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Original Article

Steroid Therapy versus Conservative Management in Patients with Focal Segmental Glomerulosclerosis and Proteinuria

Rumeyza Kazancioglu[1], Meltem Gursu[1], Savas Ozturk[1], Hatice Kucuk[2], Fuat Sar[2], Halil Yazici[3], Mehmet Kucuk[4], Vedat Celik[4], Tayyibe Saler[2] and Aydin Turkmen[3]

[1]Department of Nephrology, Haseki Training and Research Hospital, [2]Department of Internal Medicine, Haseki Training and Research Hospital, [3]Deparment of Nephrology, Faculty of Medicine of Istanbul University, [4]Department of Nephrology, Okmeydani Training and Research Hospital, Istanbul, Turkey

Abstract

Introductıon. The use of steroids in primary focal segmental glomerulosclerosis (FSGS) is controversial. It was our aim to compare steroid treatment with conservative management in primary FSGS.
Methods. Thirty six patients (22 males, 14 females) with biopsy-proven primary FSGS, older than 15 years were studied retrospectively. Patients treated by any immunosuppressive drug other than steroids were not included. Patients were divided in two groups: steroid treated and conservatively treated group. Proteinuria less than 0.3 g/day was defined as a complete remission; decrease of proteinuria by more than 50% of the basal level but still higher than 0.3 g/day as partial remission; and decrease in proteinuria by less than 50% as proteinuria resistant to treatment.
Results. Sixteen patients (44.4%) received corticosteroids (0.87±0.25 mg/kg/day methyl prednisolone equivalent) that was gradually tapered after 1.5-3 months. At the last control, 11 out of 36 patients had proteinuria resistant to treatment (2 from the steroid group), 15 had partial remission (9 from the steroid group) and 10 patients were in complete remission (5 from the steroid group). Although remission rates of both groups were not different, combined partial and complete remission rates of the steroid group were significantly higher (85.5 % vs. 55 %, p=0.035).
Conclusıon. The administration of corticosteroids is followed by partial and complete remission of proteinuria in the majority of proteinuric patients with primary FSGS and represents the treatment of choice.

Keywords: focal segmental glomerulosclerosis; outcome; proteinuria; remission; steroid therapy.

Introductıon

Focal segmental glomerulosclerosis (FSGS) is an idiopathic glomerular disease characterized histologically by segmental involvement of some of the glomeruli and clinically by proteinuria that may lead to end-stage renal failure. Contrary to secondary FSGS, presentation with nephrotic syndrome and hypoalbuminemia is more frequent whereas spontaneous remissions can frequently occur especially in patients with non-nephrotic range proteinuria and preserved renal function [1]. Serum creatinine levels at onset, degree of interstitial fibrosis and remission of proteinuria with treatment are considered as important prognostic factors [2-4].
Although there are no prospective randomized studies, patients with primary FSGS and in particular those with nephrotic-range proteinuria, are generally considered for immunosuppressive treatment. The response rate of primary FSGS to immunosuppressive therapy is differrent among various studies [2-5]. Although the definitions of partial and complete remission of proteinuria differ from one study to another, the remission rate to corticosteroids is reported between 40% and 80% [2-6]. On the other hand, there are studies showing higher probability of spontaneous remission favoring conservative management [1].
In our study we aimed to evaluate the response rate to steroid therapy in comparison to conservative treatment and to present data of patients with biopsy-proven primary FSGS.

Patıents and methods

Data of patients older than fifteen years with biopsy proven idiopathic FSGS, who were followed up in three different departments of nephrology in the same city (İnstanbul, Turkey), were collected retrospectively from outpatient clinic files between October 2000 and May 2007. All patients included: a) had initial estimation of renal function and creatinine clearance, serum albumin,

Correspondence to: Meltem Gursu, Haseki Egitim ve Arastirma Hastanesi, Nefroloji Klini-i, Haseki/Fatih/34390 Istanbul, Turkey; Phone: 05052953371; Fax: +902125294453 E-mail: meltem1401@yahoo.com

basal proteinuria, b) showed good compliance with at least two visits in the outpatient clinic or at least six months of follow-up, c) received conservative treatment with renin-angiotensin-aldosterone system (RAAS) blockers, non-dihydropyridine calcium channel blockers, statins, antiaggregant agents and/or corticosteroids.

