# Can Prolonged Treatment Improve the Prognosis in Adults With Focal Segmental Glomerulosclerosis?

Claudio Ponticelli, MD, Margarita Villa, MD, Giovanni Banfi, MD, Bruno Cesana, MD, Claudio Pozzi, MD, Antonello Pani, MD, Patrizia Passerini, MD, Marco Farina, MD, Claudio Grassi, MD, and Ambrogio Baroli, MD

• **Eighty nephrotic adults with focal segmental glomerulosclerosis (FSGS) and plasma creatinine lower than 3 mg/dL were given corticosteroids (53 patients) or immunosuppressive agents (27 patients) for a median of 16 and 75 weeks, respectively. Forty-two patients responded with complete remission (29 patients, 36%) or partial remission (13 patients, 16%). Twenty-six patients who did not respond were treated again. Two patients obtained complete remission and 13 partial remission. The probability of remission was associated with treatment with corticosteroids (*P* = 0.0001; RR, 3.93; 95% CI, 2.00 to 7.72), absence of arterial hypertension (*P* = 0.0023; RR, 2.59; 95% CI, 1.41 to 4.79), and a percentage of hyaline glomeruli lower than 5% (*P* = 0.0152; RR, 2.04; 95% CI, 1.15 to 3.64). The probability of being alive at 110 months without doubling of plasma creatinine was 69%. The risk of renal insufficiency was correlated with mesangial proliferation (*P* = 0.0025; RR, 5.50; 95% CI, 1.82 to 16.60) and with interstitial fibrosis (*P* = 0.0231; RR, 4.44; 95% CI, 1.23 to 16.08) at initial biopsy. Considering partial or complete remission as a time-dependent variable, only the lack of remission (*P* = 0.0027; RR, 7.23; 95% CI, 1.98 to 26.33) and mesangial proliferation (*P* = 0.0069; RR, 4.59; 95% CI, 1.52 to 13.88) were correlated with renal failure. Major side effects were observed in 11 patients (5 infections, 1 peptic ulcer, 2 diabetes, 3 neoplasias). This study shows that 70% of nephrotic adults with FSGS may obtain complete or partial remission and maintain stable renal function for about 10 years when given a prolonged therapy with corticosteroids or immunosuppressive drugs.**
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**INDEX WORDS: Focal segmental glomerular glomerulosclerosis; nephrotic syndrome; glomerulonephritis; corticosteroids; immunosuppression.**

FOCAL AND SEGMENTAL glomerular sclerosis (FSGS) is a primary glomerular disease that usually progresses to renal failure. Approximately 50% to 70% of adults with FSGS and an associated nephrotic syndrome either die or need regular dialysis within 10 years of clinical onset.[1-4]

FSGS is considered to be refractory to treatment. Two reviews of the literature showed that only 15% to 25% of adults obtained a complete remission of proteinuria with corticosteroids or immunosuppressive agents.[5,6] Most patients had been treated, however, for short periods, namely, 2 to 3 months. Better results were observed when corticosteroids and/or immunosuppressive agents were given for more prolonged periods.[7-10]

In this study, we retrospectively reviewed the outcome of 80 white adults with FSGS and a nephrotic syndrome at presentation to evaluate whether prolonged treatment with corticosteroids or immunosuppressive agents could modify the prognosis of this severe disease and to find which factors could predict the outcome for treated patients over the long term.

## PATIENTS AND METHODS

This was a retrospective collaborative study. Patients had been followed up by several different units cooperating together for several years. For each patient, the treatment and its modifications over the follow-up were discussed and agreed on in regular meetings among the participating units.

### *Patients*

We reviewed all patients seen in the participating units between January 1979 and January 1997 who met the following criteria for inclusion: adult age (older than than 16 years), a biopsy-proven diagnosis of FSGS, and a proteinuria of 3 g/d or greater on at least 2 consecutive measurements. Criteria for exclusion were patients younger than 16 years at biopsy, those with a stable plasma creatinine higher than 3.0 mg/dL (or 264 µmol/L) at presentation, and those

