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Clinical trials treating focal segmental glomerulosclerosis should measure patient quality of life

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Abstract

Optimal therapy of patients with steroid-resistant primary focal segmental glomerulosclerosis (FSGS) remains controversial. This report describes the initial study design, baseline characteristics, and quality of life of patients enrolled in the FSGS Clinical Trial, a large

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multicenter randomized study of this glomerulopathy comparing a 12-month regimen of cyclosporine to the combination of mycophenolate mofetil and oral dexamethasone. Patients with age ranging 2–40 years, with an estimated glomerular filtration rate >40 ml/min per 1.73 m^2, a first morning urine protein-to-creatinine ratio over one, and resistant to corticosteroids were eligible. The primary outcome was complete or partial remission of proteinuria over 52 weeks after randomization. In all, 192 patients were screened, of whom 138 were randomized for treatment. Ethnic distributions were 53 black, 78 white, and 7 other. By self- or parent-proxy reporting, 26 of the 138 patients were identified as Hispanic. The baseline glomerular filtration rate was 112.4 (76.5, 180.0) ml/min per 1.73 m^2, and urine protein was 4.0 (2.1, 5.3) g/g. Overall, the quality of life of the patients with FSGS was lower than healthy controls and similar to that of patients with end-stage renal disease. Thus, the impact of FSGS on quality of life is significant and this measurement should be included in all trials.

Keywords

focal segmental glomerulosclerosis; proteinuria; quality of life; randomized controlled trial

Focal segmental glomerulosclerosis (FSGS) can be a primary glomerular disorder or develop secondary to a variety of insults.[1] Primary FSGS can arise as a consequence of genetic mutations in structural podocyte proteins[2] or reflect the presence of unidentified immunologic abnormalities that increase glomerular permeability to protein.[3] The diagnosis of FSGS is contingent on demonstrating the presence of segmental sclerosis within the glomerular tuft.[4,5]

The initial treatment of primary FSGS in children and young adults usually involves corticosteroids.[6,7] Approximately 25% of patients with primary FSGS respond to an initial course and enter remission.[8–10] Patients who are steroid resistant have a chronic disease and are at increased risk of progressing to end-stage kidney disease (ESKD),[6,8,11] complications related to uncontrolled nephrotic syndrome, and impaired quality of life.

The optimal therapy of patients with steroid-resistant primary FSGS remains controversial.[7] Many agents have been evaluated, including methylprednisolone, cyclophosphamide, mycophenolate mofetil (MMF), calcineurin inhibitors, and rituximab, but not in randomized trials.[12,13] The only medication that has been evaluated in well-designed clinical trials and has shown to increase the rate of partial and complete remission is cyclosporine (CSA).[14,15] The high relapse rate following discontinuation of CSA[14] and side-effect profile, including risk for nephrotoxicity and cosmetic effects, has stimulated a desire for an alternative treatment regimen in FSGS.

Extended and continuous exposure to corticosteroids improves the complete and partial remission rates in patients with FSGS in observational studies and uncontrolled trials. Kopp *et al.* (J Kopp, NIDDK, personal communication) evaluated pulse oral dexamethasone 25 mg/m^2 administered days 1–4 of each 28-day cycle and repeated over 32 weeks in 15 adults with idiopathic FSGS and proteinuria ≥3.5 g/day. One patient entered complete remission (urine protein/creatinine ratio (Up/c) <0.3 g/g) and six patients entered partial remission (Up/c <2 g/g), for an overall response rate of 47%. The sustained response rate fell to 20% with longer follow-up (J Kopp, NIDDK, personal communication, and presented in abstract in Smith *et al.*[16]). Uncontrolled data from a single-center suggest improved control of FSGS with long-term pulse corticosteroid therapy in conjunction with cytotoxic agents if the response to corticosteroids alone was insufficient.[17] MMF may reduce urine protein excretion in steroid-dependent and steroid-resistant patients with FSGS with a better side-effort profile compared with CSA and cytotoxic agents.[18,19] Nonetheless, all of the above

agents and regimens have significant side effects, which spur interest in the development of new therapies for FSGS.

The National Institutes of Health-funded FSGS Clinical Trial (FSGS CT) was a multicenter randomized clinical trial comparing the efficacy of a 12-month course of CSA to a combination of oral pulse dexamethasone and MMF in children and adults with steroid-resistant FSGS. The objectives of this article are to: (1) document the trial design; (2) describe the baseline clinical and laboratory features; and (3) evaluate the quality of life (QOL) in the FSGS CT cohort.

