Nonimmunosuppressive Therapy of Membranous Nephropathy

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Idiopathic membranous nephropathy (MN) has a variable rate of progression to end-stage renal failure, with a significant number of patients going into spontaneous remission without therapy. For those who have persistent nephrotic proteinuria or manifest deterioration of renal function, steroids and immunosuppressive drugs are used. However, their long-term efficacy is challenged by a meta-analysis presented here. A different approach to reduction of proteinuria, a recognized progression promoter, is based on the notion that angiotensin II inhibition controls proteinuria and slows progression. Further, a more complex approach is required than simple administration of an angiotensin-converting enzyme (ACE) inhibitor: a multidrug approach to remission of nephrotic syndrome therefore is described here.

THE CLINICAL COURSE of membranous nephropathy (MN) is characterized by great variability of the rate of progression.[1-3] A significant number of patients, up to one third of patients in some series, experience spontaneous remission of the nephrotic syndrome (ie, proteinuria disappears without therapy within months or a few years from onset). It even has been reported that in some patients histologic resolution also may occur. On the other hand, another one third of patients have a slow tendency toward progression but remain heavily proteinuric and suffer the consequence of nephrotic syndrome. In a final third of patients, the disease takes an ominous course, and causes the complete loss of renal function within a few years.

Despite efforts to identify risk factors for progression, it remains difficult to distinguish at the time of diagnosis those patients who may be candidates for immunosuppressive therapy from those who are destined to spontaneous remission. Therefore, nephrologists are divided between the supporters of immediate immunosuppressive therapy and those prone toward a more conservative approach.[4] Indeed, the second group of physicians have argued against these protocols on the grounds that immunosuppressive drugs could be too strong a measure because their side effects could be much worse than the disease they pretend to cure.

Before considering whether or not a patient should be treated with potentially dangerous therapy, closer scrutiny of the available evidence of efficacy of tested treatment in clinical trials is warranted.

RESULTS OF A SYSTEMATIC REVIEW ON IMMUNOSUPPRESSIVE TREATMENTS

We conducted an updated meta-analysis on all available data from reports of randomized controlled trials, published as full articles, in abstract form or partially/totally unpublished, addressing the effect of immunosuppressive agents in patients with nephrotic syndrome. This meta-analysis included a larger number of studies as compared with previous systematic reviews and almost 400 more patients.[5-7]

The selected patients were adult subjects with idiopathic MN, aged 16 years or older, who had the nephrotic syndrome. The assessment of nephrotic syndrome relied on that chosen by the authors of each study. It must be said that this definition was heterogeneous. In trials that included a minority of nonnephrotic subjects, when possible analyses were restricted to nephrotic patients only. Absent of an explicit definition of nephrotic syndrome, the cut-off level of a urinary protein excretion greater than 3.5 g/24 hr was used.

Studies were identified according to the principles of the Cochrane Collaboration.[8] Electronic databases, Medline (1968-September 2000), and Embase (1980-September 2000) were searched by using the optimally sensitive strategy developed for the Cochrane Collaboration for the identification of randomized controlled trials, together with a specific search strategy for immunosuppressive treatment in MN.

One or more of the following outcome measures for efficacy were considered: (1) definite end points of death, and end-stage renal failure that required initiation of dialysis or renal transplantation; and (2) surrogate end points of partial remis-

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sion: proteinuria level between 0.2 and 2 g/24 hr and a serum creatinine level less than or equal to 2.0 mg/dL (180 μmol/L); complete remission: proteinuria level of less than 0.2 and a serum creatinine level of less than or equal to 2.0 mg/dL (180 μmol/L); final proteinuria level: measured as g/24 h; final serum creatinine level: measured as μmol/L; and final glomerular filtration rate (GFR): measured as mL/min/1.73 m^2.

Recently published clinical trials were selected, including a total of 1,025 randomized patients.[9-18] Four different classes of therapeutic interventions were evaluated: (1) steroids (alone), (2) alkylating agents (alone or in combination with steroids), (3) calcineurin inhibitors (alone or in combination with steroids), and (4) antiproliferative agents (alone).

By combining data of all these treatment categories as a group and comparing them with placebo or no treatment it was found that there were no difference between the 2 groups as far as patient or renal death. When partial or complete remission of nephrotic syndrome was considered as an end point, active treatment showed a favorable effect over placebo or no treatment (Fig 1). This, however, was observed in the presence of statistically significant heterogeneity. When a random effects model was used, the difference was no longer statistically significant (random effects: odds ratio [OR], 1.57; 95% confidence interval [CI], 0.76-3.24; $P > .05$).

