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Original Article

Cyclosporine is not inferior to cyclophosphamide in the treatment of idiopathic membranous glomerulonephritis: single centre experience

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Abstract: Objectives: Membranous glomerulonephritis remains the most common cause of adult-onset nephrotic syndrome and its management is still controversial. In our study we aimed to compare the response rates of cyclophosphamide and cyclosporine treatment during a 12-month treatment period. This study was a retrospective trial at the Nephrology Department of Numune Research and Education Hospital, Turkey. Methods: Fourty-seven patients with well-preserved renal function and we have analyzed treatment response with cyclosporine and prednisone or cyclophosphamide and prednisone. All patients were followed for an average of 12 months, and the partial and complete remission rates were assessed at 12th month with serum albumin, serum creatinin, glomerular filtration rate and 24-hour urine protein levels. Results: Fourty-seven patients (33 male and 14 female) with a mean age of 37.68±13.18 years were included in the study. 17 (36.2%) patients were in the cyclosporine group and 30 (63.8%) were in the cyclophosphamide group. Baseline characteristics of the groups were similar. Seventy-six percent of the cyclophosphamide group versus 82.4% of the cyclosporine group had a partial or complete remission of proteinuria at the end of 12 months (P=0.89). Serum albumin levels increased and proteinuria were significantly reduced in all groups (P=0.001). Conclusion: This study suggests that cyclosporine-based regimens are not inferior than cyclophosphamide in the treatment of membranous glomerulonephritis.

Keywords: cyclosporine, cyclophosphamide, membranous glomerulonephritis

Introduction

Membranous glomerulonephritis (MGN) remains the most common cause of idiopathic nephrotic syndrome. The treatment, based on immunosuppressive drugs is still controversial because of frequent spontaneous remission. However, we know that for untreated patients renal survival is less than 50% within 10 years of clinical onset [1]. In general, it has been known that older patients, males, and those with heavy persistent proteinuria were most likely to progress to renal failure and more likely to see the benefits from therapy. Corticosteroids are the basic drugs of the therapy but there are no clinical data about benefical effect of using steroids alone. The most favorable results have been obtained with cytotoxic agents. As first-line therapy, KDIGO (Kidney Disease Improving Global Outcomes) guidelines recommend alternating months of corticosteroid therapy and cytotoxic therapy (cyclophosphamide or chlorambucil) over 6 months to achieve both total and partial remissions up to 70-90% of patients [2].

The incidence of end stage renal disease (ESRD) secondary to MGN has decreased during 2000-2005 in respect of 1991-1995, according to an epidemiological study. But only 18% of patients with ESRD were on alkylating agent treatment in this group [3]. Toronto group analyzed MGN patients in two groups as conservative and immunosuppressive groups; and documented that in immunosuppressive group renal survival was >90% and 82% of patients in this group were on alkylating agent treatment [4].

Many physicians advised to delay immunosuppressive agents in MGN because of high spon-

Table 1. Baseline demographic and laboratory data of patients

Initial	Cyclophosphamide (n: 30)	Cyclosporine (n: 17)	P
Age (years)	37.37±13.54	38.24±12.90	0.831
Gender			
Female (n, %)	8 (26.7)	6 (35.3)	0.534
Male (n, %)	22 (73.3)	11 (64.7)	
Serum urea (mg/dl)	34.43±15.18	31.53±18.84	0.567
Serum creatinine (mg/dl)	0.96±0.41	0.75±0.21	0.057
Serum total proteinine (g/L)	45.70±8.18	49.47±11.61	0.200
Serum albumin (g/L)	21.13±7.04	23.76±10.18	0.354
Proteinuria (g/day)	8.47±5.48	5.68±2.84	0.057
GFR (ml/min/1.73 m^2)	100.77±29.19	112.23±27.26	0.192

Data are presented as number, mean ± SD. GFR, glomerular filtration rate.

taneous remission rates in proteinuria. But main reason in this hesitation is to avoid serious side effects of cytotoxic agents such as opportunistic infections, bone-marrow toxicity, gonadal dysfunction, or malignancy. Cancer risk associated with this therapy increased three-fold [5]. Cyclosporine (CsA) is an alternative treatment for MGN is of low to moderate quality. It is useful in cases more likely to have serious side effects with alkylating agents with a remission rate of 80% [6, 7].

There is no well powered, randomized, controlled trials that formally compare therapies of CsA to standard regimens of alkylating agents. In this study, we aimed to compare the remission rates of two different agents, CsA with cyclophosphamide.

