks.

In a small study by Black et al,¹ 19 patients with MN and NS were assigned randomly to symptomatic therapy or to prednisone, at a mean dose of 20 to 30 mg/d for at least 6 months. After 2 years, 20% of controls and 40% of the treated patients had daily proteinuria less than 1 g, the difference being nonsignificant. Side effects were frequent. There were 6 cardiovascular deaths in the treated group versus 1 in the control group.

Another protocol, based on moderate doses of prednisone, was used in a Canadian study² in which 120 patients with nephrotic proteinuria and 38 with nonnephrotic proteinuria were assigned to receive symptomatic therapy or prednisone at a dose of 45 mg/m² every other day for 6 months. Patients were followed-up for up to 4 years. Therapy usually was well tolerated. No difference could be seen between the 2 groups at any time point,

either in the mean urinary protein excretion or in the mean creatinine clearance. Although the size of the study was adequate, untreated controls had a better outcome than usually reported in the literature, probably because of the inclusion of nonnephrotic patients.

In a multicenter study in the United States,³ 72 nephrotic patients with MN were allocated to symptomatic therapy or to high-dose alternate-day prednisone (mean dose 125 mg) for 2 months with gradual reduction until withdrawal. During the study there were significantly more remissions of the NS in steroid-treated patients than in controls (22 versus 11), but because of frequent and early relapses at the end of a mean follow-up period of 23 months, the number of patients in complete remission was similar in the 2 groups. However, the mean creatinine clearance declined more quickly in controls (–10% per year) than in treated patients (–2% per year). Treatment was well tolerated with major side effects occurring only in 2 patients. There are some concerns with this study because the outcome of the control group was worse than that usually observed in patients with MN.

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More than 10 years later, a multicenter trial organized in the United Kingdom by the Medical Research Council⁴ repeated the same study but in a double-blind fashion. A total of 107 nephrotic patients with MN were allocated randomly to prednisone, 125 mg every other day for 8 weeks, or to placebo. All patients had a potential follow-up period of at least 3 years. A few treated patients had an early but transient reduction of proteinuria. No difference was seen between the 2 groups in the mean levels of proteinuria or serum creatinine at 1, 2, or 3 years.

In summary, controlled trials have not shown a clear benefit of corticosteroids in patients with MN. This impression has been confirmed by a meta-analysis that showed that corticosteroids when compared with symptomatic therapy neither improved the probability of remission of proteinuria nor reduced the risk for developing renal failure.⁵ However, in these studies, prednisone was given either at low doses or for short periods of time. One cannot exclude a better efficacy of corticosteroids when given at higher doses or for more prolonged periods.

CYTOTOXIC AGENTS

A few randomized trials have evaluated prospectively the role of cytotoxic agents in MN.

Donadio et al⁶ randomly assigned 22 patients with MN to nonspecific therapy or to cyclophosphamide at a mean dose of 1.8 mg/kg/d for 1 year. At the end of treatment, there was a tendency toward a greater reduction of proteinuria in treated patients (mean reduction 4.7 g/d versus 2.6 g/d in controls), but the difference was not significant. However, the number of patients enrolled was too small to detect a significant difference, if any.

In a trial including several forms of primary glomerulonephritis, Lagrue et al⁷ randomly allocated 41 nephrotic patients with MN either to chlorambucil (0.2 mg/kg/d for 6 mo then 0.1 mg/kg/d for a further 6 mo), azathioprine (3 mg/kg/d for 6 mo then 2 mg/kg/d for a further 6 mo), or placebo. After a mean follow-up period of 2 years there were 9 complete and 4 partial remissions among the 16 patients treated with chlorambucil. There was only 1 partial remission among the 11 patients receiving azathioprine and there were 2 complete and 1 partial remission among the 14 patients who were given placebo. Unfortunately, of 37 patients with various types of glomerulonephri-

tis treated with chlorambucil for at least 1 year, 3 developed malignancy.

