Corticosteroids and Ciclosporin A in Idiopathic Membranous Nephropathy: Higher Remission Rates of Nephrotic Syndrome and Less Adverse Reactions than after Traditional Treatment with Cytotoxic Drugs

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Key Words
Membranous glomerulonephritis • Nephrotic syndrome • Ciclosporin A • Immunosuppression

Abstract

Background/Aim: Idiopathic membranous nephropathy, the most common cause of nephrotic syndrome in adults, has been traditionally treated with corticosteroids and cytotoxic drugs. Ciclosporin A (CsA) is used in resistant cases, but also as a first-line treatment, due to the serious side effects of cytotoxic drugs. In this study, the remission rates of nephrotic syndrome and the incidence of side effects of corticosteroids and low CsA doses are compared with those after treatment with cytotoxic drugs. Methods: Seventy-seven nephrotic patients with well-preserved renal function who were treated with methylprednisolone and CsA (n = 46) or cytotoxic drugs (n = 31) were studied. The effects of treatments were estimated on the basis of remission rates of nephrotic syndrome and preservation of the renal function. Results: Remission (complete or partial) of nephrotic syndrome was observed in 85\% of the patients treated with CsA and in 55\% of the patients treated with cytotoxic drugs (p < 0.01). Deterioration of the renal function, more common in patients with multiple relapses and interstitial fibrosis, was observed in 26 and 23\% of the patients, respectively (p = NS). Serious side effects and discontinuation of treatment were more frequent in patients treated with cytotoxic drugs (10 vs. 4\%). Conclusion: The combination of corticosteroids with CsA represents a better regimen for patients having idiopathic membranous nephropathy, since it is associated with higher remission rates of nephrotic syndrome and less severe side effects than corticosteroids and cytotoxic drugs.

Introduction

Idiopathic membranous nephropathy (IMN), the most common cause of nephrotic syndrome in adults, usually follows an indolent course, since one third of the patients show a spontaneous remission. However, about 25\% of the patients reach end-stage renal failure (ESRF) 10 years
after the diagnosis. Heavy proteinuria, arterial hypertension, impaired renal function, and severe histological involvement are related to a poor outcome and should be considered in the treatment with immunosuppressive drugs [1, 2].

Various immunosuppressive regimens, including corticosteroids, cytotoxic drugs, and ciclosporin A (CsA), have been used in several trials. The effect of corticosteroids did not prove to be superior to that of a placebo [3, 4]. A 6-month course of corticosteroids and chlorambucil or cyclophosphamide is effective in inducing remission of nephrotic syndrome and in the preservation of the renal function [5–7]. However, the risks of marrow toxicity, gonadal dysfunction, and malignancy make physicians reluctant to use them. Azathioprine, a less toxic drug, did not prove effective [8]. CsA has been used in patients with nephrotic syndrome resistant to corticosteroids or cytotoxic drugs and frequently led to remissions [9, 10]. Although it is potentially nephrotoxic, low doses of the drug are not followed by characteristic lesions of nephrotoxicity [11]. The combination of CsA with corticosteroids as initial treatment leads to a remission in more than 80% of the IMN patients [12, 13].

The purpose of this study was to compare the effect of treatment with corticosteroids and low doses of CsA on remission rate of nephrotic syndrome, preservation of the renal function, and incidence of side effects with that of the traditional treatment with cytotoxic drugs in IMN patients.

Patients and Methods

Patients

Seventy-seven patients (55 males and 22 females) with nephrotic syndrome (urinary protein excretion $8.2 \pm 4.5$ g/24 h) and well-preserved renal function (baseline serum creatinine $1.1 \pm 0.5$ mg/dl) who were referred – due to biopsy-proven IMN – to the Departments of Internal Medicine/Nephrology of the University Hospitals of Patras, Ioannina, Alexandroupolis, Heraklion, and Larissa, Greece, between 1995 and 2005, were evaluated in this retrospective analysis. Patients with secondary forms of the disease, due to drugs or systemic diseases, were excluded after clinical and laboratory investigation. The inclusion criteria were age <65 years, creatinine clearance >60 ml/min, urinary protein >3.5 g/24 h for at least 6 months on conservative management, and the initiation of treatment with corticosteroids and cytotoxic drugs or CsA. All patients fulfilling these criteria were included in the study and separated into two groups for comparison according to the therapeutic regimen used.

