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Review

Therapy of Idiopathic Membranous Nephropathy

Claudio Ponticelli

Istituto Auxologico Italiano, Milano, Italy

Abstract

Whether and how treating idiopathic membranous nephropathy (IMN) is still a matter of debate. While there is general agreement that nonnephrotic patients should be given symptomatic treatment alone, the results of specific therapy addressed to interfere with direct or indirect causes of renal damage are controversial. There is no evidence in favour of therapies based on corticosteroids alone. A few old randomized controlled trials (RCT) reported that alkylating agents, cyclophosphamide and chlorambucil, may increase the probability of remission, but the prolonged use of these agents may cause disquieting adverse effects. RCT showed that a treatment based on alternating corticosteroids and a cytotoxic agent every other month for 6 months may favour remission of the nephrotic syndrome (NS) and may protect renal function in the long-term. More recently, good results have also been reported with synthetic adrenocorticotropic hormone (ACTH), cyclosporine, tacrolimus, mycophenolate mofetil (MMF), and rituximab. Unfortunately, however, most of the therapeutical attempts with these drugs have not been tested in controlled, randomized trials and the follow-up in these studies was generally short-time. Attempts of modifying the natural course of IMN have also been tried in patients with an established renal insufficiency. A number of patients showed improvement of proteinuria and renal function after treatments based on corticosteroids and cytotoxic drugs. However, in most responders the values of creatinine clearance did not return to normal and little information is available about the long-term follow-up of these patients.

Keywords: membranous nephropathy, glomerulonephritis, immunosuppressive therapy, nephrotic syndrome, corticosteroids, cytotoxic drugs

Introduction

Membranous nephropathy is a renal disease histologically characterized by the uniform thickening of the glomerular capillary wall. This is caused by subepithelial deposits of immune complexes which appear as granular deposits of IgG with immunofluorescence and as electron-dense deposits on electron microscopy. IMN is typically a disease of adults with a peak incidence at between 30 and 50 years of age, although the clinical impression is that the number of elderly patients with IMN is progressively increasing. The disease may have a variable natural course. A number of untreated patients may experience a partial (proteinuria between 0.21 and 2 g per day with normal renal function) or even complete (proteinuria < 0.20 g per day with normal renal function) remission of proteinuria, while other patients maintain proteinuria fluctuating in a nephrotic - subnephrotic range or may slowly progress to end-stage renal failure. However, it is difficult to assess the percentage of patients with either outcome because most of the available studies reporting the outcome of untreated patients have had too a short follow-up and included both nephrotic and nonnephrotic patients. Furthemore, many patients may show a relapse of NS, so that only a part of those who entered remission will have remained nonnephrotic in the long-term. In a randomized study made in Italy, of untreated patients with MN and NS followed for 10 years only 5% were in complete remission and another 28% were in partial remission, 27% had NS and 40% of either died or entered dialysis [1]. Du Buf-Vereijken et al. [2] analyzed the reports published during the past 25 years by excluding patients with a follow-up of less than 3 years. Overall, nearly half the patients with NS developed renal function deterioration and were probably destined to enter end-stage kidney IMN may also be responsible for extrra-renal life-threatening complications. If one includes death as a cause of failure, it appears that more than 65% of untreated nephrotic patients followed for 15 years or more either suffered endstage renal failure or died [3]. Cardiovascular [4] and thrombotic complications [5,6] are the more frequent causes of death in nephrotic patients. Hypoalbuminemia, hyperlipemia, hypercoagulability, hypertension and renal insufficiency strongly correlate to morbidity and mortality in patients with IMN and NS [7].

Treatment

Symptomatic therapy

The amount of proteinuria may drive the therapy. There is evidence that patients with nonnephrotic proteinuria neither progress to renal failure [1,3, 8-10] nor are likely to develop the harmful consequences of NS. Therefore treatment of these patients is generally based on correction of proteinuria and of hypertension or hyperlipidademia, when present. Independently from the decision about "specific" therapy, patients with NS should also receive a symptomatic treatment. Edema should be treated with dietary salt restriction and low-dose hydrochlorothiazide in mild cases, or with increasing doses of loop diuretics in more severe cases. Angiotensin converting enzyme inhibitors (ACEI) and/or angiotensin receptor blockers (ARB) are usually given both for treating hypertension and for reducing proteinuria. My own clinical impression is that ACEI and ARB may be very effective in patients with mild to moderate proteinuria, but are of little benefit in patients with nephrotic proteinuria. Hydroxy-methylglutaryl coenzyme A reductase inhibitors can be used to manage hypercholesterolemia. Whether nephrotic patients should be anticoagulated is still controversial. However, as decision analyses concluded that the benefits of oral

Correspodence to: Claudio Ponticelli, Istituto Auxologico Italiano, Via Ampere 126, 20131, Milano Italy;
Tel +390226112952; Fax +390226112951; Email: claudio.ponticelli@ fastwebnet.it

anticoagulation are superior to the risks [11,12], it seems that prophylactic anticoagulation may be advisable in certain circumstances .The decision needs to take into account the nature of the underlying disease, the severity of the nephrotic syndrome (as assessed by serum albumin concentration), preexisting thrombophilic states, and the overall likelihood of serious bleeding events consequent to oral anticoagulation. The optimal duration of prophylactic anticoagulation is unknown but very likely extends to the duration of the nephrotic state per se [13].