RESULTS

Enrollment into the trial commenced on 9 November 2004 and the last follow-up visit in the treatment phase of the study was completed on 30 November 2009. A total of 192 patients were enrolled and screened for the FSGS CT; 54 patients were excluded and 138 were randomized. The most common reasons for screen failure were Up/c ratio <1 g/g ($n =20$) and a kidney biopsy that was inconsistent with primary FSGS ($n =18$; Figure 1). Other causes for exclusion included previous therapy with one of the study agents ($n =1$); ineligible age ($n =1$); study team recommendation ($n =1$); and acute kidney injury ($n =1$). Age, race, ethnicity, and proteinuria were similar in the screened and randomized groups.

Randomized sample

The 138 randomized subjects were evenly distributed between three age categories: 2–12, 13–17, and 18–40 years. The racial and ethnic distribution was diverse, with 38.4% ($n =53$) black, 56.5% ($n =78$) white, 5.1% ($n =7$) other races, and 18.8% ($n =26$) Hispanic. Of the patients, 65 (47.1%) were female.

The subjects were diagnosed with FSGS 6.7 (3.6, 16.2) months before enrollment (range 1.0–131.1 months). Cumulative time of corticosteroid exposure at study entry was 3.0 (2.0, 6.0) months with no difference between adult and child participants ($P =0.84$; Table 1). The number of previous courses of steroids was not recorded and the distinction between primary versus secondary steroid resistance was not distinguished in trial participants. At screening, 58% ($n =80$) of subjects had hypertension by history and 20.3% ($n =28$) had office blood pressure measurements in the hypertensive range. Antihypertensive therapy was prescribed for 81.2% of the patients ($n =112$), including 72.5% ($n =100$) angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker and 8.7% ($n =12$) other classes of agents.

Signs and symptoms

Edema was present on examination in 57.3% ($n =79$) of subjects and was most often pretibial in 29.0% of the cohort. It was a symptom at disease onset in 67.0% of the children and 65.9% of the adults. Other symptoms reported within 2 weeks of enrollment included cough 26.8% ($n =37$), nausea 19.6% ($n =27$), orthostatic symptoms 18.8% ($n =26$), diarrhea 18.8% ($n =26$), and emesis 13.0% ($n =18$).

Laboratory and pathology findings

The subjects had an estimated glomerular filtration rate (eGFR) of 112.4 (76.5, 180.0) ml/min per 1.73 m^2 (range: 37.6–408.8) and Up/c of 4.0 (2.1, 5.3) g/g (range: 1.0–31.8; Table 1). Serum albumin was lower and total and low-density lipoprotein cholesterol higher in children compared with adults. Only eight participants had anemia with a hemoglobin level <11 g/dl. The collapsing variant of FSGS was present in 11.6% ($n =16$) of subjects, and histology subtypes were not different by age group. There were 11 randomized patients in

whom the diagnosis of FSGS was made >1 year before enrollment. The histological subtypes of FSGS were not different in this group compared with the remaining 127 patients (*P* =0.18).

Medical and family history

Premature birth was reported by 13% of subjects. Past, passive, and current smoking exposure was reported by 6.5% (*n* =9), 15.9% (*n* =22), and 7.3% (*n* =10), respectively. Adults were more likely to have had exposure to tobacco compared with children (51.2 vs 20.6%, *P* =0.003). Other health conditions were uncommon and did not differ by age, including 2.2% (*n* =3) thromboembolic events, 5.1% (*n* =7) seizures, 5.8% (*n* =8) attention deficit disorder, and 2.9% (*n* =4) insomnia or other sleeping disorders. Subjects had a cumulative family history of proteinuria, FSGS, kidney disease, and ESKD of 10% (*n* =14).

Quality of life

Children in FSGS CT compared with controls—The health-related QOL in child participants was reported by parents and patients and compared with published results from healthy and ESKD populations[20,21] (Table 2). Compared with healthy controls, children with FSGS and their parents independently reported a lower total QOL score and in the specific domains of Physical, Emotional, and School Functioning. The only domain in which children and parents in the FSGS cohort reported scores comparable to healthy controls was Social Functioning. In contrast, children and parents in the FSGS CT reported QOL scores comparable to the ESKD group, except for the Social Functioning domain, in which the FSGS patients had higher values than the ESKD cohort. Parents reported better School Functioning QOL but the children did not report significantly different School Functioning than their ESKD peers. In the overall QOL score and the Physical and Emotional Functioning domains, the FSGS CT QOL results were similar to the ESKD cohort.