*From the Divisione di Nefrologia e Dialisi, IRCCS Ospedale Maggiore di Milano; the Laboratorio Epidemiologico, IRCCS Ospedale Maggiore di Milano; Divisione di Nefrologia e Dialisi, Ospedale Provinciale di Circolo, Lecco; Divisione di Nefrologia e Dialisi, Ospedale Regionale "S. Michele G. Brotzu," Cagliari; Divisione di Nefrologia e Dialisi, Ospedale Provinciale Maggiore, Lodi; Divisione di Nefrologia e Dialisi, Ospedale Provinciale Predabissi, Melegnano; and the Divisione di Nefrologia e Dialisi, Ospedale Provinciale G. Fornaroli, Magenta, Italy.*

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*Address reprint requests to Claudio Ponticelli, MD, Divisione di Nefrologia e Dialisi, IRCCS Ospedale Maggiore di Milano, Via Commenda 15, 20122 Milano, Italy. E-mail: croffl@polic.cilea.it*

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with a postbiopsy follow-up shorter than 1 year. No patient showed progression to end-stage renal failure before the first year of observation. Efforts were made to search for possible causes of a secondary FSGS. Patients with diseases or conditions potentially associated with the development of a secondary FSGS[11] were not included in the study.

The diagnosis of FSGS was made at light microscopy when at least 1 glomerulus showed the characteristic sclerotic lesion in a segment of the tuft. We tried to establish by serial section analysis whether the position of sclerotic lesions in the glomerular tuft was ilar, at the tip, or peripheral. Only in 10% of cases was the lesion constantly confined to the tip. In all of the other cases, sclerotic lesions did not show a constant localization. The proportion of obsolescent glomeruli and the proportion of glomeruli with segmental sclerosis were evaluated. Mesangial hypercellularity, interstitial fibrosis, and arteriolar sclerosis were evaluated according to an ordinal scale (absent, mild, moderate, severe). Immunofluorescence findings were reviewed in all cases to exclude other conditions associated with FSGS. Electron microscopy was performed to confirm the diagnosis in doubtful cases.

## *Treatments*

After histological diagnosis was made, all patients were given a treatment with corticosteroid or immunosuppressive agents. Most patients started with corticosteroids. Some patients who had relative contraindications to corticosteroids (eg, obesity, glucose intolerance, hyperlipidemia, mood instability) started with immunosuppressive drugs. Fifteen patients who participated in a randomized controlled study (data not published) started with methylprednisolone alternated with cytotoxic agents for 6 months.

*Corticosteroids (53 patients).* Thirty patients were initially treated with prednisone 1 mg/kg/d for 8 weeks, then gradually tapered by 5 to 10 mg/d every 1 to 2 weeks until a maintenance of 10 to 15 mg/d. The mean treatment lasted 24.5 ± 25.68 weeks (median, 16 weeks; range, 8 to 125). The median cumulative dose of prednisone was 92 mg/kg (range, 56 to 268 mg/kg). Twenty-three other patients were initially given 3 pulses of intravenous methylprednisolone, 1 g each every 24 hours, followed by oral prednisone, 0.5 mg/kg/d, for 8 weeks then gradually tapered to 10 to 15 mg/d. The mean treatment lasted 19.1 ± 12.34 weeks (median, 16 weeks; range, 8 to 50). The median cumulative dose of prednisone, excluding intravenous methylprednisolone pulses, was 42 mg/kg (range, 28 to 138 mg/kg). With either treatment, if complete remission of proteinuria developed, corticosteroids were gradually tapered off, and treatment was continued for at least 6 months in the other patients, unless side effects developed or patients asked for the treatment to be stopped.

*Immunosuppressive drugs (27 patients).* Five patients were initially given oral cyclophosphamide (1 to 2 mg/kg/d). Five other patients were given a combination of oral cyclophosphamide (1 mg/kg/d) and azathioprine (1 mg/kg/d). Two patients were given azathioprine (1.5 mg/kg/d). All of these 12 patients also received low-dose prednisone (5 to 10 mg/d). The mean period of treatment in these 12 patients was 87.1 ± 84.23 weeks (median, 75; 8 to 336 weeks). Fifteen other patients were treated with a fixed schedule of 6 months that we are using in membranous nephropathy.[12] It consists of 1 month with 3 consecutive intravenous pulses of 1 g methylprednisolone, given every 24 hours, followed by oral prednisone at a dosage of 0.5 mg/kg/d, alternated with 1 month of chlorambucil 0.2 mg/kg/d (or cyclophosphamide 2 mg/kg/d in 4 patients). This 2-month cycle was repeated consecutively 3 times.

