

Original Article

Cyclosporine in the Treatment of Membranoproliferative Glomerulonephritis

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Background: Therapeutic approach to patients with idiopathic membranoproliferative glomerulonephritis is still controversial. Because it is more common in developing countries, the studies about it are limited.

Methods: We used cyclosporine to treat 18 patients with membranoproliferative glomerulonephritis who were resistant to other treatment protocols such as using aspirin, dipyridamole, or steroids. All patients were treated with cyclosporine plus low-dose prednisone and were followed for an average 108 weeks.

Results: Partial or complete remission of proteinuria occurred in 94% of the patients ($P<0.01$). Relapse occurred in one (14.2%) of remitters after discontinuation of the drug. But the remainder stayed in remission to the end of the observation period. There was a 50% decrease in the baseline creatinine clearance in one patient (5.5%).

Conclusion: These results suggest that cyclosporine may be an effective therapeutic agent in the treatment of resistant idiopathic membranoproliferative glomerulonephritis. Although the response is appeared later than other types of glomerulonephritis, but a long-term decrease in proteinuria and preservation of filtration function were observed in a significant proportion of the treated patients.

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Keywords: Cyclosporine A • end-stage renal disease • membranoproliferative glomerulonephritis

Introduction

Membranoproliferative glomerulonephritis (MPGN) is an uncommon cause of glomerular disease, which in its idiopathic form primarily occurs between the ages of eight and 30 years.¹ It can be primary, or secondary to chronic infections, cryoglobulinemia, or systemic autoimmune disorders.¹⁻² The outcome is generally fair in patients with apparently idiopathic MPGN. The course is usually prolonged with a slow rate of disease progression. Up to 50 to 60% of untreated patients will progress to end-

stage renal disease within 10 to 15 years. Bad prognostic signs at presentation include the nephrotic syndrome, renal insufficiency, hypertension, and existence of crescents and tubulointerstitial disease on renal biopsy.³⁻⁴

Corticosteroids have been used more commonly in children with MPGN.¹⁻⁷ There has been no systematic evaluation of corticosteroid therapy in idiopathic MPGN in adults. Treatment of adults with idiopathic membranoproliferative glomerulonephritis (IMPGN) is often unrewarding with approximately 60% of patients progressing to end-stage renal failure within 10 years.³⁻⁴

Although children with IMPGN may respond to steroid therapy, there is no significant benefit to treat adults with IMPGN by immunosuppression. Retrospective studies have not shown any clear benefit from steroid therapy in adults, although treatment was not as prolonged as in children.⁶⁻⁸ There is probably better evidence in adults that the rate of progression of MPGN can be slowed by

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antiplatelet agents.⁹⁻¹¹

Preliminary study suggests that in the short term, the combination of mycophenolate mofetil (MMF) and prednisolone can significantly reduce proteinuria and may preserve renal function in patients with IMPGN.¹¹ In this study, five patients received MMF in combination with oral prednisolone and a significant reduction in proteinuria from a baseline of 5.09 to 1.97 g/24 hr ($P=0.003$) at six months, to 1.96 g/24 hr ($P=0.003$) at 12 months, and to 2.59 g/24 hr ($P=0.015$) at 18 months was reported.¹²

Cyclosporine is a well-known and effective immunosuppressive agent, which has been used in most solid organ transplantation and as treatment of different types of glomerular diseases.¹³ The drug-receptor complex specifically and competitively binds to and inhibits calcineurin, a calcium and calmodulin-dependent phosphatase.¹⁴ This process inhibits the translocation of a family of transcription factors and nuclear factor of activated T cells (NF-AT), leading to reduced transcriptional activation of early cytokine genes for interleukin 2, tumor necrosis factor alpha (TNF-alpha), interleukin 3, interleukin 4, CD40L, granulocyte-macrophage colony-stimulating factor, and interferon γ . It seems that this drug has some effects on the permeability of glomeruli and causes glomerular vasoconstriction.¹⁴ It has been used as treatment in different types of glomerulonephritis especially in resistant cases but not many studies about its effect on MPGN have been done.

We report a trial using cyclosporine in adults with biopsy-proven MPGN resistant to antiplatelet agents and corticosteroids.