Adults in FSGS CT compared with controls—Adults with FSGS reported a lower QOL than healthy controls in the Mental Health and Physical Health composite scores and the domains of Mental Health, Vitality, General Health, Role Physical, and Social Functioning. Compared with the ESKD group, the FSGS cohort reported a worse Mental Health composite score but a better Physical Health composite score. FSGS and ESKD cohort QOL scores were similar in the domains of Mental Health, Vitality, Role Emotional, and Social Functioning[22,23] (Table 3).

DISCUSSION

This report provides the FSGS CT design and details the key clinical and laboratory features, compares the demographic and disease-related characteristics between children and adults, and presents QOL results from patients with steroid-resistant FSGS at the time of trial enrollment. The majority of trial patients were ≤18 years of age (70%). The trial includes a high representation of Black and Hispanic patients, comparable with other cohorts and studies of FSGS in the United States.[24,25] The eGFR was well preserved in trial participants, consistent with the eligibility criterion of an eGFR ≥40 ml/min per 1.73 m^2.

The pediatric and adult patients had similar cumulative steroid exposure before the study, socioeconomic status, level of proteinuria, degree of edema, and underlying FSGS histopathology subtype. However, in children and adolescents, the eGFR was higher, the prevalence of hypertension was lower, and the severity of the metabolic features of the nephrotic syndrome, that is, hypoalbuminemia and hyper-cholesterolemia, was worse than in adult patients. These observations coincide with previous studies and suggest that the nature

of primary steroid-resistant FSGS may vary with age. After the design of this trial, Branten *et al*.[26] reported that tubular secretion of creatinine increases with hypoalbuminemia. In patients with nephrotic syndrome and hypoalbuminemia, creatinine-based equations overestimate the GFR determined by inulin clearance. The lower serum albumin in the pediatric trial subjects may contribute to the higher calculated eGFR in children.

Assessment of health-related QOL has become a standard component in the clinical evaluation of patients with a variety of chronic diseases. It has been incorporated into the predefined end points in many clinical trials to enable a more comprehensive determination of relevant clinical outcomes in response to the experimental intervention. QOL has been assessed in cohort studies in children with steroid-sensitive nephrotic syndrome, in all ages with chronic kidney disease (CKD), and in adults with autosomal dominant polycystic kidney disease but not in steroid-resistant FSGS.[21,27–30]

Children with steroid-sensitive nephrotic syndrome have been shown to have a diminished health-related QOL. In a study of 45 children, patient self-reports suggested that only the Social Functioning domain was impaired relative to healthy controls. Parents of these children report a more significant reduction in health-related QOL in the Social, Emotional, Motor, and Cognition domains. Factors associated with QOL impairment were steroid dependency, cytotoxic therapy, and maternal stress.[31]

Patients with CKD requiring renal replacement therapy have demonstrated reduced QOL scores in Physical, Emotional, and Social Function.[21,27,32,33] There have been fewer large-scale studies of patients with CKD before dialysis treatment.[28,29] In a recent study of 1186 adults with CKD, QOL declined progressively with more advanced stages of kidney disease.[33] Lower QOL scores predict a higher mortality in adults with CKD, irrespective of whether or not they are receiving renal replacement therapy.[21,27,29,33]

The baseline findings in the FSGS CT cohort indicate a significant impairment in QOL compared with healthy controls. Children showed impairment in all measured domains except Social Functioning. Adults in the FSGS CT had lower scores in Mental Health and Physical Health composite assessments and in specific domains including Social Functioning. Across the entire age spectrum, patients with FSGS had QOL scores that were comparable with patients with ESKD. Longitudinal assessment of QOL in response to the two study treatments in the FSGS CT will provide important information on the effect of specific therapies.

This trial includes children and adults because new therapeutic options are necessary across this age span and are often chosen based upon the diagnosis rather than the age of the patient. The upper age of 40 years and exclusion of significant coexisting conditions were established as eligibility criteria to decrease the likelihood of secondary or multiple causes of kidney disease. Inclusion of a wide age span adds specific challenges to the design and analysis of a trial. GFR-estimating equations and QOL assessment tools have been generated separately for children and adults. These methodological disconnects force the analysis of the secondary outcomes of the trial in an age-specific manner. However, the primary outcome of proteinuria is based on first morning Up/c and is not an age-dependent factor.

The trial protocol was based upon assessment of the literature at the time of study design and feasibility. Genetic testing was not incorporated into the main trial protocol as an association between genetic causes of FSGS and treatment resistance was not defined. Indeed, even now, as genetic causes of FSGS and other glomerular diseases are identified, it is evident that some gene mutations cause structural changes that might not be modifiable, whereas others impact disease mechanisms that increase the likelihood of a response. TRPC6 in FSGS might be considered an example.[34] Budgetary restraints and the absence of

a central genetic testing core with a short turnaround time were the major barriers to the inclusion of genetic testing as a prerandomization criterion.