*Retreatments.* Twenty-six patients who did not respond to the first treatment and who did not show major side effects from therapy were treated again after 28.3 ± 30.9 weeks (median, 16; range, 12 to 60) with oral prednisone in mean for 28.2 ± 30.9 weeks (median, 16; range, 9 to 90 weeks); 11 with immunosuppressive agents, azathioprine in 7 patients; and cyclophosphamide in 4, for a mean period of 22.0 ± 16.88 weeks (median 13; range, 16 to 88 weeks). Nine patients were treated with cyclosporine at an initial dose of 5 mg/kg/d, for a mean of 62.6 ± 46.41 weeks (median, 44; range, 5 to 150 weeks). Retreatment was started in 36.3 ± 28.21 weeks (median, 24; range, 12 to 60) after the end of the first treatment.

Another 20 patients had a relapse of the nephrotic syndrome after remission. Eight of them were retreated with corticosteroids for 26.1 ± 19.89 weeks (median, 22; range, 8 to 64 weeks), 10 with immunosuppressive drugs plus low-dose prednisone for 66.7 ± 89.73 weeks (median, 21; range, 5 to 283 weeks), and 2 with cyclosporine for 24 and 136 weeks.

*Supportive treatment.* Patients were treated with diuretics, antihypertensive agents, and hypolipemic drug therapy when appropriate. Thirty patients were given angiotensin-converting enzyme (ACE) inhibitors.

*Definitions.* Complete remission was defined as a reduction of urinary protein excretion to at least 0.2 g/d for at least 1 month, with plasma creatinine stably lower than 1.5 mg/dL (132 μmol/L). Partial remission was defined as a reduction in the rate of urinary protein excretion to between 0.21 and 2 g/d for at least 1 month, with plasma creatinine lower than 1.5 mg/dL. Nephrotic syndrome was defined by proteinuria higher than 3 g/d with albuminemia lower than 2.5 g/dL. Relapse of the nephrotic syndrome was defined as an increase in proteinuria to more than 3.0 g/d for at least 1 week in a patient who had either complete or partial remission. A stable condition was defined as a plasma creatinine lower than 1.5 mg/dL (132 μmol/L) with proteinuria between 2.1 and 3.0 g/d. Renal failure was defined as a persistent doubling of plasma creatinine over the baseline values. Arterial hypertension was defined by values of blood pressure higher than 150/90 mm Hg in 2 consecutive measurements in the supine position or the need for antihypertensive therapy.

## *Statistical Analysis*

Descriptive statistics were calculated for quantitative variables (mean, standard deviation, minimum and maximum, and median in the case of skewed distribution) and for qualitative ones (absolute and percent frequencies).

Mean of quantitative variables were compared by Student's *t*-test or Wilcoxon rank-sum test according to whether it was sensible to rely on the Gaussian distribution; those of qualitative ones have been compared by the chi-squared test.

Ninety-five percent confidence intervals were calculated for the observed percent frequencies.

Cumulative probability of complete/partial remission, complete remission alone, and thereafter of relapse, and, finally, of renal failure or death, was estimated according to Kaplan and Meier.[13] Comparison between survival curves was performed by means of log-rank test.[14]

For this analysis, variables were dichotomized (age 40 years or younger, or age older than 40 years, creatinine plasma level at biopsy less or equal to 1.0 mg/dL, cholesterol plasma level less than or equal to 300 mg/dL or higher than 300 mg/dL, percentage of hyaline disks less than or equal to 5% or more than 5%, and for the histological variables as absent versus present). To obtain more reliable estimates of the above ''survival probability curves'' the follow-ups for the analysis on the complete and partial remission or complete remission alone achievement and for that of renal failure/death were truncated at 5 and 10 years, respectively. Therefore, events after these limits were considered as no events.

