Focal and Segmental Glomerulosclerosis: Definition and Relevance of a Partial Remission

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Focal and segmental glomerulosclerosis (FSGS) is one of the most common primary glomerular diseases to terminate in ESRD. A complete remission (CR) confers an excellent long-term prognosis, but the quantitative benefits of partial remissions (PR) have not been defined. This study evaluated the rate of renal function decline (slope of creatinine clearance) and renal survival in nephrotic FSGS patients with CR, PR, or no remission. It also examined relapse rate from remission and its impact on outcome. Multivariate analysis included clinical and laboratory data at presentation and over follow-up, BP control, the agents used, and immunosuppressive therapy. The study cohort was 281 nephrotic FSGS patients who had a minimum of 12 mo of observation and were identified from the Toronto Glomerulonephritis Registry. Over a median follow-up of 65 mo, 55 experienced a CR, 117 had a PR, and 109 had no remission. A PR was independently predictive of slope and survival from renal failure by multivariate analysis (adjusted time-dependent hazard ratio, 0.48; 95% confidence interval, 0.24 to 0.96; $P = 0.04$). Immunosuppression with high-dose prednisone was associated with a higher rate of PR and CR. Relapse from PR was frequent (56%) and associated with a more rapid rate of renal function decline and worse renal survival compared with relapse-free partial remitters. Only female gender and the nadir of proteinuria during remission were associated with a sustained remission. A PR in proteinuria and its maintenance are important therapeutic targets in FSGS, with implications for both slowing progression rate and improving renal survival.

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Focal and segmental glomerulosclerosis (FSGS) is one of the most common causes of primary glomerular disease that terminates in renal failure (1,2). In most series, its 10-yr survival is in the 40 to 60% range (3–7).

Severity of proteinuria at onset and during follow-up have been associated with a poor outcome in several series (3–8). Although there is strong evidence that nephrotic patients who experience a complete remission (CR) have a very favorable prognosis (9–11), the long-term outcome in adults with only a reduction in proteinuria has seldom been reported (11,12). Despite the lack of evidence of its value as a valid surrogate for improved renal survival in FSGS, it is often reported as a positive finding in clinical studies (11–14).

This study addresses the long-term implications of a partial remission (PR) in nephrotic FSGS patients. It compares the rate of renal function decline, relapse, renal failure, and treatment effects among patients with a PR, CR, and no remission (NR).

Materials and Methods

All FSGS patients from the Toronto Glomerulonephritis Registry were considered for this study. This database began in 1974 and includes all biopsy-proven cases of glomerulonephritis from the Toronto area. Patient information at onset is compiled using a standard form, and registrars perform a periodic prospective assessment of the patients' clinical status, medications, and laboratory results (15). We reviewed all previous medical and surgical history recorded as well as results from all blood tests and radiologic evaluation to rule out potential secondary cases, such as other types of glomerulonephritis or causes such as reflux nephropathy. Only patients with definite pathologic findings of FSGS (focal and segmental consolidation of the tuft by increased extracellular matrix obliterating the capillary lumen ± hyalinosis ± glomerular adhesions with either negative immunofluorescence or only segmental IgM or C3) were considered for this study. In addition, only nephrotic FSGS patients who were older than 16 yr at presentation and had at least 12 mo of observation were included.

Parameters Collected

Demographics were gender, ethnicity, age, and body mass index (BMI) at the first clinical assessment suggestive of renal disease. Laboratory parameters collected included both initial and follow-up information on systolic and diastolic BP, weight, serum creatinine, and 24-h urine protein and creatinine. Also recorded was exposure to immunosuppressive agents and antihypertensive medications, including the angiotensin-converting enzyme inhibitor (ACEi) and angiotensin receptor blocker (ARB) classes of drugs. Finally, biopsy reports were reviewed to identify those with the features of glomerular capillary collapse associated with visceral epithelial cell hyperplasia or hypertrophy suggestive of the collapsing variant of FSGS as well as those with only features of the tip lesion variant (16).

