Treatment of Idiopathic FSGS with Adrenocorticotropic Hormone Gel

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Summary

Background and objectives Adrenocorticotropic hormone (ACTH) has shown efficacy as primary and secondary therapy for nephrotic syndrome due to membranous nephropathy. The data on using ACTH to treat idiopathic FSGS are limited. This report describes our experience using ACTH for nephrotic syndrome due to idiopathic FSGS in the United States.

Design, setting, participants, & measurements Twenty-four patients with nephrotic syndrome from idiopathic FSGS were treated with ACTH gel at two academic medical centers between 2009 and 2012, either as part of investigator-initiated pilot studies (n=16) or by prescription for treatment-resistant FSGS (n=8). The primary outcome was remission of proteinuria. The median dose of ACTH was 80 units injected subcutaneously twice weekly. Treatment durations were not uniform.

Results Twenty-two patients had received immunosuppression (mean, 2.2 medications) before ACTH therapy. Six patients had steroid-dependent and 15 had steroid-resistant FSGS. At the time of ACTH initiation, the median serum creatinine (interquartile range) was 2.0 (1.1–2.7) mg/dl, estimated GFR was 36 (28–78) ml/min per 1.73 m^2, and urine protein-to-creatinine ratio was 4595 (2200–8020) mg/g. At the end of ACTH therapy, 7 of 24 patients (29%) experienced remission (n=2 complete remissions, n=5 partial remissions). All remitters had steroid-resistant (n=5) or steroid-dependent (n=2) FSGS. Two responders relapsed during the follow-up period (mean ± SD, 70±31 weeks). Adverse events occurred in 21 of 24 patients, including one episode of new-onset diabetes that resolved after stopping ACTH and two episodes of AKI.

Conclusions Response to ACTH treatment among steroid-resistant or steroid-dependent patients with FSGS is low, but ACTH gel may be a viable treatment option for some patients with resistant nephrotic syndrome due to idiopathic FSGS. Further research is necessary to determine which patients will respond to therapy.

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Introduction

FSGS, one of the leading causes of the nephrotic syndrome, is categorized as idiopathic (primary) or secondary to another disease process or a genetic mutation. FSGS is more common in black and Hispanic patients, but its incidence has increased in all racial groups over time (1–5). Untreated, it carries a high risk of ESRD. High-dose corticosteroid treatment is considered first-line therapy for idiopathic FSGS (6), leading to complete remission of proteinuria in approximately 30%–50% of patients and partial remission in approximately 20%–30% of patients. The achievement of remission in proteinuria is associated with improved long-term renal outcomes, even if relapse occurs (7,8).

In patients who have not responded to or have relapsed after steroid treatment, immunosuppressive treatment with calcineurin inhibitors (9–16), mycophenolate mofetil (MMF) (12,17–19), cyclophosphamide (20,21), rituximab (22), and plasma exchange therapy (23) have all been used with varying success. Overall, response rates are lower in patients who relapse, and many of these patients progress to ESRD. Therefore, the demand exists for novel therapies for FSGS.

ACTH injections were one of the first therapies used for the nephrotic syndrome in children (24,25) but fell out of favor when oral prednisone became an inexpensive and easy-to-use alternative. There has been recent interest in the role of ACTH in treating the nephrotic syndrome and in the noncorticosteroid actions of this drug (26). A synthetic ACTH analogue (tetracosactide, Synacthen R, Novartis Pharmaceuticals, Basel, Switzerland) and a highly purified ACTH gel (H.P. Acthar Gel, Questcor Pharmaceuticals, Inc., Union City, CA) have been used for patients with nephrotic syndrome (26–32), predominantly in those with membranous nephropathy. To date, the literature describes only five patients (one patient in Europe and four patients in the United States) with nephrotic syndrome due to idiopathic FSGS who have been treated with ACTH; one patient achieved complete response and two patients achieved partial

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response (27,30,32). Here, we present the largest experience treating idiopathic FSGS with ACTH at Columbia and Stanford University medical centers.