After having checked the fulfillment of the hazard functions proportionality assumption by means of the log (-log) survival plots, Cox's model was used for obtaining the subset of prognostic variables related to the achievement of response (complete or partial remission) and the end point (renal failure or death). For this last analysis, a further Cox's model was fitted using the achievement of complete or partial remission as a time-dependent covariate.[15] In addition, for illustrative purposes, the time to renal failure or death unbiased curves of patients with complete or partial remission (as ''responders'') and those with no remission (as ''nonresponders'') were obtained according to the appropriate methodology proposed by Simon and Makuch.[16] Therefore, after having chosen as a clinically relevant time for this graphical display the median of the times to the complete or partial remission achievement, we obtained

1. For patient nonresponders, the probability of not having renal failure/death conditional on being in ''normal'' renal function (plasma creatinine lower than 1.5 mg/dL) and nonresponder at 9 months after biopsy. For this estimate, the transitions into the response state were treated as censored observations, and, then, it included the experience of not having renal failure or death of responders while initially they were in the nonresponse state.
2. For responder patients, the probability of not having renal failure or death was conditional on having achieved a complete or partial remission at 9 months after biopsy. This estimate excluded responders who were in the renal failure or death state before 9 months after the renal biopsy and included patients who entered in the response state (complete or partial remission achievement) after this 9 months' cutoff.

A further index of treatment effectiveness was obtained as the percentage of the remission time (partial or complete) out of the total follow-up for each patient. The 2 treatment groups were compared by means of the Wilcoxon rank-sum test according to an intention-to-treat approach.

## RESULTS

Eighty patients satisfied the criteria for inclusion and were followed-up for a median of 86 months (range, 12 to 342 months). The main demographic characteristics at the time of biopsy are shown in Table 1. There were not relevant differences between patients assigned to receive corticosteroids or immunosuppressive drugs.

Forty-two patients (52%) responded to the first treatment with a complete remission (29 patients, 36%) or a partial remission (13 patients, 16%). Of the 53 patients treated with corticosteroids, 21 (39.6%) had a complete remission, and another 10 (18.8%) had partial remission as a first event. The median period of treatment with corticosteroids was 16 weeks. Of the 27 patients treated for 16 weeks or less, only 4 (15%) attained complete remission, whereas of 26 patients given corticosteroids for longer periods, 16 (61%) entered complete remission. Of the 27 patients treated with immunosuppressive therapy, 8 (29.6%) had a complete remission, and 3 (11.1%) patients had a partial remission. At univariate analysis the probability of reaching either partial or complete remission was associated

**Table 1. Main Demographic Data at the Moment of Renal Biopsy in 80 Patients With FSGS**

| | | Patients Initially Treated With | |
|---|---|---|---|
| | All Patients | Steroids | Immunosuppressive Drugs |
| Age (y) | 39.95 ± 17.81 | 40.77 ± 19.06 | 38.33 ± 15.27 |
| Sex (male/female) | 50/30 | 30/23 | 20/7 |
| Duration of the disease before biopsy (mo) | 15.35 ± 35.46 | 13.60 ± 34.90 | 20.85 ± 36.57 |
| Plasma creatinine (mg/dL) | 1.14 ± 0.48 | 1.09 ± 0.37 | 1.24 ± 0.65 |
| Proteinuria (g/d) | 6.83 ± 4.36 | 6.96 ± 4.36 | 6.58 ± 4.42 |
| Serum albumin (g/dL) | 2.24 ± 0.87 | 2.36 ± 0.86 | 2.01 ± 0.86 |
| Plasma cholesterol (mg/dL) | 376.52 ± 116.79 | 369.22 ± 112.21 | 391.13 ± 126.77 |
| Patients with hypertension | 47 (59%) | 33 (62%) | 14 (52%) |

with treatment with corticosteroids ($P = 0.0001$), absence of arterial hypertension at presentation ($P = 0.0017$), a percentage of hyaline glomeruli of less than 5% ($P = 0.0083$), and the absence of interstitial fibrosis/tubular atrophy ($P = 0.0187$) at initial renal biopsy. At multivariate analysis, only treatment with corticosteroids ($P = 0.0001$; RR, 3.93; 95% CI, 2.00 to 7.72), absence of hypertension ($P = 0.0023$; RR, 2.59; 95% CI, 1.41 to 4.79), and hyaline glomeruli less than 5% ($P = 0.0152$; RR, 2.04; 95% CI, 1.15 to 3.64) were associated with remission. The probability of reaching complete remission was associated with the absence of hypertension ($P = 0.0066$), treatment with corticosteroids ($P = 0.0104$), and the absence of interstitial fibrosis/tubular atrophy at biopsy ($P = 0.0197$), and a percentage of hyaline glomeruli less than 5% was at borderline significance ($P = 0.0541$). Multivariate analysis was not performed because of the low number of events.