Definitions

Creatinine clearance (CrCl) values were calculated using the Cockcroft-Gault method adjusted for body surface area (BSA) (17,18). Ne-

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phrotic patients were identified by a proteinuria value ≥3.5 g/d at any point during follow-up. A CR was defined by a proteinuria value ≤0.3 g/d. A PR was defined by a >50% reduction in peak proteinuria and to subnephrotic levels (<3.5 g/d) (13). A relapse was defined by a single proteinuria value ≥3.5 g/d after any remission. Patients who had both a PR and a CR were included only in the CR group. Time to remission was calculated from the time the patient was first defined as being nephrotic. Renal failure was defined by a CrCl <15 ml/min per 1.73 m^2, the start of dialysis, or renal transplantation. Remissions in proteinuria were not ascribed when the CrCl was ≤15 ml/min per 1.73 m^2 at that proteinuria time point. Mean arterial pressure (MAP) was defined as the diastolic plus one third of the pulse pressure. For each patient, an average MAP was determined for each 6-mo period of follow-up. Time-average MAP represents the average of every period's mean.

Immunosuppressive treatment is reported as intention to treat regardless of the duration of therapy. It was further divided into high-dose steroid therapy defined as either a minimum of 0.7 mg/kg or 50 mg daily of prednisone and into exposure to other immunosuppression regimens: >10 mg/d of prednisone, 1.5 mg/kg per d of azathioprine or cyclosporine, 1 mg/kg per d of cyclophosphamide, or 1000 mg/d of mycophenolate mofetil in single or combined therapy. Therapy with ACEi or ARB is presented as any exposure to either or both classes of agents.

Statistical Analyses

Normally distributed variables were expressed as mean ± SD and compared using *t* test, one-way ANOVA, or Pearson test. Nonparametric variables were expressed as median and range and compared using either Mann-Whitney or Kruskal-Wallis test. Categorical variables were expressed in percentages and compared using χ^2 test.

The rate of renal function decline (slope of CrCl) and renal failure were the two definitive outcomes used to validate PR as a valid surrogate for outcome in FSGS. The slope was determined by fitting a straight line through the calculated CrCl using the principle of least squares. This was plotted and visually examined in each patient. Periods of reversible acute renal failure defined as a rapid reduction and recovery in CrCl of ≥40% within 1 mo were censored.

Univariate analysis followed by multiple linear regression was used to determine independent explanatory variables of slope. Only variables that were associated by univariate analysis were included in a multivariate model.

Survival analysis was performed to test the association between renal failure and each parameter collected. Survival times for each patient were obtained from first clinical assessment suggestive of renal disease to last follow-up. Univariate comparisons of renal survival were done by Kaplan-Meier curves and Cox regression. A multivariate model using only the variables associated by univariate analysis was constructed to determine independent variables associated with this outcome. Because remissions were time-dependent variables, *i.e.*, were not present at onset but appeared during follow-up, our Cox proportional hazard model was repeated using time-dependent expressions of these variables to account for the survival time of patients before the event to confirm that any survival benefit seen with remission is accounted for by the time after remission.

Different methods of variable entry (backward or block entry) and testing models with clinically relevant variables not associated by univariate analysis were also examined to determine whether the interaction between our variable of interest (PR) and outcome (slope and renal failure) was congruent (19). We also studied PR defined by various nadirs in proteinuria.

Patients with PR were compared with those with CR and NR to identify variables that predicted the type of remission. This analysis used only information preremission for PR and CR. Finally, the impact of relapse from PR was evaluated.

All *P* values were two-tailed, and values <0.05 were considered statistically significant. Confidence intervals (CI) included 95% of predicted values. Analyses were carried out using SPSS software (version 11; SPSS Inc., Chicago, IL).

Results

Patient Selection

A total of 528 patients had a diagnosis of primary FSGS and clinical information available in the Toronto Glomerulonephritis Registry from 1974 to the end of March 2003. Exclusions were 96 patients who were younger than 18 yr at presentation, nine with probable secondary FSGS on detailed review, 13 with neither proteinuria nor weight measured, and 49 with <12 mo follow-up. In the remaining 361 patients, 80 were never nephrotic and 281 were nephrotic at some time during their follow-up. The latter cohort is the subject of this report.