In an Australian trial,⁸ 54 patients were assigned to symptomatic therapy or to cyclophosphamide plus warfarin plus dipyridamole for 3 years. Patients who completed the 3-year treatment showed significantly lower levels of proteinuria and higher levels of serum albumin when compared with untreated controls, while the mean levels of creatinine clearance did not differ between the 2 groups. Side effects were frequent and several patients had to stop therapy.

More recently, Murphy et al⁹ randomized 40 nonnephrotic patients either to symptomatic therapy alone or to cyclophosphamide for 6 months plus dipyridamole and warfarin for 2 years. Treated patients showed a significantly greater reduction of proteinuria and a larger number of complete and partial remissions when compared with controls. Treatment was well tolerated.

Thus, there is the impression that cytotoxic agents can reduce proteinuria and improve the chances of remission, but little information is available about the influence of these treatments on long-term renal function.

ALTERNATING CORTICOSTEROIDS AND CYTOTOXIC DRUGS

Because MN is a chronic disease with slow progression, it is difficult to obtain a sustained remission of proteinuria and/or protection of renal function with short-term treatments. On the other hand, prolonged therapies with corticosteroids or cytotoxic agents expose patients to a high risk for side effects. This is why, many years ago, we decided to alternate a corticosteroid and an alkylating agent every other month for 6 months to allow a sufficiently long treatment, while reducing the risk for drug-related toxicity. Treatment began with a 1-g pulse of intravenous methylprednisolone repeated for 3 consecutive days followed by oral prednisolone (0.5 mg/kg/d) for 1 month; then steroids were stopped and chlorambucil (0.2 mg/kg/d) was given for 1 month. The cycles of steroids were given at months 1, 3, and 5, and those of chlorambucil at months 2, 4, and 6 (Table 1). In a randomized controlled trial,¹⁰ patients with biopsy examination-proven MN and NS were randomized to receive this treatment or symptomatic therapy (control group). After a mean follow-up period of 31 months, we observed that treated

Table 1. Therapeutic Protocols Adopted in the 3 Italian Multicenter Controlled Trials

MP + chlorambucil versus symptomatic therapy	
Months 1, 3, 5	Methylprednisolone 1 g IV for 3 days, followed by oral prednisone 0.5 mg/kg/d for 27 d
Months 2, 4, 6	Chlorambucil 0.2 mg/kg/d for 30 d
Methylprednisolone + chlorambucil versus methylprednisolone alone	
Months 1, 3, 5	Methylprednisolone 1 g IV for 3 days, followed by oral prednisone 0.5 mg/kg/d for 27 d
Months 2, 4, 6	Chlorambucil 0.2 mg/kg/d for 30 d
Months 1, 3, 5	Methylprednisolone 1 g IV for 3 days, followed by oral prednisone 0.5 mg/kg/48 h for 27 d
Months 2, 4, 6	Oral prednisone 0.5 mg/kg/48 h for 30 d
Methylprednisolone + chlorambucil versus methylprednisolone + cyclophosphamide	
Months 1, 3, 5	Methylprednisolone 1 g IV for 3 days, followed by oral prednisone 0.5 mg/kg/d for 27 d
Months 2, 4, 6	Chlorambucil 0.2 mg/kg/d for 30 d
Months 1, 3, 5	Methylprednisolone 1 g IV for 3 days, followed by oral prednisone 0.5 mg/kg/d for 27 d
Months 2, 4, 6	Cyclophosphamide 2-5 mg/kg/d for 30 d

Abbreviation: IV, intravenous.