Materials and Methods

We evaluated 24 adults with nephrotic syndrome and FSGS who were treated with ACTH gel therapy at Columbia and Stanford University medical centers between 2009 and 2012. The institutional review board on human research at both centers approved the study. Sixteen patients (patients 4, 7, 9, 10, and 13–24) were studied prospectively as part of two distinct clinical investigator-initiated studies for the use of ACTH gel in the nephrotic syndrome (National Institutes of Health Clinical Trial numbers NCT01155141 and NCT01129284), and four patients (patients 4, 7, 9, and 10) have been described previously with shorter-term results (30,32). The remaining patients were evaluated retrospectively on the basis of chart reviews.

Per study inclusion criteria, adult patients were enrolled with biopsy-proven idiopathic FSGS and evidence of the nephrotic syndrome. Columbia trial patients did not achieve sustained remission with corticosteroids and at least one other immunosuppressive agent, and the Stanford trial required proteinuria of >2 g/d. Both sites required use of birth control for women of childbearing age and excluded patients with recent active immune therapy, pregnant patients, decreased renal function (Columbia study: estimated GFR [eGFR] <30 ml/min per 1.73 m^2; Stanford study: creatinine >2.5 mg/dl), or known contraindications to ACTH therapy. Additionally, the Stanford trial excluded patients with known secondary causes of FSGS, diabetes, acute or chronic infection, active coronary disease, cerebrovascular disease, cancer, or psychiatric disease. Patients in the investigator-initiated trials provided informed consent, whereas those evaluated by retrospective chart review had institutional review board exemption from consent. A *post hoc* evaluation of enrolled and nonenrolled patients was conducted so as to include all patients with FSGS treated with ACTH at these two centers and to provide the largest possible data set.

Classification of steroid-resistant or steroid-dependent FSGS was based on the Kidney Disease Improving Global Outcomes guideline definitions (6). The primary outcome was remission in proteinuria. Complete remission was defined as stable or improved renal function (quantified by eGFR, based on serum creatinine and calculated by the Modification of Diet in Renal Disease formula) with final proteinuria falling to <500 mg/g of creatinine by spot urine protein-to-creatinine ratio or 24-hour urine protein measurement. Partial remission was defined as stable or improved renal function with at least 50% reduction in proteinuria and final proteinuria of 500–3500 mg/g. Failure to meet the above criteria was classified as treatment failure. These outcomes were determined at the time of completion of ACTH. In addition to serum creatinine and proteinuria measurements, BP, body mass index, serum albumin, and cholesterol levels were followed. Adverse events were recorded during ACTH therapy for patients who were studied prospectively and from chart reviews for the retrospectively studied patients. The Wilcoxon rank-sum test was used to evaluate differences between groups. Statistical analysis was performed using STATA (version 11.0).

Results

Patient Characteristics

Twenty-four patients with idiopathic FSGS were treated with ACTH gel between January 2009 and April 2012. Full baseline data were available for all patients (Tables 1 and 2). Mean age (±SD) was 45.3±15.8 years at initiation of treatment. Fourteen of 24 (58.3%) patients were men. Thirteen patients were white non-Hispanic, seven were white Hispanic, three were black non-Hispanic, and one was black Hispanic. The median time from diagnosis to treatment was 23 (interquartile range [IQR], 10–43) months. Twenty-two patients had received prior immunosuppression (21 having received at least one course of corticosteroids); these patients had been treated with a mean of 2.2±1.2 immunosuppressive medications before ACTH therapy. In 10 patients at least three prior immunosuppressive therapies had failed. Additionally, two patients (patient 1 and patient 12) had undergone plasma exchange therapy. At the time of ACTH initiation, six patients had steroid-dependent FSGS and 15 had steroid-resistant FSGS. The two remaining patients were treated with ACTH as first-line therapy. Patient 1 had received his fourth renal transplant for recurrent FSGS; the remaining 23 patients had native disease.