Cohort Description

The patient's baseline characteristics, follow-up, and outcomes are summarized in Table 1. The average age at presentation was 43 ± 16 yr with a predominance of men (66%) and whites (70%) and a small percentage of black patients (9%). Seventy-three patients reached renal failure, 10 died of causes not associated with renal failure, and 68 were still followed as of the end of March 2003. A total of 130 patients had no clinical information recorded since March 2000 and were considered lost to follow-up. The median duration of observation in the latter group was 61 mo; their average slope was −0.39 ± 0.76 ml/min per 1.73 m^2/mo compared with −0.29 ± 0.45 ml/min per 1.73 m^2/mo in those who were still followed by the registry (NS, *t* test). Overall, 55 patients had at least one CR, 117 had a PR with a nadir proteinuria after remission of 1.2 g/d (0.33 to 3.49), and 109 had NR.

Seventy-one patients had their renal biopsy >12 mo after the baseline assessment. These patients had a median initial proteinuria of 3.0 g/d (0.2 to 23.0) as opposed to 5.0 g/d (0.2 to 98.3) in the remaining patients ($P < 0.001$, Mann-Whitney). They were otherwise comparable in regard to baseline variables and outcome. In addition, 90 of 281 had a first proteinuria value <3.5 g/d and developed nephrotic-range proteinuria after a median of 28 mo (range, 1 to 292 mo). Again, these patients were otherwise comparable to the rest of the cohort and had a similar rate of renal function decline and renal failure.

Predictors of the Rate of Renal Function Decline and Renal Survival

Clinical and laboratory variables at onset and over follow-up were tested for association with either the rate of renal function decline or renal survival. The univariate determinants of slower progression (flatter slope) were a BMI >27 kg/m^2; lower initial proteinuria; and time-average BP, PR, CR, and ACEi or ARB exposure (Table 2). The slope in those with a PR was significantly flatter than in the NR group (−0.47 ± 0.65 *versus* −0.88 ± 1.00 ml/min per 1.73 m^2/mo; $P < 0.001$). By multivariate analysis, severity of proteinuria at onset, BMI, time-average BP,

Table 1. Baseline characteristic and outcome of 281 nephrotic FSGS patients[a]

At onset	
age (yr)	43 ± 16
gender (% female)	34
ethnicity (%)	
white	70
black	9
Asian	11
other	10
BMI	27 (15–49)
MAP (mmHg)	107 ± 15
CrCl (ml/min per 1.73 m^2)	73 ± 31
Proteinuria (g/d)	4.7 (0.2–98.3)
Follow-up	
duration of follow-up (mo)	64 (12–346)
MAP (mmHg)	101 ± 10
peak proteinuria (g/d)	7.2 (3.5–98.3)
immunosuppression[b] (%)	
high-dose corticosteroids	50
cytotoxic	19
cyclosporin	12
any form	66
ACEi or ARB therapy (%)	54
Outcomes	
remission (%)	
CR/PR/NR	20/41/39
rate of renal function decline[c]	−0.54 ± 0.83
renal failure (%)	26

aBMI, body mass index; MAP, mean arterial pressure; CrCl, creatinine clearance; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CR, complete remission; PR, partial remission; NR, no remission.

[b]One patient received plasmapheresis.

[c]Measured as change in slope of CrCl (ml/min per 1.73 m^2/mo).

PR, and CR independently predicted slope ($R^2 = 0.25$; standardized $\beta = 0.22$ and 0.40 for CR and PR, respectively; $P < 0.001$ for both).

The univariate determinants that predicted better renal survival at presentation were a higher initial CrCl, a BMI >27 kg/m^2; younger age; and, during follow-up, PR, CR, lower time-average MAP, and exposure to ACEi or ARB treatment (Figure 1, Table 3). Multivariate Cox regression identified CrCl and BMI at onset, PR, and CR as independent predictors (Table 3). The adjusted time-dependent hazard ratio of renal failure for PR in reference to NR was 0.48 (95% CI, 0.24 to 0.96; $P = 0.04$). We also repeated these analyses without using time-dependent variables and found an adjusted hazard ratio for PR of 0.23 (95% CI, 0.12 to 0.44; $P < 0.001$). Using different methods of entry of variables into the models for both multivariate linear and Cox-proportional regressions and controlling for variables not predictive by univariate analysis (*e.g.*, race) did not alter the statistically significant association between PR and outcomes.