All biopsies were performed within 3 months of the detection of urinary abnormalities and/or symptoms related to the disease. The criteria for performing a renal biopsy were proteinuria more than 1 gr/day and/or nephrotic syndrome.

Patients with FSGS secondary to decreased renal mass or renal scarring (like unilateral renal agenesis), obesity, vesico-ureteral reflux, other glomerular diseases (focal proliferative glomerulonephritis, vasculitis, lupus nephritis); those with follow-up problems with unknown outcome and discontinuation of treatment for at least four weeks; those with first degree relatives having glomerular disease; patients who were administered immunosuppressive agents other than corticosteroids as first-line therapy; patients with the collapsing variant of the disease and those with co-existing severe cardiac, pulmonary and hepatic disease or malignancy were excluded from the study.

The demographic data, age, gender, co-morbidity (diabetes mellitus, coronary artery disease, pulmonary diseases etc.) and the physical findings (including weight and height) were recorded. Fasting blood glucose, urea, creatinine, uric acid, total HDL and LDL cholesterol, triglyceride, total proteins, albumin, C-reactive protein, erythrocyte sedimentation rate, whole blood count, creatinine clearance calculated via Cockcroft-Gault formula [7], daily proteinuria levels and drugs taken by all patients were also recorded.

Patients were divided in two groups: the steroid treated group which consisted of patients who received combination of corticosteroids and conservative treatment (RAAS blockers, non-dihydropyridine calcium channel blockers, statins and antiaggregant agents) and the conservatively treated group, including those who received only conservative management.

Table 1. Baseline demographic, clinical and biochemical parameters

	All patients (n=36)	**Steroid treated group (n=16)**	**Conservatively managed group (n=20)**	**P**
Demographics				
Age (years)	36.5±16.80	30.9±16.50	41.0±16.10	NS
Gender (male/female)	22/14	10/6	12/8	NS
Smokers	13	4	9	NS
BMI (kg/m^2)	27.32±7.48	25.06±2.21	29.02±9.98	NS
Follow-up period (months)	17.8±10.10	22.6±10.00	13.9±8.70	0.012
Baseline clinical findings (number of patient)				
Edema	22	13	9	NS
Ascites	3	3	0	0.043
Hematuria	4	2	2	NS
Pyuria	3	2	1	NS
Blood pressure (mmHg)				
Systolic	129.86±29.87	122.50±22.36	135.75±34.15	NS
Diastolic	82.78±17.21	77.81±12.51	86.75±19.62	NS
Biochemical parameters				
Glucose (mg/dl)	95.05±32.56	88.12±14.48	100.60±41.41	NS
Urea (mg/dl)	33.75±26.69	31.38±30.49	35.65±23.87	NS
Creatinine (mg/dl)	1.08±0.58	0.98±0.65	1.16±0.52	NS
Uric acid (mg/dl)	5.29±1.97	4.74±1.46	5.82±2.27	NS
Total cholesterol (mg/dl)	298.15±112.80	356.50±103.61	246.28±95.78	0.03
Triglycerides (mg/dl)	235.82±154.080	292.06±173.320	185.83±118.140	0.043
HDL cholesterol (mg/dl)	51.31±15.82	52.21±18.30	50.61±14.12	NS
LDL cholesterol (mg/dl)	200±103	253±98	158.27±89.37	0.008
Total protein (g/dl)	5.57±1.21	5.04±1.16	6.01±1.10	NS
Albumin (g/dl)	2.85±0.97	2.50±0.90	3.19±0.83	0.023
Hemoglobin (g/dl)	12.80±2.14	12.97±2.21	12.66±2.12	NS
Hematocrit (%)	37.50±6.11	38.64±6.13	36.60±6.10	NS
Leukocyte (x1000/mm3)	7.5±2.30	7.9±2.90	7.3±1.70	NS
Thrombocyte (x1000/mm3)	280±881	278±968	282±830	NS
Creatinine clearance (ml/min)	83.02±34.36	76.15±34.42	89.13±35.15	NS
Daily proteinuria (mg/day)	4487.58±4426.550	5269.19±5167.740	3862.30±3753.070	NS
Erythrocyte sedimentation rate (mm/hour)	42.86±44.88	48.19±44.44	38.60±45.93	NS
CRP (mg/L)	1.35±0.49	1.47±0.52	1.25±0.45	NS

