Treatment of Idiopathic Membranous Nephropathy

C.	Claudio	Ponticelli
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Divisione di Nefrologia e Dialisi, Ospedale Maggiore Policlinico, Milano, Italia

Claudio Ponticelli, Divisione di Nefrologia e Dialisi, Ospedale Policlinico, via Commenda 15, I-20122 Milano (Italy)

Dear Sir

In their Editorial (Nephron 45:1–6, 1987) Garattini et al. criticize the use of glucocorticoids (GC) and chlorambucil in membranous nephropathy (MN) and suggest that the symptomatic treatment may still be the best choice. I wish to make some comments about their conclusions.

(1) The first argument of Garattini et al. against any form of therapy is that the untreated MN carries a good prognosis. They drew this conviction by the fact that untreated patients have a kidney survival of 90% at 2 years. However, assessing the prognosis of MN by the renal survival rate at 2 years is misleading. MN is a slowly progressive disease, so that the survival rate should be assessed only after several years from the onset. By reviewing several studies, Cameron [1] found that the percentage of kidney survival at 10 years ranged from 30 to 60%, the prognosis being more severe in patients with the nephrotic syndrome (NS). A 50% kidney survival rate at 10 years for untreated patients with MN has recently been reported by MacTier et al. [2]. We reviewed our experience with untreated patients biopsied before 1976. Considering only patients with NS and normal renal function at presentation, 48% of them were dead or in regular dialysis after 10 years. These data show that the long-term natural course of MN, at least in Caucasian population, is not benign at all.

Looking at patients with a very short follow-up, as Garattini did, there is a simple and reliable method for predicting the renal outcome. This is to plot the plasma creatinine against the time. Davison et al. [3] reported that the rate of deterioration is essentially constant in any patient with MN and that 43% of their untreated patients had a steady decline in renal function after a mean follow-up of 30 months, again suggesting a poor prognosis in the long-term for about a half of untreated patients. But, although renal failure is the most worrying complication of MN, it is not the only one. Several patients have massive edema, complain of asthenia and are unable to work. The persisting NS can expose one to infection, malnutrition, hyperlipemia, hypercoagulability with thromboembolic complications, metabolic disorders and osteodystrophy. Even if MN would not lead to renal failure (but it does unfortunately!) any therapy able to reduce proteinuria and to improve the quality of life should be welcome.

(2) Garattini et al. hypothesize that low-dose GC may be sufficient to obtain the desired effects. Of the three controlled trials [4–6] reporting the effects of GC in MN the two studies which failed to show any benefit were those using low doses of prednisone [4, 5]. Instead, in the American study [6], where the mean dose of prednisone was 125 mg every other day, a high rate of remission (although transient) of NS and a significant protective effect on renal function was obtained. Thus, from a clinical point of view, low-dose GC can be considered useless in MN. One may object that high-dose GC expose to side effects and this can overcome the possible

advantage of therapy. This is why in our protocol [7] we chose to give three pulses of methylprednisolone (MP) followed by low doses of MP1. At least two controlled trials showed that this modality of administering GC is as effective as prolonged high-dose oral GC but significantly spares the side effects [8, 9]. Garattini et al. doubt that the effects of GC are proportional to the dosage, since increasing the concentration of MP is not paralleled by a decrease of cells marked with OKT4. It is impossible, at present, to know which of the myriad of the effects of GC may be important for treatment of MN. However, many effects of MP are dose-related. As reported by

1 Our treatment consisted of 3 consecutive intravenous MP pulses, 1 g each, followed by 0.4 mg/kg of oral MP for 27 days. Then MP was stopped and chlorambucil was given for 1 month, followed by 1 month with MP, 1 with chlorambucil, and again by 1 month with MP and 1 with chlorambucil. The whole period of therapy lasted 6 months, 3 with MP pulses and low-dose MP and 3 with chlorambucil (0.2 mg/kg/day).

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Kimberly [10], several studies demonstrated a concentration-dependent effect of GC on lymphocyte blastogenesis, on suppression of MLC (with maximum effect between MP levels of 1–10 µg/ml that are achieved only after 1 g MP), on duration of depressed cellular responsiveness to mitogens, on the inhibition of 11–2. Moreover, high-dose MP modifies the renal hemodynamics, reduces the formation of immune-complexes and inhibits the alternative and the amplification pathway of complement [11].

(3) Garattini et al. think that there was no real basis for the use of chlorambucil in our protocol. In our patients assigned to receive therapy, the mean reciprocal of plasma creatinine remained unchanged while the untreated controls showed a progressive deterioration (the difference between the two slopes being significant after 2 years; $p = 0.0001$). Moreover, treated patients had significantly more remissions of NS than controls (72% vs. 30%; $p = 0.001$). In the literature, no controlled or uncontrolled trial with GC alone achieved such a high rate of sustained remission of NS. Thus, the good results observed with our schedule can actually be attributed to the addition of chlorambucil to MP. On the other hand, the effectiveness of this drug was already demonstrated by Lagrue et al. [12], who randomly assigned 43 patients with MN either to be given chlorambucil for 1 year or azathioprine or placebo. After 2 years of follow-up, 9 or 16 patients on chlorambucil were in complete remission of proteinuria vs. 2 of the placebo and none of the azathioprine group.

Garattini et al. fear that chlorambucil can expose one to neoplasia. This is a possible complication for patients receiving prolonged administration of this drug. In the literature, 46 cases of malignancy occurring in patients who had been treated with chlorambucil have been reported; 87% of these patients developed acute leukemia. In all cases chlorambucil had been given for at least 6 months, and the mean dosage was considerably greater than that used in our protocol. On the other hand, chlorambucil produces less chromosomal abnormalities than cyclophosphamide, which is currently adopted for treating several renal diseases [13].

I agree that GC and cytotoxic agents should not be used indiscriminately in patients with MN. The selection of patients should be rigorous, certain doses should not be exceeded, alternate month therapy should not be prolonged over 6 months and the patient should be carefully monitored during treatment. However, a correct caution does not justify a therapeutic nihilism in a potentially treatable disease.

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