patients showed a better slope of the reciprocal of plasma creatinine and more complete remission or partial remission than controls. After a median follow-up period of 5 years, 23 of 32 treated patients were without NS (12 complete and 11 partial remission), versus 9 of 30 controls (2 in complete and 7 in partial remission). The slope of the mean reciprocal of plasma creatinine with time was significantly better in the treated group. Multivariate analysis showed that the risk for developing renal insufficiency was associated significantly with no therapy and with the presence of tubulointerstitial lesions at renal biopsy examination.¹¹ The results of this trial were updated at 10 years of follow-up.¹² The probability of having a remission of NS (complete plus partial) was significantly higher in treated patients (83% versus 38%, $P = .0000$). At the last visit, 40% of treated patients versus only 5% of untreated controls were in complete remission. The slope of the reciprocal of plasma creatinine with time decreased after 10 years from 1.0 to 0.84 in treated patients and from 1.0 to 0.51 in controls. The probability of surviving without dialysis at 10 years was 92% for treated patients versus 60% in untreated controls ($P = .0038$). One patient in the treated group died of lung cancer a few months after randomization and 2 controls died of cardiac infarct and of hepatorenal failure, respectively. Four patients had to stop treatment because of peptic ulcer (2 cases), gastric intolerance, and pneumonia. In the long term, one treated patient became obese and another one developed diabetes.

In another controlled trial¹³ we compared the effects of the combined treatment of methylpred-

nisolone/chlorambucil with those of methylprednisolone alone given at the same cumulative dosage for 6 months (Table 1). The number of complete plus partial remissions was significantly higher at 1 year (58% versus 26%), 2 years (54% versus 32%), and 3 years (66% versus 40%) for patients assigned to combined therapy. At 4 years there was still a 20% difference of remission in favor of the combined treatment (62% versus 42%), but owing to the smaller number of patients at risk the difference was not significant. At any rate, at the end of a mean follow-up period of 54 months, 64% of patients given combined therapy versus 38% of patients given steroids alone were without NS, a significant difference. The chances of remission were associated with absence of mesangial sclerosis at initial biopsy examination, the use of combined treatment and a basal plasma creatinine level lower than 1 mg/dL (88 μ mol/L). There was also a trend toward a better slope of the reciprocal of plasma creatinine in patients treated with combined therapy but the difference was not significant. One patient per group died. Four patients in the group treated with steroids and chlorambucil had severe side effects that reversed completely after treatment was stopped (pneumonia in 2 cases, liver dysfunction, and gastric intolerance to chlorambucil). One patient treated with steroids alone stopped therapy because of pulmonary embolism.

In a further controlled trial,¹⁴ 87 patients with MN and NS were randomized to be given methylprednisolone alternated every other month either with chlorambucil (0.2 mg/kg/d), or with cyclophosphamide (2.5 mg/kg/d) (Table 1). Of 44 pa-

tients assigned to methylprednisolone/chlorambucil, 36 (82%) entered complete or partial remission of the NS, versus 40 of 43 (93%) patients assigned to methylprednisolone/cyclophosphamide. Eleven patients in the chlorambucil group versus 10 in the cyclophosphamide group had a relapse of NS. For both treatment groups the reciprocal of plasma creatinine remained unchanged in the cohort groups followed-up for 2 and 3 years when compared with baseline. Six patients in the chlorambucil group had severe side effects (2 leukopenia, 2 pneumonia, 1 anemia and thrombocytopenia, and 1 nausea). Two patients stopped treatment in the cyclophosphamide group, one because of nausea and the other one because of a cerebral transient ischemic attack. All side effects completely reversed after treatment was stopped.

Pooling the results of these 3 trials, 174 patients were treated with corticosteroids alternated with cytotoxic agents (131 patients with chlorambucil and 43 with cyclophosphamide). Of them, 72 (41.3%) entered complete remission and 72 other patients (41.3%) had a partial remission as a first event (82.6% of response). At the last follow-up evaluation, 74% of patients were in remission, either complete (34%) or partial (41%). Four patients reached end-stage renal failure and 2 had died. Sixteen patients (9%) suffered from severe side effects that, however, completely reversed after stopping therapy in all patients but one with diabetes.

TREATMENT OF PROGRESSIVE MEMBRANOUS NEPHROPATHY

A treatment based on corticosteroids and/or cytotoxic agents also has been used in progressive MN (Table 2).