Specific therapy

The first therapeutical attempts in IMN were made with corticosteroids. Retrospective noncontrolled studies provided conflicting conclusions. Three randomized controlled trials also gave controversial results. An American collaborative study [14] randomly assigned 72 patients with IMN and NS to be given alternate-day prednisone (125 mg/48 h for 2 months, with an additional 2-month taper) or symptomatic therapy. During the study there were significantly more remissions in the treated arm but after a mean follow-up of 23 months, there was no significant difference between the two arms. The mean creatinine clearance declined more steeply in the control group. This study has been criticized because the patients assigned to the control group had a worse outcome than usually seen, with 26% of them entering severe renal failure or dying within 23 months. The same protocol was evaluated in a double-blind RCT organized in the United Kingdom [15]. All of the 107 patients enrolled were followed for at least 3 years. No difference was seen between the two arms in the mean levels of proteinuria or serum creatinine. In a Canadian study, 158 patients with or without NS were assigned to receive symptomatic therapy of prednisone at a dosage of 45 mg/m2 every other day for 6 months [16]. Again there was no difference in mean proteinuria or creatinine clearance between the two groups. Thus, the current evidence speaks against a benefit of corticosteroids over symptomatic therapy, at least at the doses and for the time of administration used in the available RCT.

Some small-sized RCTs have prospectively evaluated the role of immunosuppressive agents. Donadio *et al.* assigned 22 patients with MN to receive cyclophosphamide or supportive therapy for 1 year [17]. There was a trend toward a greater reduction of proteinuria in treated patients, but the difference was not significant. Cleary the statistical power of the study was very weak and the follow-up was short. Lagrue *et al.* randomized 41 patients to receive chlorambucil, or azathioprine or symptomatic therapy for 1 year [18]. After two years of follow-up, of 16 patients who received chlorambucil, 9 entered complete remission and 4 partial remissions versus 1 patient with partial remission in the azathioprine-treated group, and 2 with complete remissions plus 1 with partial remission in the placebo group. However, a few patients given long-term chlorambucil experienced severe adverse effects including malignancy. Murphy *et al.* [19] randomized 40 patients with moderate proteinuria either to symptomatic therapy alone or to cyclophosphamide for 6 months plus warfarin and dipyridamole for two years. In spite of the weak statistical power of the study treated patients showed a significantly greater reduction of proteinuria and a larger number of complete or partial remissions when compared to controls.

A different approach consisted in alternating corticosteroids and cytotoxic drugs. A multicenter Italian RCT assigned patients with MN and NS to symptomatic therapy or to a 6-month therapy with 3 months of corticosteroids and 3 months of chlorambucil [1]. Patients assigned to treatment were given an intravenous pulse of methylprednisolone (MPP), 1 g each, for 3 consecutive days, followed by oral prednisone 0.5 mg/kg per day for 27 days, then steroid was stopped and oral chlorambucil was administered at a dose of 0.2 mg/kg per day for 1 month. At the end of the month another cycle of steroids was given, followed by one month with chlorambucil, and again by a third cycle with steroids followed by a month with chlorambucil. Therefore the whole treatment lasted 6 months, 3 with corticosteroids and 3 with chlorambucil. The doses of chlorambucil had to be halved if the number of leukoctes was falling below 5,000/cmm and chlorambucil had to be stopped if leukocytes fell below 3,000/cmm. Patients were followed for 10 years. At the last follow-up, 92% of treated patients versus 60% of untreated patients were alive with kidney function, 61% of treated patients were without NS (40% being in complete remission) versus 33% of untreated controls (5% in complete remission). The same protocol was compared with a regimen based on corticosteroids alone (3 intravenous pulses of methylprednisolone at months 1, 3 and 5, plus oral prednisone 0.5 mg/kg on alternate days for 6 months). The probability of reaching complete or partial remission was significantly higher at 1, 2 and 3 years for patients given the combined treatment. At 4 years, 62% of patients given the combined treatment and 42% of patients given steroid alone were without NS, but due to the smaller number of patients at risk the difference was not significant [20]. In a third RCT, patients with MN and NS were allocated to methylprednisolone and chlorambucil, or to the same schedule but with cyclophosphamide 2.5 mg/kg per day, instead of chlorambucil. No significant differences were found in the probability of remission of NS or in the slope of the reciprocal of serum creatinine. However, side effects tended to be more frequent in the chlorambucil arm [21]. Taking together the results of these 3 RCT conducted on a population of Italian patients with biopsy-proven MN and NS, selected with the same inclusion and exclusion criteria, out of 174 patients treated with steroids alternated with a cytotoxic agent 83% reached a complete or partial remission as a first event and 75% were still in complete or partial remission after a mean follow-up of 54 months. The actuarial probability of renal survival at 10 years was 93%, and graft survival censored by death was 98%. However, about 9% of patients had to interrupt treatment because of adverse effects [22]. Recently a RCT compared the effect of a 6-month course of alternating prednisolone and cyclophosphamide with supportive treatment in adults with nephrotic syndrome caused by IMN. Patients were followed up for 10 years. Of the 47 patients who received the experimental protocol, 34 (72%) achieved remission compared with 16 of 46 (35%) in the control group. The 10-year dialysis-free survival was 89 % in the experimental group and 65% in the control group, the likelihood of survival without death, dialysis, and doubling of serum creatinine were 79% and 44% respectively, all these differences being statistically significant. The incidence of