In conclusion, this report provides a basis for comparison with other primary FSGS patient cohorts and clinical trials. The impact of steroid-resistant FSGS on patient-reported QOL is significant and comparable in magnitude with that in children and adults with ESKD.

MATERIALS AND METHODS

Trial design

The FSGS CT was a multicenter, prospective, controlled, open-label randomized trial comparing two treatment regimens: CSA and MMF/oral dexamethasone pulses. CSA was designated as the control arm based on the results of previous clinical trials.[14,15] Dexamethasone in combination with MMF was considered the experimental therapy. The treatment schedules were guided by published reports and abstracts detailing the use of the agents chosen for evaluation.[14,16]

The organization of the project included a Data Coordinating Center at the Cleveland Clinic and three core coordinating centers—State University of New York-Stony Brook Health Sciences Center, University of North Carolina, and Children's Hospital at Montefiore. In all, 104 sites received the approval of the institutional review board and patients were enrolled at 67 participating centers. At the 53 sites where at least 1 patient was randomized, 25 managed only pediatric patients, 10 only adults, and 18 both.

Inclusion criteria—Patients were eligible if they had primary FSGS confirmed by central pathology committee review of stored kidney biopsy material, age of proteinuria onset and current age between 2 and 40 years, eGFR ≥40 ml/min per 1.73 m^2 assessed at a single study visit, Up/c >1 g/g based on an average of 2 first morning samples collected at least 24 h apart, and resistance to corticosteroid therapy. If the 2 Up/c results were different by >50%, a third first morning urine sample was collected and the results included in the average baseline Up/c to increase the stability of the baseline Up/c. There was no requirement for hypoalbuminemia or edema and, therefore, patients were not categorized as nephrotic versus non-nephrotic. Steroid resistance was defined as failure to achieve a sustained Up/c ≤1.0 g/g based on at least one treatment course with steroids before randomization that satisfied both of the following conditions: (1) minimal treatment duration of 4 weeks and (2) minimum cumulative dose of 56 mg/kg or 1680 mg of prednisone equivalent. The definition of steroid resistance was weighted toward the pediatric practice in which corticosteroid use is more uniform and better quantitated. Because the use of steroids is more variable in adult patients (dose and duration of treatment), a lower limit of steroid exposure was used to define resistance to therapy in adults to minimize potential patient exclusion from the study. The patients with the Up/c between 1 and 1.99 g/g had a level of proteinuria that persisted despite steroid therapy and were considered steroid resistant.

The initial criterion of proteinuria was 2 g/g Up/c as this reflects the diagnostic value for nephrotic-range proteinuria in children. This value was chosen instead of 3.5 *g* protein/day in a 24 h urine or Up/c of 3.5 g/g, a standard used in many adult studies, because it was anticipated that the majority of study patients would be in the pediatric age range. The Up/c eligibility criterion was reduced from 2 to 1 g/g during the study because the majority of site investigators viewed persistent proteinuria as indicative of serious disease and as a risk factor for progressive CKD. A small number of patients with Up/c values between 1.0 and 1.99 g/g were excluded before the change in eligibility criteria.

It is important to note that although the entry criterion for proteinuria was lowered from 2 to 1 g/g, the patients still required a 50% reduction in proteinuria from the baseline value to qualify for a partial remission and Up/c <0.2 g/g to achieve a complete remission. In addition, patients with the lower level of proteinuria were randomly assigned to a treatment arm. Thus, although this protocol change represented a potential flaw in design, it did not compromise the validity of the planned statistical methods. Subgroup analysis of these patients will be incorporated into the primary outcome report.

Stored kidney biopsy slides were submitted to a FSGS CT central pathologist. If the material was read as inconsistent with primary FSGS, then a second central pathologist reviewed the material. Agreement between two central pathologists was required to exclude a subject. The type of primary FSGS was classified according to the FSGS Columbia Criteria.[35]