Materials and Methods

Patients with primary MPGN were included in this study. At the entry, the mean age of the patients was 27 ± 9 years ranging from 18 – 50 years. All patients had failed to achieve a remission of proteinuria after a course of treatment with prednisone or antiplatelet agents and angiotensin-converting enzyme (ACE) inhibitors.

Exclusion criteria were serum creatinine level >2.5 mg/dL, comorbid condition with expected survival of less than two years, any serious systemic infection, secondary form of MPGN, and associated disorders requiring daily NSAIDs. Proteinuria equal or greater than 3.5 g/day was considered nephrotic. A partial remission was defined as a 50% reduction of initial proteinuria

and equal or less than 3.5 g/day with stable renal function. Complete remission was defined as proteinuria equal or less than 0.2 g/d accompanied by stable renal function.

Diagnosis

Diagnosis of MPGN was made based on the clinical and laboratory findings such as nephritic or nephrotic range proteinuria, hematuria, hypertension, serum C3 and CH50 levels, and sometimes mild renal function impairment. Renal biopsy was performed for confirmation of diagnosis.

MPGN was characterized by its peculiar histologic findings such as lobular appearance, cellular and mesangial matrix proliferation, double contoured capillary loops in light microscopy, presence of C3, IgG, or IgM deposits in immunofluorescent (IF) study, and existence of electron-dense deposits within the glomerular basement membrane and/or subendothelium and mesangium in electron microscopy.

In all the patients, the initial diagnosis was confirmed by pathologic findings in light and IF microscopy. We also had electron microscopy reports for five patients. Decreased complement level was reported in 14 patients.

Protocols

Cyclosporine-neoral (CsA-Neoral) was started at a dose of 4-5mg/kg/day (divided doses). All patients received prednisone at 0.15 mg/kg/day up to maximum of 15 mg and ACE inhibitors. The patients' clinical status and vital signs, renal and liver function tests, lipid profiles, serum creatinine, and 24-hr urine excretion rates of creatinine and protein were measured at 0, 1, 3, 6, and 12 months after starting cyclosporine. Early stop points included a confirmed rise equal or $>30\%$ in baseline serum creatinine, doubling of baseline liver enzymes, and intolerable side effects. Cyclosporine was discontinued gradually if complete remission of proteinuria was achieved.

Statistical analysis

Quantities were shown as mean \pm SD. The Student's *t*-test was used for evaluation of changes in proteinuria and creatinine before and after the study. $P<0.05$ was considered significant.

Results

Eighteen patients were included in this study.

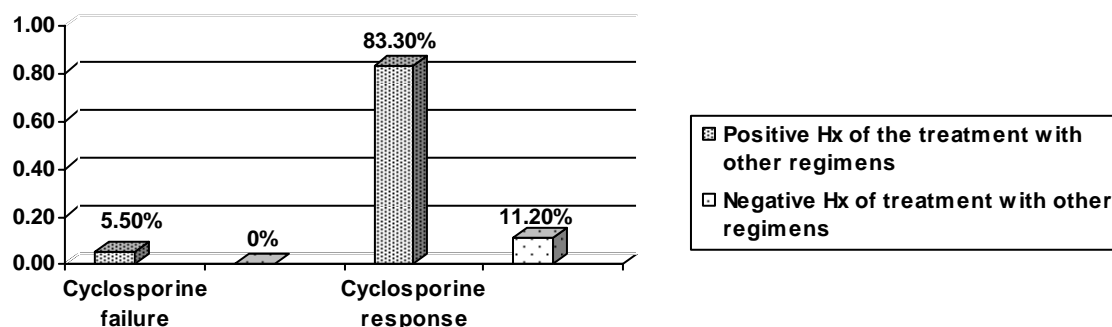


Figure 1. Response to cyclosporine in patients who did not respond to other regimens.

Of them, 16 patients (88.8%) had failed to achieve remission with other regimens.

Seventeen patients (94.5%) were responsive to cyclosporine. Twelve of responders achieved complete remission and the remainder achieved partial remission. There was failure to treatment in one patient who had been nonresponder to other regimens either. Only in this patient there was a significant decrease in renal function (Figure 1).