Of the 38 patients who did not respond to the first treatment 26 were retreated (Fig 1). Twelve patients were not retreated either because of side effects during the first treatment (9 patients), or because they refused further treatment (3 patients). Of 6 patients retreated with prolonged corticosteroid therapy, 1 attained complete remission and another 1 a partial remission, respectively, after 69 and 20 weeks of treatment. Of the 11 patients retreated with immunosuppressive drugs, 1 reached a complete remission and 5 a partial remission in mean after 40.5 ± 24.54 weeks (median, 34.5; range, 16 to 88 weeks). Of

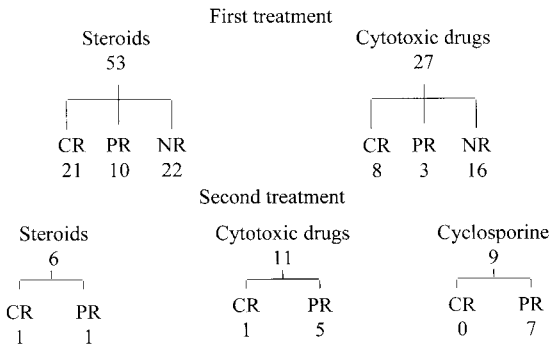


**Fig 1. Response to first treatment of 80 nephrotic adults with biopsy-proven FSGS. Of the 38 nonresponders 26 patients received a second treatment. The numbers indicate the numbers of patients. CR, complete remission (first event); PR, partial remission (first event); NR, no response.**

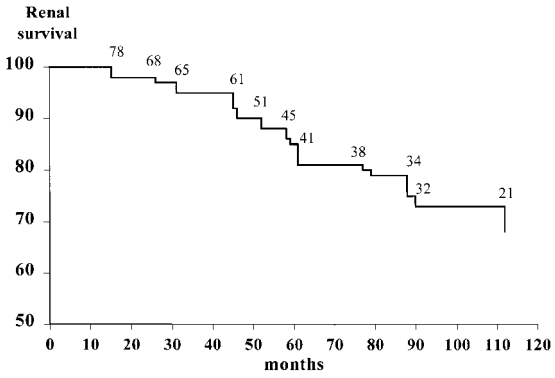


**Fig 2. Probability of reaching a complete or a partial remission in 80 patients with FSGS, treated with prolonged steroid or immunosuppressive therapy. The numbers refer to the patients at risk.**

the 9 patients given cyclosporine, 7 had a partial remission in mean after 29.6 ± 14.11 weeks (median, 30; range, 8 to 52). Taking together the results of the first treatment and of retreatments, the probability of reaching a complete remission was 50% within 3 years, and that of obtaining a complete or a partial remission was 75% within 5 years (Fig 2). All remissions occurred under treatment. No remission occurred after treatment was stopped.

Twenty responders (17 of 53 previously treated with corticosteroids and 3 of 27 with immunosuppressive drugs) had 1 or more relapses of the nephrotic syndrome. Among patients who relapsed, 8 were retreated with steroids. Of them, 5 patients had a complete remission and 3 a partial remission after a mean of 8.7 ± 7.57 weeks (median, 6.5; range, 3 to 26). Ten patients were given immunosuppressive agents. Of them, 5 patients reached complete remission and 2 a partial remission after 61.4 ± 105.46 weeks (median, 24; range, 10 to 300). Two patients were given cyclosporine. Both of them reached complete remission after 8 and 20 weeks, respectively. Patients initially treated with corticosteroids spent 48.9% of their follow-up period without nephrotic syndrome, versus 32.5% of patients initially given cytotoxic drugs ($P = 0.0385$). Thirty patients were given ACE inhibitors at various times. Of them, 8 (27%) had complete remission under corticosteroid or immunosuppressive treatment, 10 (33%) had partial remission, and 12 (40%) did not show any remission.