Exclusion criteria—Patients were ineligible if they had secondary FSGS; had received previous therapy with sirolimus, CSA, tacrolimus, MMF, or azathioprine; were treated with cyclophosphamide, chlorambucil, levamisole, methotrexate, or nitrogen mustard within 30 days of enrollment; received >3 pulses of methylprednisolone; or were allergic to the study medications. Remote exposure to cytotoxic agents for frequently relapsing or steroid-dependent nephrotic syndrome before the onset of steroid resistance was permitted because it was unlikely to change to response pattern to the randomized treatment arm. History of previous cytotoxic therapy was not collected. Additional exclusion criteria included: obesity (based on estimated dry weight at onset of disease before steroid therapy) defined as (1) body mass index >97th percentile for patients aged 2–20 years or (2) body mass index >40 kg/m^2 for patients ≥21 years old; absolute neutrophil count <2000/mm^3; hematocrit <28%; uncontrolled hypertension defined as blood pressure >140/95 for adults or >95th percentile for age/height for children <18 years of age, while receiving ≥4 antihypertensive agents; diabetes mellitus; active or serious infection; cirrhosis or chronic active liver disease; history of significant gastrointestinal disorder; organ transplantation; history of malignancy; or participation in another therapeutic trial within 30 days before randomization. Women were excluded if they were lactating, pregnant, or were of child-bearing age and refused birth control.

Equations and instruments—GFR was estimated using the Schwartz formula for participants <18 years and Cockroft–Gault formula for participants ≥18 years adjusted for body surface area.[36,37] Questionnaires included a patient symptom checklist, family history, and a QOL assessment. The Short Form-36 (SF-36) was administered to adults,[38,39] and PedsQL (Pediatric Quality of Life Inventory) self-report was used for children aged 5–17 years and parent proxy-reports for aged 2–17 years.[20] The validity of the SF-36 has been established in adults with ESKD with reliability coefficients of 0.77–0.93.[38,39] The PedsQL has been validated in general and chronic illness populations including ESKD with an internal consistency reliability of ≥0.8.[20,21] QOL was assessed at weeks 0, 26, 52, and 78. Only the baseline QOL assessment was evaluated for this analysis.

Hypertension was defined as a history of hypertension at study entry or a measured blood pressure >95th percentile for age, height, and gender for children or >140/95 for adults. These definitions were derived from the trial inclusion criteria.

Randomization—The randomization schedules were prepared by the Data Coordinating Center. Study investigators were blinded to the randomization allocation schedules. Allocation to the two treatment groups was designed to be equal and stratified by Core Coordinating Center, baseline eGFR (<90 vs ≥90 ml/min per 1.73 m^2) and participant's self-reported race (black vs non-black). Randomly permuted blocks of random sizes were used to help balance numbers of participants assigned to the two treatment regimens.

Experimental intervention—The study intervention included immunomodulating therapy for 12 months and renin–angiotensin blockade for 18 months. The control arm involved treatment with CSA, 5–6 mg/kg per day, divided into two doses (maximum 250 mg/day). The CSA dose was adjusted based on drug levels determined by high-performance liquid chromatography methods to achieve a 12-h trough concentration between 100 and 250 ng/ml. The experimental arm comprised treatment with MMF and oral dexamethasone. The MMF dose was 25–36 mg/kg per day, divided into two daily doses (maximum 2 g/day). The starting MMF dose was 0.5–0.67 of the full dose for 2 weeks before advancing to the full dose. The dexamethasone dose was 0.9 mg/kg (maximum 40 mg) given as a single dose on two consecutive days, weekly during weeks 1–8; every other week during weeks 10–26; and every 4 weeks during weeks 30–50, for a total of 46 doses.

Common therapy—Participants assigned to either study group were treated with prednisone (prednisolone in children requiring a liquid formulation), 0.3 mg/kg (maximum 15 mg), every other day for the first 6 months of treatment. The angiotensin-converting enzyme inhibitor lisinopril was prescribed in an escalating dose over 4 weeks, from 0.1 to 0.2 and then to 0.4 mg/kg/day (maximum 10, 20, and 40 mg, respectively). Participants who were intolerant of angiotensin-converting enzyme inhibitor received the angiotensin receptor blocker losartan, 0.5 mg/kg (maximum 50 mg) escalating to 1 mg/kg after 2 weeks (maximum 100 mg). Participants were not given an angiotensin-converting enzyme inhibitor and angiotensin receptor blocker simultaneously during the treatment phase.

Monitoring schedule—Eligibility was confirmed at the screening visit after review of laboratory and pathology data review before randomization. Treatment was initiated after the baseline visit (week 0), and subsequent visits occurred at weeks 2, 4, 6, 8, 14, 20, 26, 32, 38, 44, 52, 65, and 78. Long-term monitoring visits were conducted at 6-month intervals until study closeout.