Materials and methods

Data of patients with biopsy proven MGN, who were followed up in department of nephrology, were collected retrospectively from clinic files. Secondary forms of MGN were excluded before the treatment after clinical and laboratory investigation. All female patients were evaluated for breast cancer, cervix cancer and endometrium cancer. All male patients were evaluated for prostat cancer. Both male and female patients were evaluated for colon and rectum cancer and evaluated with low-dose CT for lung cancer. Patients were examined for hepatitis, autoimmune diseases and drug usage with a careful history and physical examination in addition to the laboratory parameters.

All patients included: a) had initial estimation of renal function and creatinine clearance, serum albumin, basal proteinuria, b) showed good compliance with at least six months of follow-up. The demographic data, age, gender, urea, creatinine, total proteins, albumin, GFR were calculated via Modification of Diet in Renal Disease (MDRD), 24-hour proteinuria levels were also recorded [8]. Almost all patients were treated with renin-angiotensin system blockers (the highest tolerable dose) as part of standard conservative treatment. We also followed up the patients conservatively for at least 6 months. Patients in immunosuppressive treatment group were selected according to recommendations of the KDIGO guidelines [2]. Patients were divided in two groups, first is the cyclophosphamide group and the second is CsA group with combination of corticosteroids in both groups.

The use of different therapeutic regimens in two groups reflects institutional treatment preferences over an 8-year period. Patients admitted to hospital between 2005 and 2008 were treated with cytotoxic drugs, whereas those admitted after 2008 were treated with CsA. Patients received 6 months of alternating cycles of cyclophosphamide at 500 mg/m^2 monthly intervals with prednisolone or 12 months of CsA concomitant with steroid therapy, at a starting dosage of 4 mg/kg/day. The initial steroid dose was 1 mg/kg/day and it was gradually tapered in 1.5-3 months. Patients in cyclophosphamide group received corticosteroid over the following six months for maintenance therapy. During the treatment and follow-up periods, all patients were examined every 2 months. Urinalysis, complete blood count, biochemical profile, and 24-hour urinary protein were recorded. The primary outcome was the number of complete (CR) or partial remissions (PR) in proteinuria at month 6. This was also assessed at month 12. Complete remission was defined as ≤0.3 g/day proteinuria with stable renal function, PR was defined as proteinuria more than 0.3 g/day but less than 50% of the basal level. Nonresponse pro-

Table 2. Comparison of parameters during 12-month period

Parameters	Initial			2 months			4 months			6 months			12 months			P**	
	Cyc	CsA	P*	Cyc	CsA	P*	Cyc	CsA	P*	Cyc	CsA	P*	Cyc	CsA	P	Cyc	CsA
Serum Tprot (g/L)	45.7± 8.18	49.47± 11.6	0.2	46.77± 8.1	54.37± 12.92	0,004	54.37±12.92	60.65±8.96	0.083	59.47±11.09	60.65± 10.96	0.726	61.8±9.9	59.35±9.9	0.421	0.002	0.001
Serum albumin (g/L)	21.13± 7.04	23.76± 10.18	0.302	22.73± 7.89	28.18± 8.64	0.033	31.7±10.95	32.53±7.15	0.781	35.67±10.13	33.41± 8.49	0.442	37.9±8.4	33.5±8.31	0.093	0.002	0.001
Proteinuria (g/day)	7 (1.6-25)	5.7 (1.19-10.2)	0,108	5.1 (1.85-16.7)	2.7 (0.24-14.0)	0.009	3.55 (0.06-13.7)	1.47 (0.16-10.9)	0.010	1.84 (0.09-14.0)	1 (0.04-7.1)	0.129	1.15 (0.13-13.6)	0.9 (0.1-6.0)	0.095	0.001	0.001
GFR (ml/ min/1.73 m^2)	104.5 (34-142)	111 (56-170)	0.249	110 (44-135)	112 (51-155)	0.603	111.5 (49-142)	101 (31-146)	0.715	117 (57-144)	106 (62-144)	0.381	117 (53-139)	100 (56-139)	0.025	0.001	0.037
Serum creatinine (mg/dl)	0.96± 0.41	0.75± 0.21	0.057	0.91± 0.29	0.78±0.24	0.147	0.85±0.26	0.9±0.39	0.623	0.79±0.20	0.83±0.26	0.592	0.77±0.21	0.88±0.27	0.113	0.002	0.031

Data are presented as mean ± SD or median (range). Cyc; Cyclophosphamide, CsA; Cyclosporine, GFR; glomerular filtration rate, Tprot; total protein. *statistical differences between groups in time intervals; **statistical differences between inital and 12th months in each group.