NS: not significant

The definitions below were used to interpret the response of patients to treatment. Complete response: proteinuria less than 0.3 g/day in two sequential measurements. Partial response: proteinuria more than 0.3 g/day butless than 50% of the basal level. Relapse of proteinuria: proteinuria more than 0.3 g/day in two sequential measurements in a patient with previous complete remission. Steroid resistant proteinuria: proteinuria without partial or complete remission in two sequential measurements after 3 months of 1 mg/kg/day methylprednisolone.

The statistical analysis was carried out with Statistical Package for Social Sciences for Windows, version 13.0 (SPSS Inc, Chicago, Ill, USA). Numerical variables were given as mean ± standard deviation. Two groups were compared with Student's t-test or Mann-Whitney U tests when necessary. Chi-square test with Yates correction and Fisher's exact test were used for 2X2 contingency tables when appropriate for non-numerical data. P values less than 0.05 were considered significant.

Results

General observations

Thirty-six patients (22 male and 14 female) with a mean age of 36.53±16.84 years were included in the study. Out of 36 patients, 16 (44.4% of the study population) received corticosteroids (mean age of 30.94±16.51 years and male to female ratio 10/6) and 20 patients received conservative treatment (mean age of 41.00±16.13 years and male to female ratio 12/8). The demographic, clinical and laboratory findings of patients in both groups are presented in Table 1.

The initial steroid dose was 53±17 mg/day (0.87±0.25 mg/kg/day with a range of 0.62-1.12 mg/kg/day) and it was gradually tapered in a standardized fashion after 1.5-3 months. The mean duration of treatment with steroids was 15.3±8.6 months. The mean follow-up period of patients in the steroid group was longer in comparison to that of conservatively treated patients (22.6±10.0 vs. 13.9±8.7 months; p=0.012). Edema and ascites were more common in the steroid treated patients (13 vs 9 and 3 vs 0 patients, respectively).

Systolic and diastolic blood pressure, acute phase reactant (erythrocyte sedimentation rate, C-reactive protein) levels and presence of red blood cells in the urine were not significantly different between the two groups of patients (Table 1). The number of patients who received RAAS blockers, diuretics, non-dihydropyridine calcium channel blockers, statins and antiaggregant agents was also not significantly different between the two groups (Table 2).

Table 2. Details of conservative treatment administered to both groups

	All patients (n=36)	Steroid treated group (n=16)	Conservatively managed group (n=20)	P
ACE inhibitors	22	10	12	ns
ARB	6	2	4	ns
Diuretic	5	2	3	ns
Non-dihydropyridine CCB	3	1	2	ns
Statin	27	15	12	ns
Antiaggregant agents	24	13	11	ns

CCB: calcium channel blocker, ACE: angiotensin converting enzyme, ARB: angiotensin receptor blocker

Remission of proteinuria

Complete remission of proteinuria was observed in 5 of 16 steroid treated and in 5 of 20 conservatively managed patients, partial remission in 9 and 6 patients, respectively whereas persistent proteinuria was observed in 2 of 16 steroid treated and in 9 of 20 conservatively managed patients (p=0.067) (Table 3).