ACTH treatment regimens were not uniform. The 12 Stanford patients (patients 13–24) were treated with an identical treatment regimen as part of a clinical trial: 40 units subcutaneously (SC) weekly for 2 weeks, 80 units SC weekly for 2 weeks, then 80 units SC twice weekly to complete 16 weeks of therapy. This is referred to as the Stanford regimen, with a cumulative drug exposure of 2160 units. Seven Columbia patients (patients 1, 2, 4, 6, 8–10) were prescribed 40 units SC twice weekly for 2 weeks, followed by 80 units SC twice weekly, for a goal duration of 24 weeks. This is referred to as the Columbia regimen, with a cumulative drug exposure of 3840 units. The treatment regimens for the remaining 5 patients were heterogeneous and were prescribed at the discretion of the treating physician, with a median regimen of 80 units SC twice weekly. The duration of therapy ranged from 12 weeks (in patient 6, in whom ACTH was discontinued because of failure of therapy) to 56 weeks, and the mean follow-up time after ACTH completion was 48±29 weeks after stopping ACTH therapy. Nineteen patients did not receive any additional immunosuppression therapy during ACTH therapy, whereas five patients received additional, concomitant immunosuppression (Table 3).

The median serum creatinine at the time of ACTH initiation was 2.0 (IQR, 1.1–2.7) mg/dl, with median eGFR of 36 (IQR, 28–78) ml/min per 1.73 m^2 (Table 2). The median pretreatment proteinuria was 4595 (IQR, 2200–8020) mg/g. Fourteen of 24 (58.3%) patients had proteinuria >3500 mg/g, with the remaining patients exhibiting additional signs of the nephrotic syndrome (hypoalbuminemia, hyperlipidemia, or edema). The median pretreatment albumin (available in 23 of 24 patients) was 2.9 (IQR, 2.0–3.6) g/dl and the mean pretreatment total cholesterol (available for 19 of 24 patients) was 274±113 mg/dl. As evaluated by the

Table 1. Baseline data for patients with FSGS treated with adrenocorticotropic hormone

Patient	Age/(yr)/Sex	Race/ Ethnicity	FSGS Morphology	Previous Immunosuppression	Steroid Response Category	Time from Diagnosis to Treatment (mo)	Serum Creatinine (mg/dl)	eGFR (ml/min per 1.73 m^2)	Proteinuria (mg/g)
Columbia patients									
1	42/Male	WNH	NOS	Steroids, MMF, tacrolimus[a]	SR	2[b]	2.7	28	7000
2	38/Female	BNH	NOS	Steroids, MMF, cyclosporine	SR	56	2.3	31	5046
3	21/Female	WNH	Tip	Steroids, tacrolimus, cyclosporine	SD	12	1.1	67	5200
4	40/Male	WNH	Tip	Steroids, tacrolimus, cyclosporine, MMF	SR	96	1.2	71	2100
5	18/Male	BNH	Tip	Steroids, tacrolimus, MMF	SR	13	2.6	42	11,200
6	46/Male	WNH	NOS	Steroids, cyclophosphamide, MMF, tacrolimus	SD	30	3.2	23	16,800
7	64/Female	WH	Cellular	Steroids, MMF, tacrolimus,	SD	61	1.6	35	10,300
8	60/Female	WNH	Cellular	Steroids, tacrolimus, MMF, cyclosporine	SR	23	2.3	23	2300
9	66/Male	WNH	Tip	Steroids, cyclosporine, MMF	SR	132	1.0	66	1600
10	36/Male	WNH	NOS	Steroids, cyclosporine	SR	96	0.8	116	2200
11	30/Female	WNH	Tip	Steroids, MMF, cyclosporine, tacrolimus	SR	13	3.4	17	8800
12	47/Female	BH	Tip	Steroids, tacrolimus[a]	SR	4	3.6	17	15,200
Stanford patients									
13	66/Male	WH	NOS	Steroids	SR	14	2.2	30	2020
14	65/Male	WNH	Cellular	None	NA	8	2.7	24	3170
15	64/Male	WNH	NOS	Steroids	SD	22	1.04	76	7240
16	27/Male	WH	NOS	Steroids, cyclosporine	SR	28	2.99	35	2200
17	58/Male	WNH	Tip	None	NA	4	2.2	32	3550
18	29/Male	BNH	Collapsing	Steroids, MMF	SR	6	3.3	28	23,800
19	28/Female	WH	Tip	Cyclosporine	NA	19	0.6	124	4860
20	40/Male	WH	NOS	Steroids	SD	29	1.1	84	2320
21	39/Female	WH	Tip	Steroids, MMF	SR	24	1.7	37	1710
22	69/Female	WNH	Tip	Steroids, tacrolimus	SR	94	0.6	93	4330
23	56/Female	WNH	Cellular	Steroids	SR	2	1.1	56	6560
24	39/Male	WH	Tip	Steroids, cyclosporine	SD	29	1.0	94	2000

