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Treatment of Membranous Nephropathy: an update

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Idiopathic membranous nephropathy (IMN) is a glomerular disease which occurs worldwide and usually develops in the adult age. In some 70 % of patients IMN presents with a nephrotic syndrome (NS), many of the remaining patients become nephrotic within few year after the discovery of the disease. In most untreated patients NS persists over the years, but partial remission may occur in some 20 % of patients and proteinuria may spontaneously disappear in another 15 % (table I). This usually occurs after some years of NS. In about 40 % of patients who attained a complete remision, NS tends to relapse within 10 years[11].

Thus most patients with IMN are exposed for years to the consequences of the NS. These include sodium retention and edema, protein deficiency state, derangement in trace elements, tubular dysfunction, osteomalacia, enhanced bone resorption, immunological abnormalities, hypercoagulability and hyperlipidemia. In turn these two latter abnormalities may favor an increased incidence of vascular occlusive complications[12]. Particulary striking, in this regard, are the data of MacTier et al.[8] who found 14 arterial occlusive complications and 11 episodes of venous thrombosis in 44 patients with untreated IMN followed for a mean period of 64 months. Most vascular events occrurred while the patient was nephrotic. Other investigators reported an incidence of 2-30 % of arterial thrombosis and of 20-25 % vein thrombosis in adults with NS[13]. Particulary frequent is the renal vein thrombosis. When accurately searched for, this complication has been found in up to 50 % of patients with IMN and NS[14]. Although the impact of renal vein thrombosis on proteinuria and renal function is still questionned, this complication can expose to an elevated risk of lung thromboembolism. By reviewing the literature, Cameron[13] has found that 1/3 of patients with renal vein thrombosis developed pulmonary embolism. In summary it is now clear that independently of renal failure IMN carries the risk of potential severe complications related to a prolonged NS.

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The disease can progress to terminal renal failure, but the proportion of patients who eventually develop uremia has been differently estimated. The 10-year kidney survival rate ranges, in fact, between 50 and 78 % in different series[4, 7, 8, 15-17]. This may depend on racial and geographical differences as well as on the different criteria of selection of patients. Some reports included patients with or without NS, other studies excluded non-nephrotic patients or those presenting with renal failure. In some series, for example, patients with more severe clinical picture were submitted to treatment while those with more bening course were not. Moreover the follow-ups were generally short. The few studies dealing with the long-term outcome of IMN reported a kidney survival rate of 30-40 % at 15 years[18-20].

Therefore, although some patients may have a spontaneous favorable course, IMN cannot be considered as a benign disease because of the complications related to the NS and the long-term renal dysfunction in many cases. Of course it would be of great clinical importance to recognize which patient will have a favorable course and which not. Many efforts have been made in order to identify at presentation which factor(s) might predict the final outcome for patients with IMN. Young age[21], female sex[6, 21, 22], non-nephrotic proteinuria [21, 23] have been claimed to represent possible markers of a favorable out-

Tabla I. Spontaneous remission of nephrotic syndrome at the end of the follow-up IMN

		Pts. with NS	Complete remission	Partial remission
Row[1]	1975	25	5	5
Ehrenreich[2]	1976	44	0	11
Pierides[3]	1977	18	2	3
Noel[4]	1979	88	21	17
Am. Coll. Study[5]	1979	38	4	3
Hopper[6]	1981	22	2	5
Honkanen[7]	1986	17	5	5
MacTier[8]	1986	37	8	3
Ponticelli[9]	1989	39	2	7
M. R. C. Study[10]	1990	51	7	15
Total		379	56 (15 %)	74 (19,5 %)

come, while hypertension[15], renal insufficiency[21, 22], advanced glomerular stage[2, 24] and the presence of tubulo-interstitial lesions[9, 17, 19] at initial renal biopsy have been considered as signs of an omminous prognosis in the long-term. As a matter of fact, however, when multivariate analysis was made only the presence of tubulo-interstitial lesions, was correlated with a poor renal prognosis[9]. On the other hand the strongest predictor of a favorable outcome in the long-term seems to be the achievement of a complete remission of proteinuria. In our own experience none of 33 patients who attained complete remission of proteinuria showed an increase in plasma creatinine after a median follow-up of 96 months[11].

Therefore on the basis of the available data it is impossible today to predict at patient's presentation whether the (she) will have a fair outcome in the long-term. At most, it is possible to foresee a bad renal prognosis for patients with severe tubulo-interstitial lessions at renal biopsy. The only way to know if a patient will have a good renal prognosis might be to wait until proteinuria spontaneously disappears. This will happen however in only 15 % of patients and can take several years. This means that the choice between treating or not patients wiht IMN cannot be supported by any clinical, biological or histological feature. It is our feeling that, in view of the potential complications of NS and the risks of developing renal failure in the long-term, an early treatment should be offered to nephrotic patients. But have we got any effective treatment for this disease?

Corticosteroids have been largely used in the past with conflicting results. Recently 3 well designed prospective randomized trials have been made available. An American Collaborative trial[5] showed that nephrotic patients treated with alternate-day prednisone (mean 125 mg every other day for 2 months) had significantly more remission (although transient) and better preservation of renal function than untreated controls. A recent controlled study organized by the Medical Research Council[10] assigned 103 patients with NS either to placebo or to the same treatment used in the American Collaborative Study. All patients were followed for at least 3 years. After a mean follow-up of 4.5 years no difference either in the mean levels of serum albumin or in urine protein excretion or in plasma creatinine could be seen between the two group. A recent multicenter randomized Canadian study[25] also did not find any difference in term of remission of proteinuria and renal function between 51 patients assined to receive symptomatic treatment and 52 patients who were given prednisone at a dose of 45 mg/m^2 every other day for 6 months. These data seem to speak against the use of corticosteroids in patients with IMN. It must be pointed out, however, that in the above cited studies one regimen consisted of prednisone for a short period (probably too short for a chronic disease such as IMN is) while the other regimen used relatively small doses of prednisone (probably too small to interfere with antibody production and local immunocomplex formation). Before burying corticosteroids one should keep in mind that these agents, when given more aggresively (for example in form of i.v. methylprednisolone pulses followed by moderate doses of prednisone for several months) may reverse renal dysfunction and improve proteinuria in several patients with an already established renal insufficiency[26, 27].