Table 3. Remission of proteinuria in both groups of patients

Remission of proteinuria	Steroid treated group (n=16)	Conservatively managed group (n=20)	Total
Number of patients	2	9	11
Partial	9	6	15
Complete	5	5	10

However, a significant difference in the remission rate of proteinuria was observed between the two groups when patients were divided into those who showed complete and partial remission of proteinuria with treatment and those with persistent proteinuria despite treatment. The percentage of patients with persistent proteinuria was significantly lower in the steroid treated group (16.6% vs. 45%, p=0.035) (Figure 1).

The course of 24 hr urine protein and serum albumin levels measured every three months in the two groups of patients with follow-up more than thirty months, are shown in Figures 2 and 3. Proteinuria was significantly decreased and serum albumin levels were significantly increased during the first six months of follow-up in both groups of patients. However, increase of serum al bumin was sharper and faster in patients receiving corticosteroids and slower in the other group.

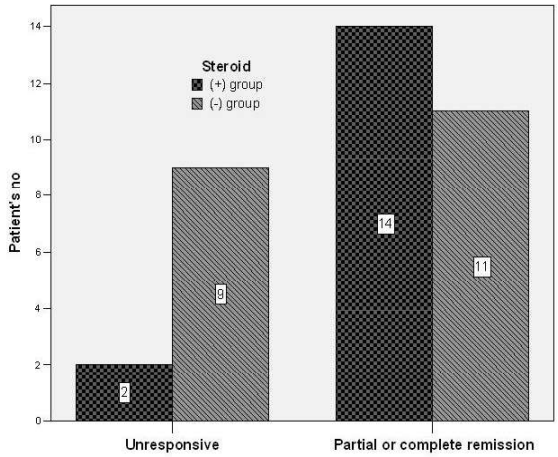

Fig. 1. Steroid treatment and remission (partial and complete) of proteinuria. Remission rate was higher in patients receiving steroid treatment (p= 0.035)

Twelve patients, (7 from the steroid treated and 5 from the conservatively treated group) with either partial remission (n=5) or no remission of proteinuria (n=7), were receiving immunosuppressive agent other than corticosteroids at the last follow-up visit.

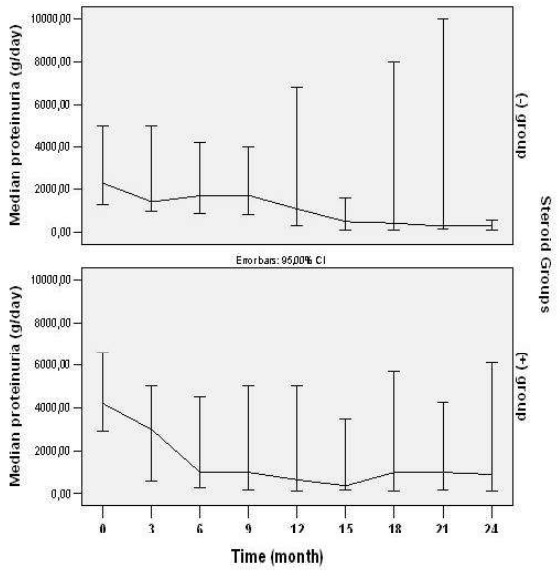

Fig. 2. Daily proteinuria levels in both groups of patients with follow-up period more than thirty months

Clinical outcome of the renal function over the follow-up period

Deterioration of renal function and need for hemodialysis was observed in 1 patient from the steroid treated group and in 2 patients from the other group during the follow-up period.

Discussion

This study showed that steroid treatment was effective in inducing partial or complete remission of nephrotic range proteinuria in patients with primary FSGS when added to conservative management. Although a rapid decline of proteinuria was observed in both steroid treated and conservatively managed patients during the first six months of the observation period, it should be noted that serum albumin level at diagnosis was lower and lipid parameters and daily proteinuria levels were higher in the steroid treated group. This suggests that patients treated with steroids had more severe disease at the beginning than the conservatively managed patients. Although the number of patients was low and the patients were selected in a non-randomized fashion, the results of this study underline the important role of corticosteroids in the treatment of patients with FSGS and significant degree of proteinuria.