infections was similar in the two groups [23]. A main concern with the use of cytotoxic agents is the possible development of malignancy. The problem is made complicated by the fact that patients with IMN have an increased risk of developing cancer. About 10% of patients with MN have malignancy at the time of renal biopsy or within a year thereafter with a standardized incidence ratio 9.8 in men 12.3 in women compared to general population [24]. Moreover, in a Norwegian study the annual incidence of cancer in patients with a MN was 24/1000/pts/year significantly higher than that observed in the general population [25]. In our own cumulative experience the incidence of malignancy was 4.5/1000 pts/year similar to that expected in a general Caucasian population [21]. In patients older than 65 years, noncontrolled studies reported that a 6-month treatment with corticosteroids alternated with a cytotoxic agent obtained a rate of response similar to that observed in younger adults [26, 27]. However, adverse effects were more frequent and severe in elderly patients. Therefore, in older patients it is recommended to halve the doses of MPP and of the cytotoxic agent in order to reduce morbidity.

A pilot study reported that synthetic adrenocorticotropic hormone (ACTH) given for 1 year resulted in complete remission of proteinuria in 7 of 8 patients with MN [28]. On the basis of these promising results, we organized a small RCT comparing the 6-month regimen based on steroids and a cytotoxic agent alternated every other month versus parenteral treatment with synthetic ACTH given at a dosage of 1 mg twice a week for 1 year [29]. In the first group, 15 of 16 patients entered complete or partial remission versus 14 of 16 in the second group. Median proteinuria decreased from 5.1 g/day to 2.1 g/day in the first group and from 6.0 g/day to 0.3 g/day in the second group. Although no adverse effects were seen in this trial, caution with such a therapy should be used in elderly patients and in those previously treated with corticosteroids.

A number of noncontrolled studies have reported a good antiproteinuric effect of cyclosporine. Taken together, the available data show that cyclosporine may be effective in favoring the remission of NS in 50%-60% of patients [30]. The addition of small doses of prednisone may favour remission. Remission often occurs within 3-4 months, but in a German study, the median time for response was 7 months [31]. Cattran *et al.* [32] conducted a RCT in 51 patients with IMN and NS who were randomized to receive 6 months of cyclosporine treatment plus low-dose prednisone or to placebo plus prednisone. All patients were followed for one year after the 6 months. Seventy-five percent of the treatment group versus 22% of the control group had a partial or complete remission of proteinuria by 6 months. Relapses occurred in 43% of the cyclosporine remission group and 40% of the placebo group by one year after treatment interruption. Renal insufficiency, defined as doubling of baseline creatinine, was seen in 2 patients in each group. Alexopoulos *et al.* [33] evaluated the efficacy of a 12-month treatment with low-dose cyclosporine alone or combined with corticosteroids. Patients who responded with complete or partial remission were placed on long-term treatment with lower doses of cyclosporine and prednisolone or cyclosporine alone. After 12 months of treatment, 26 out of 31 patients in the combination group and 17 of 20 patients in the monotherapy group had complete or partial remission. Renal function was unchanged in the two groups. During long-term treatment, relapses were more frequent in the monotherapy group and were usually associated with blood levels of cyclosporine <100 ng/mL. Goumenos *et al.* [34] administered cyclosporine, 3 mg/kg per day, and prednisone, 0.5 mg/kg per day, to 16 patients with IMN. Eight patients entered complete remission and 6 partial remissions after a mean of 5 months. However, at control renal biopsy, glomerular sclerosis, interstitial fibrosis and vascular hyalinosis had deteriorated. Thus, therapy with cyclosporine may lead to remission of NS in a consistent group of patients with MN. The addition of prednisone may increase the probability of remission, but relapses are frequent when cyclosporine is stopped or even reduced, and control renal biopsies often show progression of the disease in spite of reduction of proteinuria. Unfortunately, there are not studies clarifying the impact of cyclosporine on renal function in the long-term.