Out of 77 patients, 31 were treated with corticosteroids and cytotoxic drugs for 6 months, at monthly intervals. Methylprednisolone (1 g/day i.v. for 3 days and then 0.4 mg/kg/day p.o.) was administered during the 1st, 3rd, and 5th month. Chlorambucil (0.2 mg/kg/day) or cyclophosphamide (1.5 mg/kg/day) was administered during the 2nd, 4th, and 6th month. In 46 patients methylprednisolone (initial dose 0.4 mg/kg/day p.o., gradually reduced to 4 mg/day p.o. at 12 months) and CsA (2–3 mg/kg/day, adjusted according to the target $C_{S_0}$ – trough – blood level of 100 ng/dl for 18 months, reduced by 0.5 mg/kg/month for 6 months) were used for 24 months.

The therapeutic regimen used related to the time of referral. Most patients referred between 1995 and 2000 were treated with cytotoxic drugs, whereas most of those referred after 2000 were treated with CsA. Thus, two groups of patients with similar clinical and histological features were formed (table 1).

Conventional Pathology and Grading of the Histological Lesions

IMN was diagnosed by means of appropriate renal biopsy (>10 glomeruli), showing typical features on light microscopy and immunofluorescence [14]. On light microscopy, the presence of thickened capillary loops, glomerular sclerosis, interstitial fibrosis, tubular atrophy, and vascular hyalinosis was examined in multiple sections. On immunofluorescence, the presence of IgG and C3 deposits in the biopsy specimens was confirmed. The severity of glomerular sclerosis was expressed as percentage of totally sclerosed glomeruli, whereas other parameters were evaluated using Masson’s trichrome stained sections by a semiquantitative method and expressed as absent, mild, or moderate [15].

Treatment and Follow-Up

During the treatment and follow-up periods, all patients were examined every 2 months. Body weight, blood pressure, urinalysis, complete blood count, biochemical profile, and 24-hour urinary protein were recorded. Monitoring of the blood pressure and treatment of hypertension were performed according to established standards, aiming at $130/85$ mm Hg, using restricted salt intake and appropriate drug therapy. Angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II subtype 1 receptor blockers (ARBs), calcium channel blockers, beta blockers, and diuretics were used in both groups of patients. ACEIs and ARBs were used in 23 patients treated with cytotoxic drugs and in 36 patients treated with CsA (74 vs. 78%, $p = NS$). ACEIs were used in 20 of the 23 patients (87%) of the first group and in 28 of the 36 patients of the second group (72%), whereas ARBs were used in 13 and 28% of the patients, respectively. The less frequent use of ARBs in patients treated with cytotoxic drugs is related to the fact that most of these patients were treated at a period of time when ARBs were not available. Calcium channel blockers and beta blockers were used in 8 patients (26%) of the first group and in 13 patients (28%) of the second group.

Remission of the nephrotic syndrome was defined as complete, if proteinuria was $<0.3$ g/24 h; as partial, if it was between 0.3 and 3 g/24 h, and no remission was present, if proteinuria remained $>3.5$ g/24 h. Relapse was considered, if edema and proteinuria $>3.5$ g/24 h reappeared in the patients having a remission.

The clinical outcome was assessed using the end points of doubling of baseline serum creatinine and/or ESRF during the follow-up period (48 ± 36 months). The influence of therapeutic regimen and clinical and histological parameters on the clinical course of patients was determined.
CsA Level Determination

CsA was analyzed in whole-blood samples on a TDx analyzer (Abbott Laboratories, Abbott Park, Ill., USA). The method utilizes fluorescence polarization immunoassay technology. A pretreatment step is performed on each sample to minimize interference from endogenous protein-bound fluorescence compounds. After centrifugation, the assay was performed in the sample supernatant. The CsA blood levels were determined before the intake of the drug (C0).

Statistics

Mean values ± SD were used for continuous variables. A t test was used to compare the mean values of clinical and biochemical features, and a chi-square test was used for histological data and remission rates of nephrotic syndrome. The probability of development of end points was estimated by a multivariate nonlinear probit model. This model provides estimates of the probability that a patient will reach the end point under the simultaneous effect of many independent variables. p < 0.05 was considered significant. All analyses were carried out using SPSS for windows version 14 (SPSS, Chicago, Ill., USA).

Results

Remission of Nephrotic Syndrome

Remission was observed in 39 out of the 46 patients (85%) treated with corticosteroids and CsA and in 17 out of the 31 patients (55%) treated with corticosteroids and cytotoxic drugs (p = 0.004). Complete and partial remissions were observed after 6 ± 3 months in 29% of cytotoxic treated patients and 26%, and in 63% and 22% of CsA treated patients, respectively (fig. 1).

Persistent nephrotic syndrome was observed in 14 out of the 31 patients (45%) treated with corticosteroids and cytotoxic drugs. Administration of CsA in 8 of these patients was followed by complete remissions in 2 patients and by partial remissions in 4 patients (86%). Persistent nephrotic syndrome was observed in 7 out of the 46 patients (15%) treated with corticosteroids and CsA.