The probability of being alive without dou-

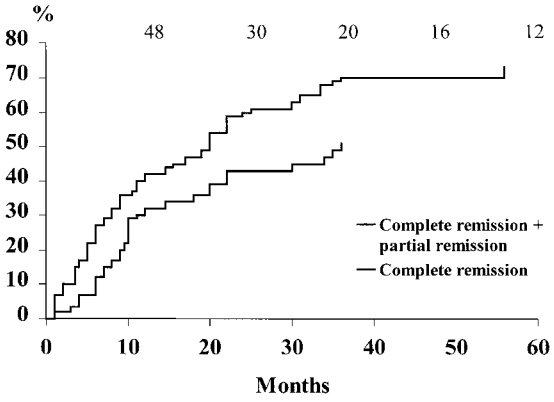


**Fig 3. Probability of being alive without doubling of plasma creatinine in 80 patients with FSGS and nephrotic syndrome.**

bling plasma creatinine was 69% at 110 months (95% CI, 65.1 to 83.1%; Fig 3). Two patients showed a rapid evolution to end-stage renal failure. Another patient with profuse proteinuria and rapid renal function deterioration had a leg arterial thrombosis that required a foot amputation. At univariate analysis, the risk of dying or doubling plasma creatinine was associated with mesangial proliferation ($P = 0.0007$) and with interstitial fibrosis ($P = 0.0126$) at the initial biopsy, whereas arterial hypertension was at borderline significance ($P = 0.0578$). The type of treatment did not influence the results. The multivariate analysis showed that interstitial fibrosis/tubular atrophy ($P = 0.0231$; RR, 4.44; 95% CI, 1.23 to 16.08) and mesangial proliferation ($P = 0.0025$; RR, 5.50; 95% CI, 1.82 to 16.60) were correlated with the risk. However, if we consider the achievement of partial or complete remission as a time-dependent variable, only lack of remission ($P = 0.0027$; RR, 7.23; 95% CI, 1.98 to 26.33) and mesangial proliferation ($P = 0.0069$; RR, 4.59; 95% CI, 1.52 to 13.88) remained in the Cox's model. In particular, patients with complete or partial remission tended to maintain normal renal function over time, which was different from nonresponders (Figs 3, 4).

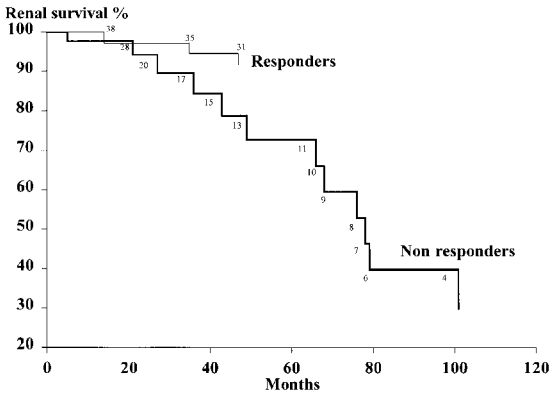


**Fig 4. Survival without renal failure in patients who had a complete or partial remission as a first event (responders) and in the nonresponders. The numbers refer to the patients at risk. The curves and the definitions were made according to Simon and Makuch.[12] See also Statistical Methods.**

Three patients died, 2 of lung cancer and 1 of cardiac failure. Of the 2 patients with cancer, 1 died of lung adenocarcinoma 21 months after the clinical onset of FSGS, while in complete remission. This patient had received a cumulative dose of chlorambucil of 0.9 g. The second patient died of lung cancer 183 months after the clinical onset of FSGS, while he was in complete remission. This patient, who was a heavy smoker, had received a cumulative dose of cyclophosphamide of 42 g plus a cumulative dose of azathioprine of 174 g. The patient who died of cardiac failure had a plasma creatinine of 5.0 mg/dL at the moment of the death, 91 months after the clinical onset of FSGS.