We then analyzed the contribution of each type of therapeutic regimen to this favorable effect on proteinuria. Oral glucocorticoids had no beneficial effect on any of the end points chosen for efficacy. Alkylating agents were associated with more complete or partial remissions (Peto odds ratio [OR], 2.52; 95% confidence interval [CI], 1.39-4.57; $P = .002$). However, there was significant heterogeneity and the effect was no longer significant when a random effects model was applied (random effects OR, 2.48; 95% CI, 0.53-11.60; $P > .05$).

In calcineurin inhibitor–treated patients, the rate of complete or partial remission increased a little compared with control patients, although not significantly. Paucity of data on antiproliferative agents did not allow any conclusion.

Within the class of alkylating agents, there is weak evidence of a relative beneficial effect on partial or complete remission of nephrotic syndrome of cyclophosphamide treatment compared with chlorambucil (Peto OR, 0.39; 95% CI, 0.16-0.94; $P = .04$). As far as safety is concerned, cyclophosphamide treatment resulted in a statistically significant lower rate of discontinuations owing to adverse events compared with chlorambucil (8 events versus 21, respectively; Peto OR, 4.24; 95% CI, 1.72-10.47; $P = .002$). The meta-analysis failed to show any long-term effect of treatment on patient and/or renal survival. Although there is some evidence that in adult patients with MN and nephrotic syndrome, immunosuppressive regimen increased the rate of remission, this evidence is weakened greatly by the fact that studies exhibited significant heterogeneity and results were not robust enough after sensitivity analysis. Specifically, the inclusion of patients with particularly well-preserved renal function can influence study findings. Review of safety showed that there was an increased number of discontinuations owing to adverse events in immunosuppressive treatment groups. Within the class of alkylating agents there is weak evidence supporting the efficacy of cyclophosphamide compared with chlorambucil. On the other hand, cyclophosphamide was significantly safer.

In summary, although a number clinical trials have reported positive results with immunosuppressive regimens in MN, and despite the common wisdom of many clinicians claiming that active treatment frequently is successful, according to our meta-analysis the present treatments of MN are far from ideal. Alternative approaches therefore are needed.

ALTERNATIVE IMMUNOSUPPRESSIVE REGIMENS

In view of the pathogenic potential of B cells in this disease, we studied the effects of rituximab[19,20]—a monoclonal antibody to B-cell antigen CD20—in 8 patients with idiopathic MN and persistent nephrotic syndrome. Four weekly infusions of 375 mg resulted in a decrease of urinary proteins from a mean of (SE) 8.6 g/24 h (1.4) to 3.8 (0.8) at 4 weeks and 3.7 (0.9) at 20 weeks, respectively ($P < .0001$). At week 20, albuminuria and albumin fractional clearance decreased by 70% and 65%, and serum albumin increased by 31%. CD20 B lymphocytes decreased below normal ranges up to study end.[21] The short-term risk-benefit profile of rituximab seems more favorable than any other immunosuppressive drug used to