We also examined the difference in outcome between PR patients who reached a minimum proteinuria <1 g/d ($n = 43$), between 1 and <2 g/d ($n = 48$), and between 2 and <3.5 g/d ($n = 26$). The renal survival was not statistically different among these three groups, but the rate of renal function decline was slower with a lower proteinuria nadir (−0.29 ± 0.36, −0.52 ± 0.71, and −0.69 ± 0.83 ml/min per 1.73 m^2 in the low, mid, and high nadir groups, respectively; $P = 0.01$, trend test). These three groups had a similar delta in terms of reduction in proteinuria: The peak to nadir was −6.0 g/d (−2.6 to −27.4) in those who reached a PR with a nadir <1 g/d, −5.3 g/d (−2.0 to −17.3) in those with a nadir between 1 and <2 g/d, and −5.8 g/d (−2.3 to −95.8) in those who reached between 2.0 and <3.5 g/d (NS, Kruskal-Wallis). Renal survival in the high remission nadir group still remained superior to the NR patients (data not shown). Finally, within the NR group, the patients who had a 50% reduction in proteinuria but did not reach <3.5 g/d ($n = 19$) did not have a better renal survival or slower rate of progression compared with the rest of the NR group (data not shown).

Predictors of a PR

Patients with PR were compared with CR and NR groups to identify predictors of this outcome (Table 4). Compared with NR, patients with a PR had a higher proportion exposed to high-dose prednisone and maintained a lower preremission MAP despite similar antihypertensive medication. When compared with CR, the PR group had lower proteinuria at onset, had a lower percentage exposed to high-dose prednisone, and maintained a higher follow-up MAP despite more antihypertensive drugs. Race was not identified as a predictor, *i.e.*, blacks had a similar rate of remission as whites.

Relapse from a PR

Of the 117 PR patients, 47 never relapsed, 61 relapsed after a median time of 7 mo (range, 1 to 66), and nine had no proteinuria measurement after their remission. Thirty-two of the relapsers (32 of 61) had a second remission either spontaneously ($n = 15$) or after immunosuppressive therapy ($n = 17$), and 19 of these (19 of 32) had multiple relapses and remissions. The median maximum proteinuria during the first relapse was 6.5 g/d (3.8 to 22.8), a peak similar to that seen before remission (Table 1). Duration of follow-up after remission was 44 mo (4 to 207 mo) in relapsers compared with 30 mo (1 to 164 mo) in nonrelapsers ($P = 0.01$, Mann-Whitney). Male gender and the nadir in proteinuria in remission were significantly associated with the risk of relapse: 64% of men *versus* 41% of women relapsed ($P = 0.03$, χ^2), and the nadir proteinuria after remission was 1.6 (0.7 to 3.4) in those who relapsed *versus* 0.9 (0.4 to 2.4) in the nonrelapsers ($P < 0.001$, Mann-Whitney). A relapse from a PR was significantly associated with outcome. Patients who had a PR and relapsed had an overall rate of renal function decline significantly worse than those who did not (−0.59 ± 0.69 *versus* −0.31 ± 0.61 ml/min per 1.73 m^2/mo; $P = 0.03$, t test), and it was associated with a higher risk for renal failure compared with the PR group without a relapse (time-dependent hazard ratio adjusted for the clearance at the time of relapse, 2.90; 95% CI, 1.09 to 7.72; $P = 0.03$). However, patients

Table 2. Univariate and multivariate determinants of slope (ml/min per 1.73 m^2/mo)[a]

	Univariate		Multivariate	
	Mean/Standardized β	*P*	Standardized β	*P*
Presentation				
proteinuria (g/d)	−0.17	0.005	−0.25	<0.001
BMI[b]				
low	−0.44 ± 0.85	0.03	–	NS
mid	−0.70 ± 1.10	High<Mid	Reference	
high	−0.37 ± 0.55		0.18	0.006
Follow-up				
MAP	−0.24	<0.001	−0.20	0.003
remission				
NR	−0.88 ± 1.00	<0.001	Reference	
PR	−0.47 ± 0.65	NR<PR<CR	0.22	0.003
CR	−0.02 ± 0.36		0.40	<0.001
ACE				
yes	−0.44 ± 0.53	0.03	–	NS
no	−0.67 ± 1.07			

[a]Gender, ethnicity, age, CrCl, and MAP at onset as well as immunosuppressive therapy were not predictive of slope.
[b]BMI divided into three categories low (BMI <20), normal (BMI 20 to 27), and high (BMI > 27).