Excluding these 3 deaths, at the last follow-up visit, 60 patients (78%) had a plasma creatinine lower than 1.5 mg/dL. Of them, 31 were in complete remission and 14 were in partial remission. Seventeen patients developed renal failure. Of them, 15 were on regular dialysis (Table 2). Several side effects were encountered during the follow-up (Table 3). Besides the 2 patients with lung cancer, a 73-year-old woman who had already been treated with corticosteroids for 6 months, followed by 2 months of cyclophosphamide, developed a cutaneous form of Kaposi's sarcoma after 11 weeks of cyclosporine. Treat-

**Table 2. Renal Status of 77 Patients With FSGS and Nephrotic Syndrome at Presentation at the Last Follow-Up Visit (Median, 86 months; 12-342. Three Patients Who Died Are Excluded)**

| | |
|---|---|
| Stable or improved patients | |
| Complete remission | 31 patients (40.2%) |
| Partial remission | 14 patients (18.2%) |
| Nephrotic syndrome | 11 patients (14.3%) |
| Stable condition | 4 patients (5.2%) |
| Doubling of plasma creatinine | |
| Regular dialysis | 15 patients (19.5%) |
| Renal insufficiency | 2 patients (2.6%) |

**Table 3. Main Side Effects Possibly Related to Therapy**

| | |
|---|---|
| Severe side effects | |
| Infections | 5 (3 pneumonias)<br>(1 herpes zoster)<br>(1 abscess) |
| Gastric hemorrhage | 1 |
| Diabetes | 2 |
| Neoplasia | 3 (2 lung cancer)<br>(1 Kaposi sarcoma) |
| Mild/moderate side effects | |
| Gingival hyperplasia | 5 (under cyclosporine) |
| Gastric discomfort | 4 |
| Cushingoid appearance | 4 |
| Alopecia | 3 |
| Leukopenia | 4 |
| Anemia | 4 |

ment was stopped, and the signs of Kaposi's sarcoma disappeared. Five other patients developed infections that reversed after appropriate treatment. One patient suffered from a gastric hemorrhage caused by peptic ulcer while taking corticosteroids. Gastric disease healed after stopping steroids and with appropriate therapy. Two patients treated with corticosteroids developed diabetes mellitus. Hyperlipidemia was not considered among side effects, all patients being nephrotic at presentation and showing relapses of nephrotic syndrome in some cases. We did not perform serial measurement of computed bone mineralometry. No patient, however, complained of major bone complications.

## DISCUSSION

The aim of this study was to reassess the long-term prognosis of patients with FSGS and the nephrotic syndrome who had been treated with corticosteroid or immunosuppressive therapy. Only nephrotic adults with a biopsy-proven diagnosis of FSGS, not secondary to identifiable causes, and followed-up for at least 1 year, were included in this study. We excluded patients with severe renal insufficiency who were likely to have a bad outcome with little probability of benefit from therapy. The initial treatments were different, but patients could be divided into two main groups one treated with corticosteroids and the other with immunosuppressive drugs for at least 6 months. The agents we used have different mechanisms of action and a different magnitude of immunosuppression. The unifying hypothesis for this variety of treatments was to try a prolonged treatment. We gave corticosteroids as a first-line treatment in 2/3 of patients. In patients who had some contraindications to vigorous corticosteroid treatment, we started with cytotoxic drugs, mainly cyclophosphamide. Finally, a few patients were given corticosteroids alternated with cytotoxic drugs according to a schedule of a controlled trial that has not concluded. The rate of response to the initial treatment was good, with 36% of patients attaining a complete remission of proteinuria and another 16% reaching a partial remission of the nephrotic syndrome. After further treatments, 2 other patients attained complete remission and 13 a partial remission. The probability of reaching a complete remission was 50%, and that of reaching a complete or a partial remission was 75% within 5 years. These results are better than the 15% to 25% cases, with complete remissions reported in treated adults by 2 extensive reviews of the literature.[5,6] The difference is probably accounted for by the fact that most patients of previous studies received only short courses of treatment, whereas many of our patients received a prolonged initial treatment. As a matter of fact, in this study, only 15% of patients who received corticosteroids for 16 weeks or less entered complete remission of proteinuria, whereas, of patients given initial corticosteroid treatment for longer periods, 61% obtained complete remission. Most responders obtained remission after 6 months or more. A relatively small number of patients had a relapse of proteinuria, the risk of relapse being higher in patients given corticosteroids than in those given cytotoxic agents. Most of them responded to further treatments with steroids, immunosuppressive agents, or cyclosporine. After a median follow-up of 86 months, 58% of surviving patients were still without nephrotic syndrome, and 40% were without proteinuria at all. Multivariate analysis showed that patients treated with corticosteroids, those with normal blood pressure, and those with a small percentage of obsolescent glomeruli had the highest chances of obtaining remission of the nephrotic syndrome.