Anecdotal cases of success with tacrolimus have been reported. Praga *et al.* [35] conducted a prospective randomized trial. Twenty-five patients received tacrolimus (0.05 mg/kg/day) over 12 months with a 6-month taper, whereas 23 controls received symptomatic therapy alone. The probability of remission in the treatment group was 82%, and 94% after 12, and 18 months but only 24%, and 35%, respectively in the control group. Six patients in the control group and only one in the treatment group had a 50% increase in their serum creatinine. However NS reappeared in almost half of the patients who were in remission by the 18th month after tacrolimus withdrawal.

Mycophenolate mofetil has also been used. Two non-controlled studies [36,37] reported a significant decrease in proteinuria and serum cholesterol levels after a treatment with MMF that ranged from 6 to 18 months. Side effects of MMF were infrequent and generally mild. However the doses of MMF were variable (from 0.5 to 2 g per day) and the follow-ups short. Branten *et al.* [38] retrospectively compared 32 patients with MN who were given MMF at a dose of 2 g per day for one year with 32 historic controls treated with cyclophosphamide. Both groups also received intermittent MPP and alternate-day prednisone. Median follow-up was 23 months. Proteinuria values at baseline and after 12 months were 8.40 and 1.41 g/day in the MMF group versus 9.19 and 1.13 g/day in the cyclophosphamide group respectively. Cumulative incidences of remission of proteinuria at 12 months were 66% in the MMF group versus 72% in the cyclophosphamide group. Five patients (16%) in the MMF group versus none in the cyclophosphamide group had disease that did not respond to therapy. Twelve patients (38%) experienced a relapse in the MMF group compared with 4 (13%) in the cyclophosphamide group. Side effects occurred in 24 patients (75%) in the MMF group and 22 patients (69%) in the cyclophosphamide group.

Rituximab, a chimeric monoclonal antibody directed against the the non-glycosylated phosphoprotein CD20 which is expressed on the surface of mature B cells, was administered to 14 MN patients with persistent nephrotic proteinuria at a dosage of 375 mg/m2 weekly for 4 weeks. Proteinuria decreased from a mean 9.1 to 4.6 g/day in 8 patients with mild tubulointerstitial lesions but did not change in 6 patients with more severe histological lesions. No major drug-related events or major changes in laboratory parameters were observed [39]. In another study, 15 patients received rituximab 1 g on days 1 and 15. At 6

months, patients with persisting proteinuria >3 g/day received a second course of rituximab. Mean proteinuria decreased from 13.0 to 5.5 g/day at 12 months. Complete remission was observed in only 3 patients, 5 patients did not respond at all. Two patients with declining renal function entered end-stage renal failre within one year, one patient died from lung cancer [40].

The above-quoted trials have been performed in patients with normal or subnormal renal function. In patients with deteriorating renal function a number of investigators reported satisfying results also. The best results have been obtained with a 6-month treatment based on corticosteroids alternated with chlorambucil [41-44] or with 1-year treatment based on the association of cyclophosphamide with corticosteroids [2,38, 45,46]. A complete or partial remission of NS could be seen in more than 60% of patients and a similar percentage of patients showed an improvement of renal function. On the basis of these good results, a number of nephrologists prefer to start an immuno-suppressive treatment only when there is a deterioration of renal function, in order to spare the potential toxicity of immunosuppression to patients with stable renal function. However, it should be pointed out that in most cases serum creatinine did not return to normal values in the available studies. Moreover limitations of the studies in patients with renal insufficiency are the lack of RCT, the short-term follow-ups, and the insufficient information on renal histology. Of concern, many patients experienced severe side effects, mainly bone marrow toxicity and infection. To reduce the risk of iatrogenic toxicity we recommended that the doses of MPP and cytotoxic agents should be halved in patients with renal insufficiency [47]. Actually, such an adjustement of therapy proved to minimize the incidence and severity of side effects while keeping efficacy in a study [42]. Although a small RCT showed that cyclosporine could improve proteinuria and slow the decline of creatinine clearance in MN patients with renal insufficiency [48] the use of cyclosporine in patients with renal insufficiency should be cautious, being a damaged kidney more vulnerable to the nephrotoxic effects of cyclosporine [49].

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