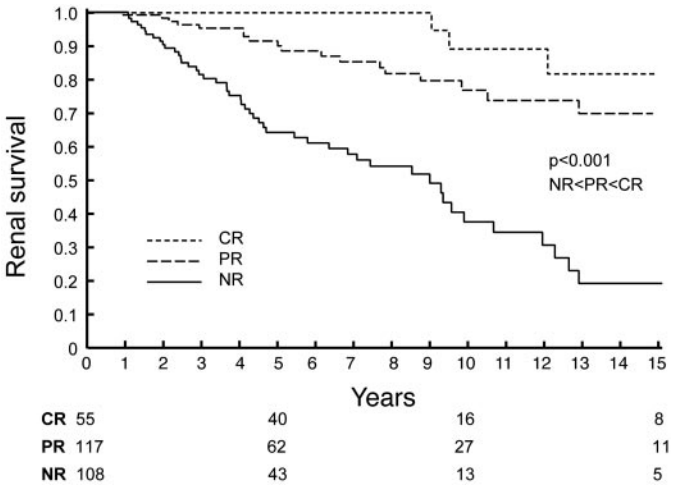

Figure 1. Survival from renal failure in patients with complete (CR), partial (PR), and no remission (NR). One patient in the NR group had a creatinine clearance <15 ml/min per 1.73 m^2 at presentation and was excluded from the survival analysis.

who had a PR and relapsed still had a better renal survival than the NR group (Figure 2).

Benefits of ACEi or ARB Therapy

The median time from first clinical assessment to the introduction of these drugs was 17 mo (0 to 289 mo), and during that period, patients had lost an average 8 ± 20 ml/min per 1.73 m^2 ($P < 0.001$, paired *t* test). The use of ACEi or ARB therapy was associated with a slower progression and a better renal survival by univariate analysis but not by multivariate linear regression or time-dependent Cox regression (Tables 2 and 3).

CR

A total of 55 patients had a CR, 20 relapsed after a median time of 20 mo (range, 4 to 112), six had no proteinuria measurement after their remission, and 29 never relapsed, although three of these developed a minor relapse (proteinuria between 1 and <3.5 g/d after their CR). Three patients in the CR group progressed to renal failure. On closer examination, one relapsed and did not remit a second time, and the other two patients had an adjusted CrCl of 25 and 40 ml/min per 1.73 m^2 when their proteinuria was documented as ≤0.3 g/d and both slowly progressed to renal failure after 7 and 8 yr, respectively. Six of 55 patients experienced a CR without immunosuppressive treatment. These patients had a median peak proteinuria of 4.2 g/d (3.8 to 4.8) in contrast to the rest of the cohort, whose peak was 9.9 g/d (4.0 to 41.0).

Histology Findings

We reviewed the pathology reports of all patients. Twenty-nine biopsies had visceral epithelial cell hyperplasia or hypertrophy, and 14 had coexisting capillary wall collapse in that area. When we examined these 29 cases, there was a disproportionate percentage of black origin (29%). Overall outcome was 14 NR, 10 PR, and five CR, with eight of 14 of the NR, one of 10 of the PR, and zero of 5 of the CR progressing to renal failure. If we consider those with both collapse and hyperplasia, 36% were of black origin and outcome was six NR, four PR, and four CR, with one patient (NR) progressing to renal failure. Five patients had a clear histologic description of a tip lesion as the only lesion of FSGS seen on light microscopy. None of these progressed to renal failure.