Another traditional therapeutic approach in IMN is based on the use of cytotoxic drugs. A French controlled trial compared the effects of chlorambucil for 1 year to those of azathioprine or placebo[28]. At the end of the first year, proteinuria significantly decreased in chlorambucil treated group while did not modify in the other two groups. In a controlled study with cyclophosphamide Donadio et al.[29] did not find significant differences between 11 patients assigned to receive cyclophosphamide for 1 year and 11 untreated controls. However there was a greater decrease in proteinuria and a greater increase in inuli clearance in treated patients. Suki et al.[30] reported excellent results with prolonged administration of cyclophosphamide in patients with normal renal function. More recently West et al.[31] gave cyclophosphamide for a mean period of 2 years to 9 patients with an incipient renal insufficiency. They observed an improvement (but not the normalization) of plasma creatinine and a significant decrease in proteinuria. It seems therefore that alkylating agents may be effective in reducing proteinuria and also in improving renal dysfunction. However a prolonged administration either of cyclophosphamide or chlorambucil may expose not only to bone marrow depression, infections, alopecia, etc., but also to an increased risk of neoplasia and gonadal toxicity. From the available literature only comulative doses lower than 200 mg/kg of cyclophosphamide or 30 mg/kg of chlorambucil might be considered relatively safe.

Since a long-term treatment is probably necessary to obtain effective results in IMN, we chose to test a therapeutical protocol based on the alternance of corticosteroids and chlorambucil in order to spare the side-effects of a prolonged monotherapy. In a multicenter randomized study we assigned 81 patients with IMN and NS either to symptomatic treatment or to a six-month course with corticosteroids (i.v. methylprednisolone 1 g/day for 3 consecutive days then oral prednisone 0.5 mg/kg/day for 27 days) alternated with chlorambucil (0.2 mg/kg/day for 1 month)[32]. After a median follow-up of 5 years 68 % of patients were without NS in the treated group vs 23 % in the control group. Moreover the mean reciprocal of the serum creatinine signficantly worsened in the control group, while remained almost unchanged in the treated group. In 4 patients the treatment had to be stopped for severe side-effects[9]. Although some cilinicians could not reproduce our results[33] we are aware of many unpublished trials that could obtain a rate of remission similar to that observed in our studies. A troublesome complication referred by some collegues has been severe leucopenia. Let us stress again the need for a careful control

of white blood cells during treatment. The dose of chlorambucil should be halved wheneer leucocytes range around 5,000 and the drug should be stopped if leucocytes drop to 3,000 or less. The protocol with methylprednisolone and chlorambucil has been adopted by Mathieson et al.[34] to treat patients with declining renal function. Of 8 patients who received treatment 1 continued to progress to terminal renal failure while in the other 7 the mean proteinuria dropped from 15 to 2 g/day and creatinine clearance increased from 51 to 81 ml/min. However serious side-effects were encountered during chlorambucil administration. Four patients complained of severe nausea, vomiting and anorexia, pancytopenia developed in another patient. In summary a 6-month course of corticosteroids and chlorambucil may obtain sustained remission of the NS in about 2/3 of patients with IMN and can preserve renal function in the long-term. This regimen may also be effective in patients with an already established kidney dysfuncion, but without any doubt the administration of chlorambucil induces more severe side-effects in these patients. Lower dosage of clorambucil or substitution for cyclophosphamide may be suggested in patients with renal insufficiency.

Other therapies have been recently tried. Some investigators reported a good rate of remission of proteinuria with the use of ciclosporin[35, 36]. However it is well known that proteinuria tends to recur whenever cyclosporin is reduced or stopped. Moreover because of the potential thrombophylic effect of cyclosporin the use of this drug might implicate some particular risk in patients who are already exposed to thromboembolic complications[37]. Encouraging results have been reported with the logn-term use of intravenous immunoglobulins. This treatment could favor the solubilization of the immune complexes located in the subepithelial position or an inhibition of antibiodiotypic antibodies. Unfortunately, however, the available reports have been published only in form of abstract[38, 39] and only small groups of patients with a relatively short follow-up were studied. Should these results be confirmed a treatment almost free of side-effects (although rather expensive) might be available in the next future.

In conclusion there is an emerging evidence showing that the natural course of IMN can be altered by treatment. In view of the slow course of the disease many clinicians are still reluctant to give potentially toxic drugs to their patients. This attitude may be fully shared but, on the other hand, one cannot forget the risks related to the nephrotic condition and the poor quality of life of many nephrotic patients. Therefore an effective treatment should be welcome also for those patients who will not progress to renal failure. A lot of work is still necessary to recognize which factors can predict a spontaneous remission of NS and a stable renal function in the long-term. This could avoid an useless and potentially dangerous therapy for some patients. Futher studies are also needed to verify whether less toxic regimens than that suggested by ourselves may also effective. We are therefore only at the beginning of a long tunnel but we may see some light at the bottom.

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