Treatment with corticosteroids alone did not show a clear benefit in progressive MN. In a small uncontrolled study 15 patients were treated with high-dose intravenous methylprednisolone pulses for 5 days and oral prednisone. Renal function initially stabilized in 9 of these patients, but at the last follow-up evaluation 7 either died or were on dialysis.¹⁵

The response of MN with renal insufficiency to a 6-month course with methylprednisolone alternated with chlorambucil every other month was evaluated in 6 studies.¹⁶⁻²¹ Of 78 treated patients, 57 (73%) responded with an improvement or stabilization of their renal function. Little information

was given about renal biopsy examinations, which showed mild to moderate histologic lesions in most of the cases reported.

Three retrospective studies showed a benefit from cyclophosphamide associated with prednisone.

Bruns et al²² treated 11 patients with 100 mg/d of cyclophosphamide plus prednisone 60 to 100 mg every other day for 1 year. The plasma creatinine level decreased in all patients during the first 6 months of therapy and remained stable in 9 of them after 1 year of follow-up evaluation, but in no case returned to normal values. Urinary protein excretion decreased in all but one patient. No information about renal biopsy examination was given.

Branten et al²⁶ treated 39 patients with a 12-month cycle of oral cyclophosphamide (1.5-2 mg/kg/d) plus intravenous methylprednisolone and/or oral prednisone for 1 year. Treatment resulted in a significant decline in proteinuria and in a median 38% reduction of serum creatinine levels. As in the previous study, no information about renal biopsy examination was given.

Similar results have been reported by Jindal et al²³ who treated 9 patients with oral cyclophosphamide alone or associated with steroids. At the end of treatment serum creatinine level decreased from 2.6 to 2.2 mg/dL and proteinuria decreased from 11.1 to 2.2 g/24 h. After a mean follow-up period of 83 months, serum creatinine level increased to 2.9 mg/dL, one patient reached end-stage renal disease and another died.

Finally, 2 controlled trials did not show any benefit of intravenous pulses of cyclophosphamide. In the first study Falk et al²⁴ found no difference in the risk for progression to end-stage renal failure between 13 patients assigned to receive alternate-day prednisone, 2 mg/kg per 48 hours for 8 weeks, and 13 patients treated with alternate-day prednisone plus 3 pulses of intravenous methylprednisolone plus monthly intravenous pulses of cyclophosphamide (0.5 g/m²) for 6 months.

Reichert et al²⁵ reported that serum creatinine level significantly decreased from 260 to 186 $\mu\text{mol/L}$ in 9 patients assigned to receive a 6-month treatment with methylprednisolone alternated every other month with chlorambucil, whereas in 9 patients given monthly intravenous pulses of 750 mg/m² of cyclophosphamide for 6 months, serum

Table 2. Results of Therapeutic Trials in Patients With MN and Deteriorating Renal Function