Patients Who Were Followed for Less Than 12 Months

A total of 49 patients had <12 mo of follow-up. Eight of this group had a fall in clearance >30 ml/min per 1.73 m^2 during

Table 3. Univariate and multivariate determinants of renal failure[a]

	Univariate		Multivariate	
	Hazard Ratio (95% CI)	*P*	Hazard Ratio (95% CI)	*P*
Onset				
CrCl (ml/min per 1.73 m^2)	0.97 (0.96–0.99)	<0.001	0.97 (0.95–0.98)	<0.001
BMI[b]				
low	0.73 (0.17–3.05)	NS	1.12 (0.25–5.06)	NS
normal	1		1	
high	0.39 (0.21–0.71)	0.002	0.35 (0.19–0.65)	<0.001
age (yr)	1.02 (1.01–1.04)	0.002	1.01 (0.98–1.07)	NS
Follow-up				
MAP (mmHg)	1.04 (1.01–1.06)	0.009	1.02 (0.98–1.07)	NS
remission				
NR	1		1	
PR	0.27 (0.16–0.45)	<0.001	0.48 (0.24–0.96)[c]	0.04
CR	0.07 (0.02–0.21)	<0.001	0.23 (0.07–0.77)[c]	0.02
ACEi or ARB therapy	0.43 (0.27–0.67)	<0.001	0.85 (0.46–1.57)[c]	NS

[a]Gender, ethnicity, proteinuria, and MAP at onset as well as immunosuppressive therapy were not predictive of renal survival by univariate analysis. CI, confidence interval.
[b]BMI divided into three categories low (BMI <20), normal (BMI 20 to 27), and high (BMI > 27).
[c]Expressed as a time-dependent variable. For PR and CR, the multivariate analysis used clearance at time of remission.

the follow-up period (seven NR and one PR). Five of these patients had a biopsy with epithelial cell hyperplasia accompanied by capillary collapse. Eight others had ESRD at time of biopsy.

Discussion

The long-term outcome in FSGS has been associated with the level of initial proteinuria and creatinine clearance, tubulointerstitial disease on histology, and CR (3–8,20). Although a partial reduction in proteinuria has also been linked with an improved outcome, the definitions used have varied and the description of this cohort has been very limited (11,12). This analysis of FSGS patients from the Toronto Glomerulonephritis Registry was undertaken to determine whether PR in proteinuria was a valid surrogate end point predictive of both survival from renal failure and the rate of progression of renal disease. This review included 281 patients with a median follow-up of >5 yr, and although 124 of the cohort were lost to follow-up, this was only after 5 yr of observation and the majority of them were nonnephrotic at their last observation point.

We reviewed all of the clinical, laboratory, and histologic information to ensure that patients had primary FSGS. Although we did find nine secondary cases, it is possible that others were missed. Such misclassification is unlikely to have an impact on the main purpose of this study, which is to quantify the benefits associated with a partial reduction in proteinuria. We excluded patients who had <12 mo follow-up, because small variations in creatinine can have an important impact on the slope estimation if the points used for linear regression are close together. However, because it is recognized that FSGS can follow a very malignant course, we reviewed all of our cases with a shorter follow-up and found eight patients who lost ≥30 ml/min per 1.73 m^2 within 1 yr, and only one of these experienced a PR. Five of these patients had features of the collapsing variant FSGS, supporting the poor prognosis associated with this histology. At the other extreme, five patients had a clear histologic description of a tip lesion as the only lesion of FSGS seen on light microscopy. Because this description was not commonly reported or labeled as a specific lesion before 1990, it is possible that other cases existed and were not reported as such. Because the number was small, these cases were included in our cohort.

The primary thrust of the study was to examine outcome in those who did achieve a PR, regardless of their histology or treatment. We found that in addition to a CR, achieving a PR was independently associated with a slower rate of renal function decline and a reduced risk for renal failure. We deliberately did not include stable creatinine in the definition of PR to avoid introducing a bias that would inevitably lead to a greater renal survival in that group because stable renal function and renal survival are clearly strongly associated. However, we did exclude the diagnosis of PR once the CrCl permanently dropped below 15 ml/min because proteinuria is often reduced at such low GFR. We also found by univariate analysis that BP and ACEi or ARB therapy were associated with our main outcomes, but the impact of either a PR or a CR overwhelmed these in the multivariate analysis (21,22). We used the same definition of PR as in our trial (13) and confirmed that a more clinically meaningful benefit is achieved when the 50% reduction in proteinuria is combined with a nadir <3.5 g/d. We further found that the nadir proteinuria in the subnephrotic range in the PR group correlated with the rate of renal function decline. Whether