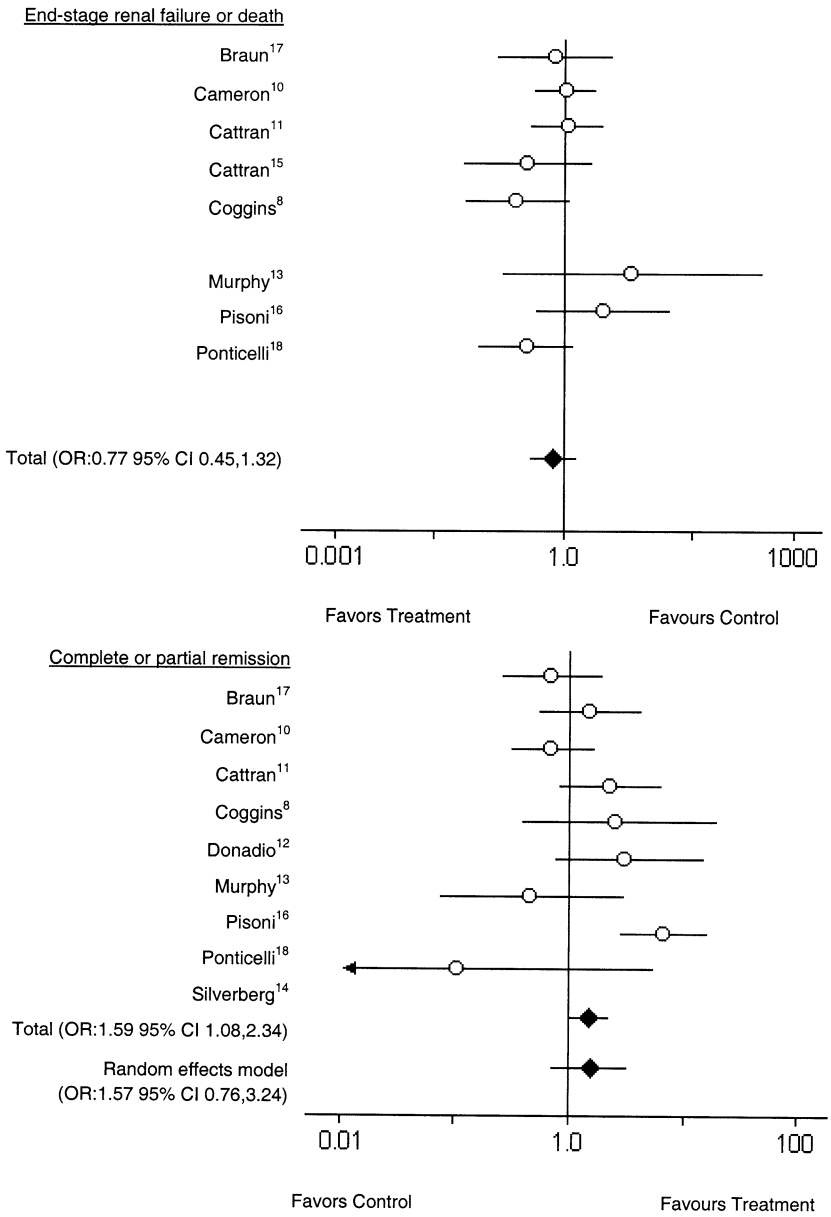

Fig 1. Overall comparison of definite and surrogate end points for all immunosuppressive treatments versus placebo or no treatment for MN.

treat idiopathic MN. These preliminary data await confirmation from a large-scale clinical trial.

Limited clinical experience of treating MN with mycophenolate mofetil has been reported in the literature. Miller et al[22] treated patients with MN who previously were treated unsuccessfully with steroids and cytotoxic drugs or cyclosporin. Six of 16 patients had a 50% reduction of proteinuria.

In another study by Choi et al,[23] mycophenolate mofetil was used in 15 patients with MN and nephrotic syndrome. Overall, a 61.1% reduction of proteinuria was obtained; of 15 patients, 8 had partial and 2 had complete remission of proteinuria.

Again, these observations await confirmation by randomized controlled studies; however, mycophenolate mofetil may represent a suitable alternative to other immunosuppressive treatments.

REDUCTION OF PROTEINURIA WITH NONIMMUNOSUPPRESSIVE DRUGS

Truly alternative treatments, however, are those not immunosuppressive in nature, that should be

considered as initial treatment in most patients with MN. Nonimmunosuppressive therapy is directed to reduction in proteinuria, a major progression promoter, and inhibition of the renin-angiotensin system is the keystone of such an approach. Numerous studies have shown in both diabetic and nondiabetic chronic nephropathy that angiotensin-converting enzyme (ACE) inhibitors reduce proteinuria and arrest progression of renal disease. This class of drugs reduces glomerular intracapillary pressure and protein ultra-filtration, and improve glomerular barrier size selectivity in experimental models of renal diseases and in humans.[24-25]