Outcome measures—The primary outcome was based on achievement of remission of proteinuria during the first 52 weeks after randomization. A partial remission was defined as ≥50% decline in Up/c, calculated as the mean of two baseline measurements, to a level between 0.2 and 2.0 g/g. A complete remission was defined as Up/c ≤0.2 g/g. Patients were categorized by level and persistence of proteinuria reduction using the Up/c values from all study visits (Figure 2). The main secondary outcome was persistence of the reduction in proteinuria after withdrawal of immuno-suppressive agents, based on the level of proteinuria during weeks 52–78. A relapse was defined as a complete remission (Up/c <0.2 g/g) followed by the occurrence of a Up/c >2.0 g/g or a partial remission (Up/c of 0.2–2.0 g/g and <50% of baseline value) followed by the occurrence of a Up/c >2.0 g/g, which is twofold greater than the nadir of the Up/c documented by the central laboratory. Additional secondary outcomes were QOL assessed using SF-36 for adults and PedsQL for children, adverse events, and preservation of kidney function. Clinical sites were not blinded to the results of the central Up/c measurements for individual subjects under their care. Study investigators were blinded to the results of interim analyses.

Statistical analysis of baseline manuscript—This report of baseline characteristics of FSGS CT participants utilizes descriptive statistics, including medians and interquartile range, means, s.d., and ranges for continuous variables and percentage of patients for categorical variables. Analysis of variance, t-tests, χ^2 tests (when sample size was >5 in all subgroups), and Fisher's exact tests (when sample size was ≤5 in one or more subgroups) were used as appropriate to compare mean values for continuous variables and proportions for categorical variables. Regression analyses were performed on a comparison-wise basis without adjustment for multiple comparisons. QOL scores for FSGS CT participants were

compared with published data from the general US population and from patients with ESKD using two-sample *t*-tests.[20–23]

Analysis plans and power calculations for the FSGS CT

Statistical analysis plans for the primary and secondary outcomes were defined before initiation of recruitment. The intent-to-treat primary statistical analysis will compare the six-level ordered categorical variable characterizing status during the first year of follow-up (Figure 2) between the treatment groups. The six levels will be assigned scores ranging from 1 (for the most favorable category) to 6 (for the least favorable category). The mean response score will be compared between the CSA and MMF/dexamethasone groups within each of the four randomization strata defined by baseline eGFR (GFR <90 vs ≥90 ml/min per 1.73 m^2) and race (black vs non-black). A related five-level ordered outcome was used at week 78. The six-level ordered categorical variable characterizing the study outcome represents a new approach to assessing changes in proteinuria over time during the trial and has no precedent in the literature.

The FSGS Clinical Trial was originally designed to randomize 500 patients with equal allocation to the CSA and MMF/dexamethasone groups. Because existing data did not allow the remission rate to be forecast reliably, power calculations were performed assuming combined partial and complete remission probabilities scenarios ranging from 32.5 to 60.0% in the CSA control arm. The study's original design with 500 randomized patients would have provided 80% power at a two-sided α-level of 5% to detect an absolute increase in remission probability ranging from 10.8% (from 32.5 to 43.3%) to 11.5% (from 60 to 70.5%) under these remission rate scenarios. The analysis incorporates the score for the primary outcome based on the six-level ordered categorical variable. Efforts for enrollment resulted in a pool of 192 subjects, from which 138 subjects meeting eligibility criteria were randomized. The final sample size of 138 randomized patients provided 80% power at the α-level of 5% to detect an absolute increase in the probability of remission ranging from 20.9% (from 32.5 to 53.4%) to 18.2% (from 60.0 to 78.2%) under the same scenarios.

Ethics—This study was registered in clinicaltrials.gov, identifier NCT00135811, and monitored by a Data and Safety Monitoring Board. The study protocol was reviewed and approved by the institutional review board at each participating site. Informed consent and, when appropriate, assent was obtained before enrollment.

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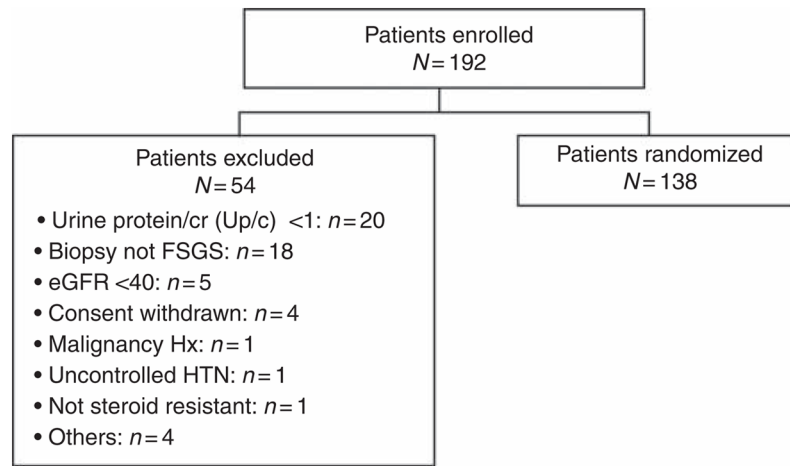**Figure 1. Focal Segmental Glomerulosclerosis (FSGS) Clinical Trial enrollment, screening, and randomization summary**