Table 4. Comparison of CR, PR, and NR[a]

	NR	PR	CR	*P*	*Post Hoc*
N	109	117	55		
At onset					
gender (% female)	29	32	45	NS	
ethnicity (% white/black/Asian/other)	75/8/8/9	66/11/9/13	67/8/17/8	NS	
age	45 ± 17	42 ± 16	40 ± 16	NS	
BMI	27 (15–47)	27 (17–49)	26 (18–45)	NS	
MAP (mmHg)	108 ± 15	107 ± 15	104 ± 16	NS	
CrCl (ml/min per 1.73 m^2)	67 ± 30	76 ± 32	77 ± 30	NS	
proteinuria (g/d)	4.0 (0.4–19.6)	4.7 (0.2–98.3)	6.6 (0.2–41.0)	<0.001	NR,PR<CR
Follow-up					
duration of follow-up (mo)	50 (12–273)	64 (12–346)	93 (14–315)	<0.001	NR<PR<CR
time to remission[b] (mo)	–	12 (1–153)	14 (2–197)	NS	
peak proteinuria[c]	7.5 (3.5–43.5)	6.9 (3.5–98.3)	7.2 (3.8–41.0)	NS	
MAP[c] (mmHg)	104 ± 11	101 ± 8	96 ± 8	<0.001	NR>PR>CR
antihypertensive medications[c] (*n*)	1.1 (0–4.2)	1.3 (0–3.8)	0.8 (0–2.9)	<0.001	NR,PR>CR
immunosuppression[c] (%)					
high-dose corticosteroids[c]	33	49	75	<0.001	NR<PR<CR
cytotoxic[c]	15	11	17	NS	
cyclosporin	9	11	8	NS	
any form	51	66	89	<0.001	NR<PR<CR
ACEi or ARB therapy[c] (%)	43	50	31	NS	
Outcome					
slope (ml/min per 1.73 m^2/mo)	−0.88 ± 1.00	−0.47 ± 0.65	−0.02 ± 0.36	<0.001	NR>PR>CR
relapse[d] (%)	–	56	41	NS	
renal failure (%)	45	18	6	<0.001[e]	NR>PR>CR

[a]Normally distributed variables (expressed as mean ± SD) are compared using one-way ANOVA with *post hoc* analysis using the least significant difference method for significant results. Nonparametric variables (expressed as median and range) are compared using Kruskal-Wallis with *post hoc* analysis using the Mann-Whitney test for significant results. Categorical variables were expressed in percentage and compared using χ^2 test.
[b]Measured from first nephrotic measurement.
[c]Information from first clinical assessment up until remission for PR and CR groups.
[d]Patients with no proteinuria measurements after remission were excluded from the denominator.
[e]Log-rank test.

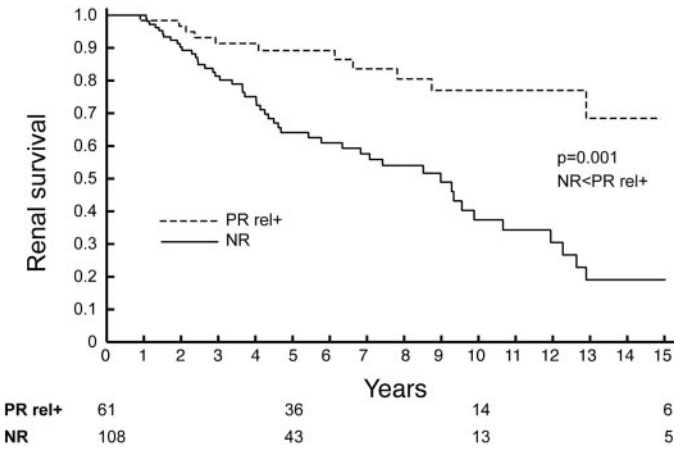

Figure 2. Survival from renal failure in patients with NR and a PR with a relapse. One patient in the NR group had a creatinine clearance <15 ml/min per 1.73 m^2 at presentation and was excluded from the survival analysis.

further immunosuppressive therapy or high-dose ACEi and/or ARB therapy is warranted to gain this additional benefit cannot be answered by this study, but these findings suggest that lower nadir proteinuria targets should be considered important outcomes in future studies.