Table 3. Comparison of remission rates of therapy in two groups

	Cyclophosphamide n (%)	Cyclosporine n (%)	Chi squareValue	*P*
Therapy response (n, %)				
No response	7, 23.3	3, 17.7	0.209	0.727
Partial remission	16, 53.3	10, 58.8	0.132	0.478
Complete remission	7, 23.3	4, 23.5	0.000	0.627

teinuria was proteinuria, without PR or CR in two sequential measurements after 3 months of therapy.

The statistical analysis was carried out with Statistical Package for Social Sciences for Windows, version 13.0 (SPSS Inc, Chicago, Ill, USA). Normally distributed continuous data are summarized as means and standard deviations; non-normal distributions were summarized with medians and ranges (minimum-maximum). Two groups were compared with Student's t-test or Mann-Whitney U tests when necessary. Analysis of variable (ANOVA) was used for the comparison among serial changes of parameters. *P* values less than 0.05 were considered significant.

Results

Fourty-seven patients (33 male and 14 female) with a mean age of 37.68±13.18 years were included in the study. Seventeen (36.2%) patients were in the CsA group (mean age of 38.24±12.90 years and male to female ratio 11/6) and 30 (63.8%) patients were in the cyclophosphamide group (mean age of 37.37±13.54 years and male to female ratio 22/8). There were no significant differences in any of the demographic or laboratory feature at baseline between the two groups (**Table 1**). The mean duration of treatment was 6 months in the cyclophosphamide group and 12 months in the CsA group. Although protein excretion tended to be higher in patients assigned to cyclophosphamide group (mean 8.47 g/day) than in those assigned to CsA group (mean 5.68 g/day), the difference was not statistically significant. Overall cumulative incidence of remission rates were similar in both treatment arms at the end of 12th months of treatment (82.4% in CsA versus 76.7% in cyclophosphamide group, P=0.72). Proteinuria was significantly decreased and serum albumin levels were significantly increased at the end of 12th months in both groups of patients (P=0.001) (**Table 2**).

In CsA group mean eGFR levels were significantly lower compared to cyclophosphamide group at the end of 12 months (P= 0.025). But none of patients had serious renal function deterioration or hemodialysis need during this period. There were no differences in levels of proteinuria, serum albumin or serum protein in both treatment arm at the end of 12 months (**Table 2**).

Complete and PR were observed after 12 months in 23.3% and 53.3% of cyclophosphamide treated patients, and in 23.5% and 58.8% of CsA treated patients, respectively. Persistent nephrotic syndrome was observed in 7 of 30 patients (23.3%) treated with cyclophosphamide and in 3 of 17 patients (17.7%) treated with CsA (**Table 3**) (P>0.05).

Discussion

The treatment of MGN is still controversial. There are different opinions about immunosuppressive treatment procedures in this patient group. Some authors advocate not to treat these patients due to 30% spontaneous remission rate, while others suggest to treat with aggressive cytotoxic based regimen. Immunosuppressive therapies mostly popular for MGN are alkylating agents such as cyclophosphamide and chlorambucil, calcineurin inhibitors (CNI) such as CsA and tacrolimus, mycophenolate mofetil, rituximab, and adrenocorticotropic hormone (ACTH). The first-line treatment for MGN is a combination of glucocorticoids and alkylating agents, but life-threatening adverse reactions have limited the use of this treatment. CNIs are an alternative therapeutic agents to alkylating agents. Furthermore, there is a lack of randomized, controlled trials that compare all these therapies. In this retrospective study, the effects of treatment with corticosteroids and cytotoxic drugs on the remission rates of patients with MGN were compared to those of treatment with corticosteroids and CsA. A similar remission rate was observed in both treatment arms.