Renal Function during Follow-Up and Clinical Outcomes

Doubling of the baseline serum creatinine levels during the follow-up period was observed in 19 out of the total 77 patients (25%). Twelve of them were from the CsA group and 7 from the group treated with cytotoxic drugs (26 vs. 23%, p = NS). Four patients (2 from each group) developed ESRF.

Most patients with doubling of baseline serum creatinine levels had either persistent nephrotic syndrome or multiple relapses (58 and 71%, respectively). The blood pressure of most patients remained <140/90 mm Hg, and in 70% of them it was <130/85 mm Hg at the last follow-up examination. The blood pressure during the follow-up

| Table 1. Clinical, biochemical, and histological features of the patients at presentation |
|-------------------------------------------------|-------------------------|-------------------------|
|                                                  | Corticosteroids + cytotoxic drugs (n = 31) | Corticosteroid + CsA (n = 46) | p         |
| Male/female ratio                                | 21/10                   | 34/12                   | NS        |
| Age, years                                       | 49 ± 15                 | 56 ± 16                 | NS        |
| Serum creatinine, mg/dl                          | 1.2 ± 0.6               | 1.1 ± 0.3               | NS        |
| Serum albumin, g/dl                              | 2.5 ± 0.6               | 2.4 ± 0.5               | NS        |
| Urinary protein, g/dl                            | 9.3 ± 4.7               | 7.4 ± 4.3               | NS        |
| Systolic blood pressure, mm Hg                   | 134 ± 32                | 139 ± 24                | NS        |
| Diastolic blood pressure, mm Hg                  | 82 ± 8                  | 82 ± 13                 | NS        |
| IMN stage, n (%)                                 |                         |                         |           |
| I                                                | 16 (52)                 | 24 (53)                 | NS        |
| II                                               | 7 (22)                  | 14 (30)                 | NS        |
| III                                              | 8 (26)                  | 8 (17)                  | NS        |
| Glomerulosclerosis, n (%)                        |                         |                         |           |
| No                                               | 13 (42)                 | 14 (30)                 | NS        |
| <25% of the glomeruli                            | 11 (36)                 | 28 (61)                 | NS        |
| >25% of the glomeruli                            | 7 (22)                  | 4 (9)                   | NS        |
| Interstitial fibrosis, n (%)                     |                         |                         |           |
| Absent                                           | 13 (42)                 | 15 (33)                 | NS        |
| Mild                                             | 10 (32)                 | 24 (52)                 | NS        |
| Moderate                                         | 8 (26)                  | 7 (15)                  | NS        |
period and at the last examination was 135 ± 15/81 ± 8 mm Hg and 131 ± 17/82 ± 6 mm Hg, respectively, in the patients treated with cytotoxic drugs and 135 ± 17/80 ± 8 mm Hg and 133 ± 20/79 ± 10 mm Hg, respectively, in the CsA-treated patients (p = NS). No difference in the blood pressure control was observed with the antihypertensive drugs used in the two groups of patients.

Relapses of the Nephrotic Syndrome

Relapses were observed in 21 out of 56 patients (37.5%) who showed complete (n = 9) or partial (n = 12) remission. Out of these, 16 were from the CsA group, and 5 were from the group treated with cytotoxic drugs (41 vs. 29%, p = NS). Readministration of steroids and CsA in 13 patients after relapse was followed by complete or partial remission in 7 and 5 patients (92%), respectively. Multiple relapses were observed in 6 out of 21 patients (28%).

Parameters Related to the Clinical Outcome

Firstly, the bivariate relation between each independent factor separately and the clinical outcome was examined by independent sample t test and chi-square tests. The therapeutic regimen used was not recognized as a statistically significant independent factor influencing the clinical outcome (p = 0.726). Multiple episodes of relapse (p = 0.05), glomerular sclerosis (p = 0.05), and interstitial fibrosis (p = 0.006) were identified as independent risk factors for doubling of the baseline serum creatinine level. Secondly, the multivariate relation among all variables that was significant in the aforementioned bivariate analyses and in the clinical outcome was examined by a probit model. Patients with multiple relapses had a 54% (p = 0.0059) higher risk to reach the end point than those without relapses, and patients with mild and moderate interstitial fibrosis had a 35% (p = 0.0137) higher risk to develop end points than those without fibrosis.