eGFR, estimated glomerular filtration rate; HTN, hypertension; Hx, history; Up/c, urine protein/creatinine ratio.
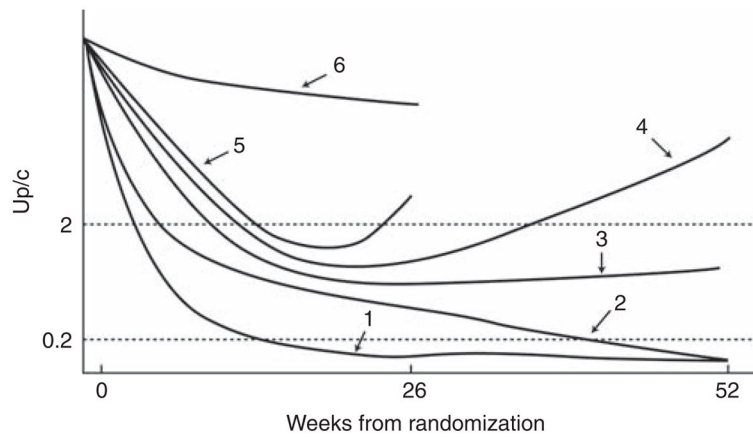
Figure 2. Focal Segmental Glomerulosclerosis (FSGS) Clinical Trial primary outcome definitions

Category 1, patients who achieved a complete remission by week 26 that was sustained to week 52; category 2, patients who achieved a partial remission at week 26 and then a complete remission at week 52; category 3, patients who achieved a partial remission by week 26 that was sustained to week 52; category 4, patients who achieved a partial remission at week 26 and then had recurrence of proteinuria before week 52; category 5, patients who achieved a partial remission before week 26 and then had a recurrence of proteinuria before week 26; category 6, patients who never had a urine protein/creatinine ratio (Up/c) <50% of the baseline value and an absolute value below 2 g/g. Participants with a baseline Up/c between 1 and 1.99 g/g were required to meet the 50% reduction in Up/c to meet the criteria of partial remission and <0.2 g/g for complete remission consistent with subjects entering with a baseline Up/c ≥2 g/g.

Table 1

Cohort baseline characteristics

Variable	Children <18 (n=93)	Adults >18 (n=45)	P-value
Age	13 (2, 15)	31 (25, 35)	<0.0001
Female	44 (47.3%)	21 (46.7%)	0.94
eGFR (ml/min per 1.73 m²)			<0.0001
40–60	7 (7.5%)	9 (20.0%)	
61–75	4 (4.3%)	8 (17.8%)	
76–90	6 (6.5%)	14 (31.1%)	
91–120	18 (19.4%)	9 (20.0%)	
>120	58 (62.4%)	5 (11.1%)	
Up/c (g/g)			0.06
1–1.99	18 (19.3%)	15 (33.3%)	
2–3.99	21 (22.6%)	15 (33.3%)	
4–7.99	24 (25.8%)	7 (15.6%)	
8+	30 (32.3%)	8 (17.8%)	
Albumin (g/dl)	2.7 (2, 3.5)	3.6 (2.7, 3.8)	0.006
Cholesterol, total (mg/dl)	318 (264, 484)[a]	261 (230, 368.5)[f]	0.01
Cholesterol, LDL (mg/dl)	184 (147, 275)[b]	152 (121, 203)[g]	0.04
Cholesterol, HDL (mg/dl)	64 (48, 89)[a]	69.5 (50.5, 93.5)[f]	0.94
Hemoglobin (anemia levels)			0.91
<11	5 (5.4%)	3 (6.7%)	
11–12	5 (5.4%)	3 (6.7%)	
≥12	83 (89.3%)	39 (86.7%)	
FSGS pathology subtype			0.25
NOS	68 (73.1%)	26 (57.8%)	
Perihilar	6 (6.5%)	4 (8.9%)	
Cellular	1 (1.1%)	3 (6.7%)	
Tip	8 (8.6%)	6 (13.3%)	
Collapsing	10 (10.8%)	6 (13.3%)	
Duration of FSGS (months)	6.4 (2.9, 12.1)	12.3 (5.4, 19.7)	0.12
Previous steroid exposure (months)	3 (2, 4)[c]	4 (2, 6)[h]	0.84
Hypertension	49 (52.7%)	31 (68.9%)	0.07
Premature birth	15 (16.1%)	3 (6.7%)	0.24
Smoking exposure			0.0001
Former smoker	2 (2.1%)	7 (15.6%)	
Passive smoker	17 (18.3%)	5 (11.1%)	
Current smoker	0 (0.0%)	10 (22.2%)	
Thrombotic events	1 (1.1%)	2 (4.4%)[h]	0.15
Family history			
Proteinuria	3 (3.4%)[a]	5 (12.2%)[i]	0.14