It was shown that CsA is an effective agent in MGN but also associated with a significant

relapse rate [9, 10]. Cumulative data indicate that CNIs are efficient treatment to induce a remission in up to 80% of patients [11-14]. Favorable responses with CNIs were detected in patients who have been unresponsive to other immunosuppressants, including alkylating agents [10, 13, 14]. A recent randomized controlled trial reported treatment with CsA for 2 years (plus low-dose prednisone) led to remissions in 80% of patients and stabilization of renal function in patients who previously failed the Ponticelli protocol [14]. De Santo et al. [15] treated the patients who failed to respond to methylprednisolone and chlorambucil with CsA and steroids, and reported 80% of remission, while an another study reported 80% of response in chlorambucil group and 37% of response in CsA group [16]. Beyond this, in a meta-analysis of six studies with 202 patients, it has been reported that treatment with CsA was not superior to conservative treatment or treatment with cyclophosphamide [17]. Although no prospective randomized head-to-head comparisons of CNIs to standard regimens of alkylating agents have been conducted, a retrospective study by Goumenos et al. compared the 6-month Ponticelli protocol (steroids plus chlorambucil or cyclophosphamide) with CsA plus steroids for 2 years and high remission rates observed with the CsA-based regimen than alkylating agents (85% versus 55%) [18]. Relapses tended to occur more often in the CsA-treated group but the differences were not significant. During a mean follow-up of 48±36 months, there were no differences in rates of doubling of serum creatinine or requirement for renal replacement therapy between groups. In our study, comparing the treatment efficacy of cyclosporine and cyclophosphamide, CR, PR and overall cumulative incidence of remission rates were similar in both groups at the end of 12th months of treatment. We also reported that in CsA group, CR rate was 23.5% and PR rate was 58.8%, lower than Fritsche [10] but higher than Meyrier [19] study. Meyrier obtained a CR in 20% and PR in 25% patients treated with CsA [19].

The initial treatment of MGN is combination of steroids and alkylating agents. Jha et al. [20] compared cyclophosphamide versus conservative treatment and at the end of 11 years, cyclophosphamide proved more effective than placebo treatment. Ponticelli et al. [21] reported higher remission rate (>80%) with chlorambucil and cyclophosphamide at the end of five years therapy. In our study we showed that in cyclophosphamide group, the rate of CR, PR and overall remission rate were 23.3%, 53.3% and 76.7%, respectively.

The antiproteinuric effect of CNIs is obvious in the late period. The majority of CR with CNIs occur after at least 6 months of therapy and the rate increases as treatment continues for >12 months for patients who show an initial response to these agents [10]. In this study, serum total protein and albumin levels increased and proteinuria levels decreased significantly from basaline at 2nd month of follow up in CsA group. At the end of 12 months of therapy, the group receiving the CsA regimen had same remission rate that observed in the 6th month. No significant differences were found in the probability of remission in extented period. Conversely, a prospective study by Naumovic et al. [14] showed that a prolonged course of CsA for 24 months have increased the cumulative remission rates from 50% at 6th months to 80% by 18 months, and CR have increased 40% from 6th months to 18th months. These outcomes are consistent with the results of studies reported by Cattran et al. [13] and Praga et al [11].

In this study we found a greater reduction of eGFR in CsA group compared with cyclophosphamide group. The efficiency of CsA can largely be due to the adjustment of haemodynamics and glomerular permselectivity [22]. This adjustment can decrease the GFR, leading to a decline in renal function. This is an expected condition as we have observed in our study. Beyond this, we have not noticed any serious renal function deterioriation. In many studies, it was documented that risk of a further decline in renal function was similar with CsA and supportive treatment groups such as in the study of Cattran et al. [23] and UK multicenter randomized trial [24].

The main problem with CNIs withdrawal is probability of relapse, occurring in 13% to almost 50% of patients within 1 year of drug withdrawal [11]. Maintenance therapy with low-dose CsA (1.4-1.5 mg/kg daily; trough levels >100 ng/ml), in conjunction with low-dose steroids (0.1 mg/kg daily), may reduce the likelihood of relapses [7]. We didn't detect any relapse dur-

ing 1 year follow up but our study was not designed to formally evaluate whether the treatment strategy have significant benefit on renal prognosis on long term period.

In summary, this retrospective study added more evidence on the use of CsA with corticosteroids in adult idiopathic MGN. This treatment is effective in inducing remission of nephrotic syndrome in these patients and improves the recent prognosis. Patients with MGN with well-preserved renal function, and elderly patients who are more prone to adverse effects of cytotoxic agents, are candiates for this regimen. Although our study is a retrospective study consisting of low patient number due to single center and not insufficient to estimate the remission rate for long term proteinuria, this study underlines similar efficiency of CsA in the treatment of MGN with cyclophosphamide with statistically significant findings.

Disclosure of conflict of interest

None.

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