Side Effects

Serious side effects that needed discontinuation or change of treatment were observed in 3 patients (10%) from the cytotoxic drug group and in 2 patients (4%) from the CsA group. The adverse reactions observed in patients treated with cytotoxic drugs were bone marrow toxicity (n = 4), infections (n = 3), and proximal myopathy (n = 1), whereas the CsA-treated patients showed infections (n = 2), elevated bilirubin levels (n = 1), proximal myopathy (n = 1), and gingival hyperplasia (n = 2).

Discussion

In this study, the effects of treatment with corticosteroids and cytotoxic drugs on the remission rates of nephrotic syndrome and on the clinical course of patients...
with IMN were compared to those of treatment with corticosteroids and low-dose CsA. A higher remission rate was observed in the CsA-treated patients which was followed by less frequent adverse reactions.

Treatment of IMN continues to be a matter of debate. The combination of prednisolone with chlorambucil at three cycles for 6 months versus placebo and corticosteroids has been studied in prospective randomized trials [5, 6]. Most patients included had a normal renal function and mild histological lesions (IMN stages I and II, absence of mesangial sclerosis and tubulointerstitial injury). The combination proved more effective than placebo treatment with regard to remission of nephrotic syndrome and long-term preservation of the renal function, and it was followed by earlier remissions than after corticosteroids alone [5, 6]. Patients with renal insufficiency or mesangial sclerosis responded to treatment less frequently [6]. A higher remission rate (>80%) was observed more recently by the same authors [7] with chlorambucil and cyclophosphamide. In our study, the combination of corticosteroids with cytotoxic drugs was followed by a remission in 55% of the patients, possibly due to more severe disease with longer duration. Although the use of both cytotoxic drugs was followed by side effects, discontinuation of treatment was more often necessary with chlorambucil [7]. Similarly, discontinuation or change of treatment was more frequent in the case of cytotoxic drugs than CsA. Many physicians remain reluctant to use these drugs, especially in patients with a high probability of a spontaneous remission, but relapses are common, and chronic renal failure may develop in 30% of the patients. So, therapeutic efforts are justifiable, if remission can be achieved early and maintained for long with a less toxic regimen. However, azathioprine seems to be of no long-term benefit [8].

CsA is effective in inducing remission of idiopathic nephrotic syndrome even in cases resistant to corticosteroids or cytotoxic drugs [16]. In a randomized controlled trial [10], a 6-month course of CsA (3.5 mg/kg/day) in steroid-resistant IMN patients proved more effective than placebo in inducing remission. The use of CsA (2–3 mg/kg/day) and corticosteroids as first-line treatment in nephrotic IMN patients was followed by a remission in 85% of them [12]. The high remission rate is probably related to the longer treatment period [17], whereas the high percentage of complete remissions may be due to the use of corticosteroids and CsA instead of CsA alone, which is more frequently followed by partial remissions [13]. The effectiveness of this regimen in cases resistant to cytotoxic drugs suggests that the combination of corticosteroids with CsA is more effective than cytotoxic drugs in IMN patients. However, the use of these therapeutic regimens rather during sequential time periods than concurrently and the retrospective nature of the study represent limitations that should be confirmed in a prospective randomized trial.

Relapses of nephrotic syndrome occur in about 30% of the patients having spontaneous remission. Similar results were observed in our patients treated with cytotoxic drugs, whereas a slightly higher incidence was evident with CsA. Treatment for more than 12 months followed by gradual tapering of the dose reduces relapses that more frequently occur in patients treated with CsA alone and with C₀ serum levels <100 ng/ml [13]. It is noteworthy that readministration of this regimen after relapse was followed by remission, although some patients had multiple relapses. Most physicians use low CsA doses for long periods of time in patients with relapses. However, the drug should be used with caution in IMN patients, since progression of the stage of the disease and deterioration of histological lesions occur in most patients even after clinical remission with CsA [12]. In addition, the new formulation of CsA having a better bioavailability might be toxic even at lower doses.

Deterioration of the renal function was observed in a similar proportion of the patients from both groups. It was more frequently observed in patients with multiple relapses and in those with interstitial fibrosis and glomerulosclerosis, similar to studies on the natural history of the disease. Although adverse reactions were observed with both regimens, they were more serious with cytotoxic drugs.

In conclusion, the combination of corticosteroids and low-dose of CsA is a more effective therapeutic regimen than the use of cytotoxic drugs in IMN patients to induce remission of nephrotic syndrome. It is also followed by less severe adverse reactions. Patients with nephrotic syndrome and well-preserved renal function are the best candidates to receive this regimen as initial treatment, but it is also effective in cases resistant to cytotoxic drugs. However, randomized prospective trials are necessary in order to establish CsA as first-line treatment of nephrotic patients with membranous nephropathy.
References