Variable	Children <18 (n=93)	Adults >18 (n=45)	*P*-value
FSGS	2 (2.3%)[d]	1 (2.4%)[j]	0.95
Kidney disease	5 (5.6%)[e]	7 (15.9%)[h]	0.03
ESKD	3 (3.4%)[e]	4 (9.8%)[h]	0.31

Abbreviations: eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; FSGS, focal segmental glomerulosclerosis; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NOS, not otherwise specified; Up/c, urine protein/creatinine ratio.

Continuous variables are presented as median (interquartile range).

Numbers of subjects:

[a]=87;

[b]=71;

[c]=83;

[d]=88;

[e]=89;

[f]=40;

[g]= 35;

[h]=44;

[i]=41; and

[j]=42.

Table 2

QOL assessment of children with steroid-resistant FSGS compared with healthy and ESKD controls

	FSGS CT			ESKD[a]			Healthy[b]		
	N	Mean	s.d.	N	Mean	s.d.	N	Mean	s.d.
Physical functioning									
Parent[c,d]	94	73.5	26.0	186	68.24	24.09	9430	84.48	19.51
Child[c]	80	77.7	19.1	190	74.97	19.37	5480	87.53	13.50
Emotional functioning									
Parent[c]	94	66.2	22.1	188	68.93	21.13	9430	81.31	16.50
Child[c]	80	71.0	19.0	190	72.53	20.80	5480	79.33	18.15
Social functioning									
Parent[d]	94	81.1	20.6	188	70.43	23.77	9430	83.70	19.43
Child[d]	80	85.3	16.5	189	77.80	20.96	5480	85.15	16.76
School functioning									
Parent[c,d]	89	70.0	20.8	181	59.16	25.04	9430	78.83	19.59
Child[c]	80	69.8	17.7	188	63.57	22.18	5480	81.12	16.45
Total score									
Parent[c,d]	94	72.7	17.8	186	67.02	19.84	9430	82.70	15.40
Child[c]	80	76.0	13.3	190	72.53	16.16	5480	83.84	12.65

Abbreviations: ESKD, end-stage kidney disease; FSGS CT, Focal Segmental Glomerulosclerosis Clinical Trial; QOL, quality of life.

[a] Goldstein, 2008.[21]

[b] Varni, 2007.[20]

[c] FSGS <Healthy, *P*=0.00005 to *P*<0.0000.

[d] FSGS >ESKD, *P*=0.05–0.00005.

Table 3

SF-36 QOL comparison of FSGS CT adult subjects compared with ESRD and general US population controls

	FSGS, N=43		ESKD, N=1896[a]		Healthy, N=2474[b]	
	Mean	s.d.	Mean	s.d.	Mean	s.d.
Mental health (MH)[c]	72.2	18.7	71.6	19.3	84.2	18.1
Vitality (VT)[c]	47.8	24.9	50.0	21.8	60.9	21.0
General health (GH)[c,d]	50.6	10.4	46.3	21.2	72.0	20.3
Bodily pain (BP)[d]	72.3	27.3	62.8	27.9	75.2	23.7
Physical functioning scale (PF)[c,d]	77.6	26.7	48.1	26.9	84.2	23.3
Role, emotional (RE)	71.3	42.2	63.8	41.9	81.3	33.0
Role, physical (RP)[c,d]	65.3	43.2	44.0	40.5	81.0	34.0
Social functioning (SF)[c]	75.9	28.4	70.6	27.0	83.3	22.7
Mental health composite t-score (MH)[c,f]	44.1	12.6	49.9	10.9	50.0	10.0
Physical health composite t-score (PH)3[c,d]	44.3	10.3	35.7	10.1	50.0	10.0

Abbreviations: ESKD, end-stage kidney disease; ESRD, end-stage renal disease; FSGS CT, Focal Segmental Glomerulosclerosis Clinical Trial; QOL, quality of life; SF-36, Short Form-36.

[a] Unruh, 2004.[22]

[b] Ware, 2003.[23]

[c] FSGS <Healthy, P=0.09 to <0.000001.

[d] FSGS >ESKD, P=0.01 to <0.00001.

[e] Based on 42 FSGS trial subjects.

[f] FSGS <ESKD, P=0.001.