Duration of disease was less than one year in eight patients (44.5%), between one to two years in four patients (22.2%), and more than two years in six patients (33.3%).

Complete remission was achieved in six patients during six months, in three patients (25%) between six to 12 months, and in three patients (25%) after 12 months. The mean time for achievement of remission was 3.8 months. During the two-year follow-up, cyclosporine was discontinued in seven patients (41.1%) and only in one patient (14.2%) relapse occurred (Figure 2).

Discussion

MPGN was defined as a distinct histologic variant of glomerulonephritis. Although it was most common during the 1970s – 1980s and is now a rare finding in adults but in some countries it occurs more frequently. It has been suggested that chronic infections are responsible for the disease in many of these cases.²

Treatment of MPGN depends in part upon the underlying cause. Compared with secondary forms, the outcome is generally fair in patients with apparently IMPGN.³ The course is usually prolonged with a slow rate of disease progression.

Antiplatelet agents and corticosteroids have been evaluated in the treatment of those patients with apparently IMPGN who are at risk for progressive disease.⁶⁻⁸ There is probably better evidence in adults compared to children that the rate of progression of MPGN can be slowed by antiplatelet agents.⁸⁻⁹ Despite this short-term

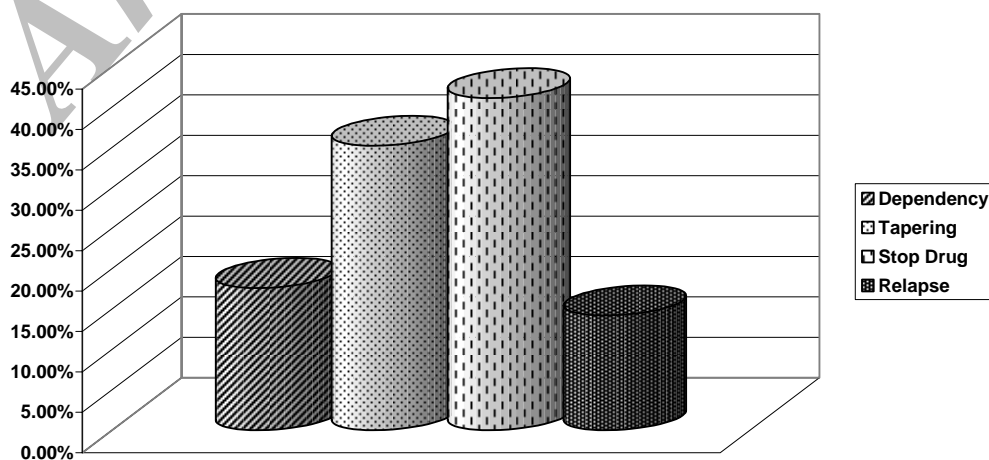


Figure 2. Result of treatment with cyclosporine

benefit, there was no difference in 10 years outcome, and these studies generally had not control groups.¹⁵

There are only limited data on the use of cytotoxic drugs in MPGN too. No benefit was observed when compared with a control group.⁹ No controlled study has been performed for evaluation of cyclosporine treatment in MPGN.

There are a few case reports about usage of this agent in MPGN but the final result of their treatment was not mentioned clearly.¹⁶ In our study, proteinuria was decreased from 4.5 ± 2.8 g/day to 0.7 ± 2.2 g/day after initiation of cyclosporine ($P < 0.01$). The mean serum creatinine level was 1.01 ± 0.6 mg/dL before treatment with cyclosporine and 1.1 ± 0.4 mg/dL after it. Only in one patient (5.5%) treatment was failed and in 66.6% of the patients, complete remission was achieved. In comparison with other types of primary glomerulonephritis, the mean time of partial remission was longer (about 3.8 months versus two months). Most of remissions occurred during the first six months of treatment and the shorter duration of disease was accompanied by more response to treatment.

Having considered that proteinuria decreased with cyclosporine treatment without any significant reduction in renal function, especially in patients who were nonresponder to other regimens or in those who had recurrence, it seems that cyclosporine can be a good choice in some patients with primary and resistant MPGN.

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