Study	No. Patients	Agent	Duration	Results	Side Effects
Steroids alone					
Short et al, ¹⁵ 1987	15	MP + prednisone	6 mo	Better serum creatinine in 6 patients	Pneumonia 1 patient cataract 2 patients
Steroids and chlorambucil					
Mathieson et al, ¹⁶ 1988	8	MP + chlorambucil	6 mo	Mean creatinine clearance from 52 to 81 ml/min; mean proteinuria from 15 to 2 g/24 h	Numerous and severe
Wetzels et al, ¹⁷ 1989	8	Prednisone + chlorambucil	6 mo	Better serum creatinine in 2 patients	Numerous (50%) and severe
Araque et al, ¹⁸ 1993	4	MP + chlorambucil	6 mo	Mean serum creatinine from 2.2 to 1.3 mg/dL; mean proteinuria from 14 to 2.8 g/24 h	?
Warwick et al, ¹⁹ 1994	21	MP and/or prednisone + chlorambucil	6 mo	Better serum creatinine in 7 patients (treated with MP)	Numerous (>50%) and severe
Brunkhorst et al, ²⁰ 1994	17	MP + chlorambucil*	6 mo	Mean serum creatinine from 162 to 127 μ mol/L; mean proteinuria from 17 to 5.5 g/24 h	Mild and rare
Torres A et al, ²¹ 2002	19	Prednisone + chlorambucil*	6 mo	Mean serum creatinine from 2.3 to 2.0 mg/dL; mean proteinuria from 11.2 to 5.2 g/24 h	Numerous and severe
Steroids and/or cyclophosphamide					
Bruns et al, ²² 1991	11	Prednisone + cyclophosphamide	1 y	Mean plasma creatinine from 2.2 to 1.5 mg/dL; mean proteinuria from 12 to 4.8 g/24 h	Cushingoid features in all patients Pneumonia 2 patients leukopenia 2 patients
Jindal et al, ²³ 1992	3 6	Cyclophosphamide Prednisone + cyclophosphamide	23 mo	Mean serum creatinine from 2.6 to 2.9 mg/dL; mean proteinuria from 11.1 to 1.9 g/24 h	Numerous
Falck et al, ²⁴ 1992 (controlled study)	13	Prednisone MP + IV cyclophosphamide	3 mo 6 mo	No difference at 2 years in renal survival	
Reichert et al, ²⁵ 1994 (controlled study)	9	MP + chlorambucil iv cyclophosphamide	6 mo	Mean serum creatinine from 260 to 189 μ mol/L; mean serum creatinine from 218 to 297 μ mol/L	Numerous
Branten et al, ²⁶ 2001	39	MP and/or prednisone + cyclophosphamide	12 mo	Serum creatinine from 226 to 143 μ mol/L; mean proteinuria from 10.3 to 2.2 g/24 h	Numerous

Abbreviations: MP, methylprednisolone; IV, intravenous.

* Low dose compared with the Italian therapeutic protocol.

creatinine level significantly increased from 218 to 297 μ mol/L after a follow-up of 6 to 36 months.

It is possible that the different results depended not only on the different therapeutic regimen used, but also on the severity of the underlying histologic

lesions, although no study provided complete details on renal biopsy examination. All the studies reported a particularly high incidence of side effects, suggesting that patients with renal insufficiency are more susceptible to this risk. Thus, a

reduction of the dosage of steroids and cytotoxic agents is necessary in patients with declining renal function, as already recommended years ago.²⁷

CONCLUSIONS

At present, a 6-month course with steroids and a cytotoxic agent alternated every other month has one of the highest therapeutic indices among the various regimens suggested for MN. This treatment may favor remission of the NS, and protect long-term renal function in a large proportion of patients. Treatment was well tolerated by more than 90% of patients with normal renal function. In those who had to stop therapy because of toxicity, side effects completely reversed. Because chlorambucil as well as cyclophosphamide can cause azoospermia, young men should be encouraged to deposit their semen in a sperm bank before starting therapy. A main concern with the use of cytotoxic drugs is the possible development of cancer. However, with a cumulative treatment of not more than 3 months, there is little, if any, oncogenic risk with chlorambucil.¹⁴

A number of studies reported the possibility of improving the prognosis in patients with established renal insufficiency. On the basis of those results, some investigators suggested postponement of treatment until renal insufficiency develops.^{20,21,23,28} It should be pointed out, however, that the presence of renal insufficiency increases the risk for side effects caused by treatment and if the kidney develops glomerular sclerosis and/or interstitial fibrosis it is difficult to obtain complete recovery of renal function. For these reasons, and also to prevent the consequences of NS in responders, we prefer not to postpone too long the treatment in nephrotic patients. For patients who present with renal insufficiency a rescue treatment with reduced doses of steroids and/or cytotoxic agents may be justified. But any therapeutic attempt probably is useless and perhaps dangerous in patients with a serum creatinine level higher than 4 mg/dL, with shrunken and hyperechogenic kidneys at ultrasonography, and/or with extensive glomerular sclerosis and severe tubulointerstitial changes at renal biopsy examination.

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