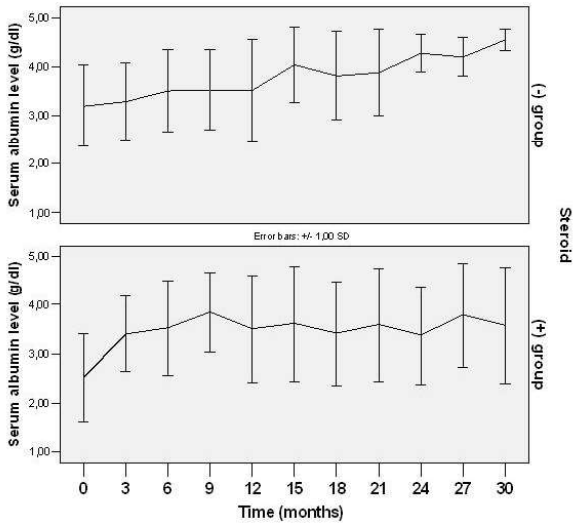

Fig. 3. The course of changes of serum albumin levels in both groups of patients

The prognosis and outcome of treated patients with primary FSGS are fairly different in the literature. There are no randomized trials comparing corticosteroids with placebo for initial therapy of primary FSGS. Stirling *et al.* [5] reported that steroid therapy was effective in achieving remission in about two thirds of patients in a retrospective study carried out in 136 patients with nephrotic syndrome due to FSGS. Cattran *et al.* [4] reported that the complete remission rate in adult patients on steroid treatment was 44% (8 of 18 patients). Moreover, Ponticelli *et al.* [7] reported complete or partial remission with steroid therapy in 42 of 80 adults with FSGS. Spontaneous remission rate in FSGS with nephrotic syndrome is not known and the results of various studies are conflicting. However, the spontaneous remission rate seems to be about 10% [2,4,8,9]. In one study, including 20 patients with primary FSGS who received no treatment, spontaneous remission was observed in 14 (70%) patients within five years. Out of 14 patients, 11 showed complete and 3 partial remission. However, 13 of 20 patients included had tip variant FSGS, which is known to have a favorable outcome [10]. Similarly, a high spontaneous remission rate of proteinuria was ob-

served in our study since 11 of 20 conservatively managed patients (55%) showed complete or partial remission. The different results observed in various studies emphasize the heterogeneity of the disease among different patients.

There is no consensus on the optimal duration of the steroid treatment. There are studies showing favorable outcome with long-term steroid therapy. Generally, at least 6-8 months of steroid treatment is proposed [7-10]. Pokhariyal *et al*. [11] reported remission rates of 75% (24 of 32 patients) and 46% (18 of 39 patients) in patient groups who had steroid therapy for more and less than 16 weeks, respectively. In our study, the only predictive factor of remission was the duration of the steroid therapy. The mean steroid dose at the onset (0.87 ± 0.25 mg/kg/day) was continued for 1.5-3 months and then tapered gradually. The relatively long duration of steroid treatment (15.3 ± 8.6 months) was also probably related to the beneficial effect of corticosteroids in inducing remission of proteinuria.

The major flaw of our study was the inability to re-examine the renal biopsies of patients in order to identify the contribution of histological lesions in the response to treatment and prognosis. Furthermore, the relatively short follow-up period of conservatively managed patients (about 14 months) may not be long enough to estimate the remission rate of proteinuria. Data of patients treated with other immunosuppressive agents are not reported since these patients were not included in the study.

Conclusıon

The addition of corticosteroids to the conservative management of patients with FSGS and nephrotic range proteinuria can increase the remission rate of proteinuria. Patients with less severe proteinuria can be managed with conservative therapy alone.

Acknowledgement. This manuscript has been seen and approved by all authors and it is not under consideration for publication elsewhere in a similar form, in any language, except in an abstract form. No author has a conflict of interest. No financial support was received in support of the study. It is a retrospectttive study and data were collected from outpatient clinic files.

Conflict of interest statement. None declared.

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