We have shown that ACE inhibition also is effective in idiopathic MN. In 14 patients with MN and persistent proteinuria (protein $>$ 3 g/24 h for $>$ 6 mo), we studied urinary protein excretion, GFR, and albumin and neutral dextran fractional clearance after 2 months of enalapril therapy (2.5 to 20 mg/d), and 2 months after enalapril withdrawal (recovery).[26] A group of 6 patients with MN and persistent overt proteinuria maintained on conventional treatment throughout the follow-up period served as controls. Basal mean arterial pressure, proteinuria, and GFR were similar in the 2 study groups. However, in patients at the end of the treatment period, mean arterial pressure (posttreatment, 99.6 $\pm$ 11.2 versus basal, 103.3 $\pm$ 12.1 mm Hg; $P < .05$), proteinuria (posttreatment protein, 5.0 $\pm$ 2.9 versus basal, 7.1 $\pm$ 4.9 g/24 h; $P < .05$), albumin fractional clearance (posttreatment median, 1.7×10^{-3}; range, 0.2-22.7 $\times 10^{-3}$ versus basal median, 4.1×10^{-3}; range, 0.4-22.1 $\times 10^{-3}$; $P < .05$), and fractional clearance of largest neutral dextrans (radii from 62-66 Å) were significantly less than basal values. At recovery, mean arterial pressure significantly increased to 106.6 $\pm$ 11.7 mm Hg ($P < .001$ versus enalapril), but all other parameters remained less than basal values. GFR and renal plasma flow (RPF) were similar at each evaluation. Theoretical analysis of dextran-sieving data indicated that ACE inhibitor treatment significantly improved glomerular membrane size-selective dysfunction. This effect persisted more than 2 months after treatment withdrawal. Thus, in patients with MN and long-term nephrotic syndrome, ACE inhibitor treatment, but not conventional therapy, improved glomerular barrier size selectivity. The antiproteinuric effect of ACE inhibition is long lasting, especially in patients with more severe renal insufficiency.

Other studies have confirmed that short- and long-term use of ACE inhibitors produced a substantial reduction of proteinuria. Although a relative reduction of proteinuria is always a positive result, the aim of antiproteinuric therapy is aimed to reduce urinary protein excretion less than 0.5 g/d. This goal may be not achievable with ACE inhibitors alone, even when the drug is used at the highest dose.

Other measures directed to further reduce proteinuria in association with ACE inhibitors were tested in MN.

A role of aldosterone in the development of fibrosis in animal models of kidney injury has been postulated. A potential role of the anti-aldosterone drug spironolactone in reducing proteinuria and limiting the progression of renal diseases has been suggested.[27] We have tested this hypothesis and studied the effect of 100 mg/d spironolactone, associated with an ACE inhibitor, in 11 patients with idiopathic MN for 2 months (V. Brusegan, personal communication). Although blood pressure decreased significantly, proteinuria did not improve and serum potassium level increased. Therefore, this combination has no additional antiproteinuric effect and carries a significant risk for hyperkalemia.

The antiproteinuric effect of the nonsteroidal anti-inflammatory drug indomethacin was proposed many years ago.[28] Interest for this approach has been revived recently, after a few studies showed that indomethacin may have a complementary effect to ACE inhibitors.[29] We tested this hypothesis in 19 patients with persistent proteinuria who were treated in a cross-over design with maximized doses of ramipril alone and in combination with indomethacin (75 mg 3 times/d).[30] Compared with the period of treatment with ACE inhibitor alone, addition of indomethacin did not further reduce proteinuria, and actually was associated with reversible side effects, including increased serum potassium levels.

Despite these negative results, the search for ideal combination therapy has continued. We recently have shown in a group of 24 patients with chronic nephropathy that combination therapy with an ACE inhibitor, benazapril, and an angiotensin-II receptor blocker, valsartan, given for 8 weeks, was more effective in reducing proteinuria than either