A prolonged treatment was also helpful in protecting renal function. The probability of surviving at 10 years without doubling of plasma creatinine was 69% in patients with a nephrotic

syndrome, considerably better than that of 25% to 50% reported by other adult series.[2-4] It must be pointed out, however, that in some studies a few patients with renal insufficiency were included, whereas we excluded patients with plasma creatinine higher than 3 mg/dL. This might have influenced the difference in the results. The risk of renal failure was higher in patients with interstitial fibrosis or mesangial proliferation at initial biopsy. When time-dependent variables were considered, the achievement of a complete or partial remission as a first event was the strongest predictor of renal survival in the long-term. It is possible that this variable was more powerful than interstitial fibrosis because the initial histological lesions were not particularly severe in this series.

These data show that a prolonged treatment of FSGS may obtain remission of the nephrotic syndrome in approximately 70% of patients and may prevent long-term renal function deterioration in a consistent number of nephrotic patients. The initial administration of prolonged steroid therapy proved superior to immunosuppressive drugs although the relapses in obtaining remission were more frequent in steroid-treated patients. These data would confirm some previous scattered reports. In a review of the literature, it was found that, of 110 adults with FSGS treated with prednisone for at least 6 months, 56 (51%) responded with a complete remission, and only 21 of 80 (26%) treated with immunosuppressive drugs obtained complete remission.[11] However, caution is needed in interpreting these data, because the criteria for assigning patients to corticosteroids or immunosuppressive drugs and treatment modalities were not uniform. Also, the indications for cytotoxic therapy were variable in our study. In fact, we used immunosuppressive agents in patients with contraindications to corticosteroids as well as in those who showed a relapse of the disease and in those who did not respond to the first therapeutical approach.

What is the price to pay for a prolonged therapy? Two patients died of cancer. One died of lung cancer 15 months after a 6-month treatment with steroids alternated every other month with chlorambucil. The cumulative amount of chlorambucil was relatively small. It is possible, although unproven, that this patient had an undetected cancer at the moment of treatment, because it is now recognized that small cell carcinomas have slow doubling times.[17] The oncogenic role of immunosuppressive therapy was more likely in the other patient, who had a prolonged immunosuppression that may have contributed, together with the habit of heavy smoking for many years, to the development of cancer. Another patient developed a Kaposi's sarcoma under cyclosporine. The disease reversed after the drug was stopped, similarly to what was observed in several cases of Kaposi's sarcoma in cyclosporine-treated renal transplant recipients.[18,19] Other important side effects included 5 cases of infection, 1 case of gastric hemorrhage, and 2 cases of diabetes. All of these complications could be handled successfully. Although the rate of reported side effects was low in this experience, one should be aware of the potential morbidity of prolonged corticosteroid or immunosuppressive treatment. Corticosteroids may expose the patient to the risk of infections, cosmetic changes, hyperglycemia, and hyperlipemia. Osteoporosis is another potential side effect particularly frequent and severe in postmenopausal women. A preventive treatment with biphosphonates may be helpful in preventing corticosteroid-induced osteoporosis in patients at risk.[20]

In conclusion, this study shows that approximately 70% of adults with FSGS and nephrotic syndrome given prolonged treatment with steroids, immunosuppressive agents, or cyclosporine still may enjoy normal renal function after 10 years, with a high probability of being without nephrotic syndrome. Because prolonged corticosteroid treatment seems to be at least as effective as a treatment with immunosuppressive drugs, one might suggest starting with corticosteroids while reserving immunosuppressive drugs for patients who relapse or patients with contraindications to steroids. It is more difficult to draw firm conclusions about the role of cyclosporine from this retrospective study. Of note, however, 7 of 9 patients who did not respond to previous treatments entered partial remission, and both of the 2 relapsers obtained complete remission under cyclosporine. These results confirm a possible role for this drug in steroid-resistant or in frequently relapsing patients with FSGS.[21,22] Although our data are retrospective, they seem to suggest that a prolonged treatment with corticosteroids, immunosuppressive drugs, or cyclosporine may improve the renal outcome of patients

affected by FSGS. Randomized, controlled trials are warranted to confirm the benefit of long-term treatment and to identify the most effective agent(s) in this severe disease.

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