BMI was also found to be independently associated with a better renal survival and a slower rate of renal function decline. Studies have suggested that obesity might be an important risk factor for progression of renal disease (23,24). It is interesting that a case-control study from a large cohort of FSGS patients did find differences in clinical presentation (less nephrotic) and a better outcome in obese patients compared with those with normal BMI (25). It may be that the pathogenesis of the disease is different in obese patients with perhaps a greater role for hemodynamic and less for immunologic factors in their disease progression (23).

Our study found a greater proportion of patients who were exposed to high-dose prednisone in the PR group (before remission) compared with NR patients and an even higher pro-

portion in the CR group, suggesting a relationship between exposure to these drugs and outcome. Studies on immunosuppressive treatment of FSGS have been sparse and centered on high-dose prednisone, cyclosporine, or cytotoxics (10,13,26–33). Although our findings do support the association between high-dose corticosteroid therapy and CR or PR, it is underpowered in regard to any conclusions about the benefits of other immunosuppressive agents. We recognize the many deficits of ascribing a value of treatment in this type of data analysis but have included it knowing the intense interest in this area. Our major point, however, remains not how to get a PR but the clinical relevance of achieving this goal.

There was a high rate of relapse and subsequent remissions after PR. Those who relapsed from a PR had a significantly faster rate of renal function decline and lower renal survival than those who never relapsed. This emphasizes the importance of maintaining non–nephrotic-range proteinuria. It also raises the issue of maintenance therapy rather than targeting complete withdrawal of treatment after a short exposure period, especially when the remission is only partial. It is evident that FSGS is more a pattern of injury than a specific disease. Recent findings have identified multiple genetic mutations coding for different proteins involved in the slit diaphragm that lead to heavy proteinuria and a histologic picture similar to idiopathic FSGS (34), and some of these cases could be included in our cohort. Nevertheless, the percentage of adult nephrotic patients with FSGS caused by these mutations is currently unknown; these markers are not readily available; and their capacity to predict outcome better than clinical variables such as renal function, proteinuria, and BP has not been demonstrated. Two other factors have been associated with a poor outcome: Patients of black origin and the histologic features of collapsing glomerulopathy (1,35–37). Although these factors were not common in our cohort compared with many centers in the United States, their presence did not preclude remission, leaving the issue of to treat or not to treat dependent on the specifics of each case.

Exposure to ACEi or ARB therapy was associated by univariate analysis with a slower progression (flatter slope) and improved renal survival, but these effects were lost by multivariate analysis. Certainly, randomized trials have indicated a specific renal benefit with these drugs in nondiabetic proteinuric renal disease beyond BP control (38). Possible explanations for not finding this in our study are multiple. Many patients in this review predated the availability of these classes of drugs or had them available only at the end of their disease course. Our analyses do not account for the loss of clearance before their initiation, the interaction with the severity of proteinuria, or the duration and intensity of therapy. Perhaps most important, PR and CR are such strong determinants of renal survival and rate of progression that variables that are less strongly associated with this outcome are eliminated after multivariate analysis.

The CR group presented with a higher initial proteinuria than the PR and NR groups. This may suggest that a more explosive onset is associated with a higher response rate to therapy, but an alternative explanation is that patients with severe symptoms from heavy proteinuria are more likely to receive treatment. The greater proportion in the CR group who received high-dose corticosteroids supports this notion. Also of interest was that six of 281 patients achieved a CR without immunosuppressive therapy. These had a relatively low peak proteinuria contrary to the others, and perhaps they represent another causative variant. This study has shown that a PR is a valid and important therapeutic goal for clinician to target because its achievement and maintenance are strongly correlated with both a reduction in the rate of renal disease progression and a better renal survival.

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