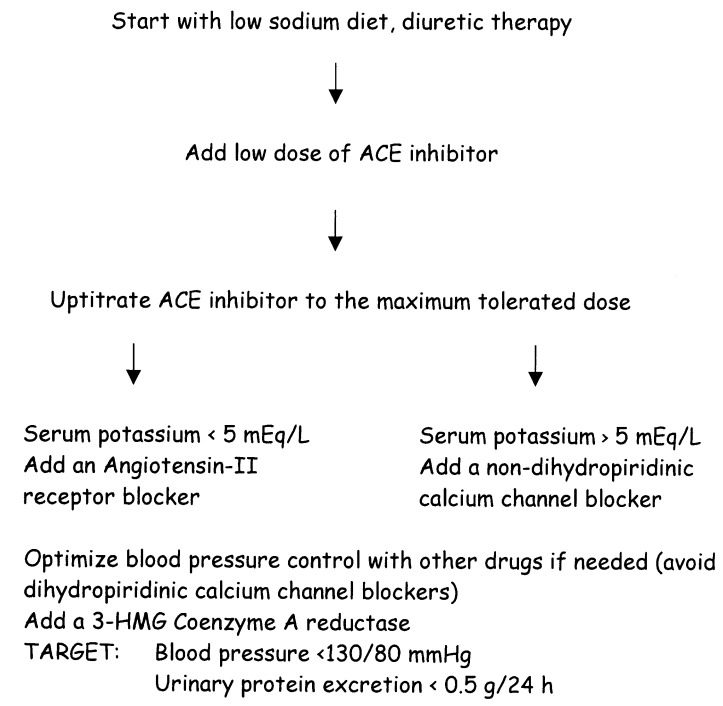

Fig 2. Algorithm of the remission clinic, a multidrug approach for patients with proteinuria.

drugs given alone, at comparable blood pressure control.[31]

These data are confirmed in a randomized controlled study, in which a combination of ACE inhibitor and angiotensin-II receptor blocker was compared with a single drug regimen in patients with chronic nephropathies.[32] Overall, 336 patients were enrolled in the study and followed-up for a median of 2.9 years. The study recruited 28 patients with MN, but this article does not report results according to the different pathology groups.

The trial showed that the combination therapy had a stronger antiproteinuric effect compared with single-drug regimens. The combination therapy also retarded progression of renal disease to a greater extent than monotherapy. The incidence of undesired side effects was not significantly higher in the combination therapy, although hyperkalemia was slightly more frequent in the combination group. Dyslipidemia is present almost invariably in patients with nephrotic syndrome, and is not only a major risk factor for cardiovascular diseases, but also may represent a promoter of progression to end-stage renal disease. Correction of dyslipidemia by dietary and pharmacologic intervention is part of the current therapy of nephrotic syndrome, although the effects of its correction on the progression of renal disease had not been tested in a formal clinical study.

ACE inhibition may be of help in the treatment of dyslipidemia. We have found that maximized doses of the ACE inhibitor lisinopril (largely exceeding the doses required to control blood pressure) ameliorated proteinuria and dyslipidemia in 28 patients with nondiabetic nephropathies (9 of whom had MN).[33] Total cholesterol decreased from 265 ± 80 mg/dL to 223 ± 62 mg/dL ($P < .01$), whereas serum triglyceride levels decreased from 202 ± 148 mg/dL to 128 ± 64 mg/dL ($P < .05$). Of note, the decrease in serum cholesterol level clearly depended on the increase of serum albumin concentration observed during lisinopril therapy in those patients with more severe hypoalbuminemia at baseline (most of these patients had MN). On the other hand, the reduction of serum triglyceride levels did not appear to be associated with amelioration of nephrotic syndrome, but rather with the dose of lisinopril, suggesting a specific effect of the drug, possibly by improving insulin sensitivity.

Recent studies have suggested that HMG CoA reductase inhibitors may act synergistically with ACE inhibitors in reducing both proteinuria and elevated serum cholesterol levels. Lee et al[34] re-

ported the results of a small trial in 63 normolipemic patients with nonnephrotic proteinuria, to whom pravastatin or placebo was given for 6 months. Blood pressure was well controlled with a variety of drugs, including the angiotensin-II receptor blocker losartan. Pravastatin lowered proteinuria by 54% in 6 months,

CONCLUSION

The nonimmunologic treatment of MN today is entirely feasible, but requires a multiple drug approach, aimed to achieve the goal of proteinuria reduction. We have established a remission clinic in our institution where proteinuric patients, including, of course, all patients with MN, are followed-up in standardized fashion.[35] Patients are treated initially with an ACE inhibitor at the lowest recommended dose (Fig 2). Then the drug dosage is up-titrated at the maximal tolerated dose, while checking serum creatinine and potassium levels at each increase.

If the goal of urinary protein excretion of less than 0.5 g/24 h is not achieved, an angiotensin II-receptor blocker is added, and again up-titrated to the maximal tolerated dose. Diuretics almost invariably are indicated not only to control edema, but also to achieve optimal blood pressure control (ie, $<$130/80 mm Hg), to maximize the effects of ACE inhibitors and/or angiotensin-II receptor blockers, and to limit hyperkalemia. Statins are used with the dual goal of ameliorating dyslipidemia and further reducing urinary protein excretion. Healthy lifestyles also are promoted, with a special regard to smoking cessation and a reduced dietary intake of salt and saturated fats.

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