eGFR, estimated GFR; WNH, white non-Hispanic; NOS, not otherwise specified; MMF, mycophenolate mofetil; SR, steroid resistant; BNH, black Non-Hispanic; SD, steroid dependent; WH, white Hispanic; BH, black Hispanic; NA, not applicable.

[a]Patients 1 and 12 also underwent plasma exchange therapy.

[b]Patient 1 had undergone four prior renal transplants for recurrent FSGS and was diagnosed with another recurrence 2 months before starting ACTH.

Table 2. Baseline characteristics for all patients

Characteristic	Value
Mean age ± SD (yr)	45.3±15.8
Sex (*n*)	
Male	14
Female	10
Race/ethnicity (*n*)	
White non-Hispanic	13
White Hispanic	7
Black non-Hispanic	3
Black Hispanic	1
FSGS morphology (*n*)	
Tip	11
NOS	8
Cellular	4
Collapsing	1
Previous immunomodulatory drugs used (*n*)	
0	2
1	5
2	7
3	5
4	5
Serum creatinine (mg/dl)	2.0 (1.1–2.7)
eGFR (ml/min per 1.73 m^2)	36 (28–78)
Proteinuria (mg/g)	4595 (2200–8020)
Time from diagnosis to treatment (mo)	23 (10–43)
Steroid response category (*n*)	
SDNS	6
SRNS	15
NA	3

Values with ranges in parentheses are medians and interquartile ranges. NOS, not otherwise specified; eGFR, estimate GFR; SDNS, steroid-dependent nephrotic syndrome; SRNS, steroid-resistant nephrotic syndrome; NA, not applicable.

Columbia Classification for the histologic morphology of FSGS (33), 11 patients had tip variant, 8 had FSGS not otherwise specified, 4 had cellular variant, and 1 had collapsing variant. One patient (patient 6) underwent genetic testing, with no identifiable mutation in *NPH52*, *ACTN4*, *TRPC6*, or *INF2*.

Outcomes

Data were available for 23 of the 24 patients for analysis; one patient (patient 19) was lost to follow-up after 5 weeks of ACTH therapy. Seven of 24 patients (29%) met criteria for remission with ACTH treatment, with 5 patients achieving partial response and 2 patients achieving complete response (Table 3 and Figure 1). Three of these patients (patients 15, 22, and 23) had been treated with the Stanford regimen, two (patients 2 and 4) with the Columbia regimen, and two (patients 3 and 12) with individualized treatment regimens. In those who achieved remission, the median time to reduced proteinuria was 5 weeks (range, 2–16 weeks) and the median time to remission in proteinuria was 16 weeks (range, 5–18 weeks) after initiation of ACTH therapy (Figure 1).

There was a trend toward decreasing median proteinuria (pre-ACTH, 4595 [IQR, 2200–8020] mg/g; post-ACTH, 2243 [IQR, 1570–5620] mg/g); not reaching significance [P=0.08]). Median serum creatinine (pre-ACTH, 2.0 [IQR, 1.1–2.7] mg/dl; post-ACTH, 1.4 [IQR, 1.1–2.0] mg/dl; P=0.34), and median eGFR (pre-ACTH, 36 (28–78) ml/min per 1.73 m^2; post-ACTH, 45 (28–74) ml/min per 1.73 m^2; P=0.69) did not change with ACTH treatment. The responders and nonresponders did not differ significantly in pre-ACTH serum creatinine (P=0.3), eGFR (P=0.5), proteinuria (P=0.4), or time from diagnosis to treatment (P=0.9). In addition to the seven responders, one patient (patient 7) experienced partial response in proteinuria, from 10,300 to 1600 mg/g, with ACTH but had 5380 mg/g of proteinuria before discontinuing therapy and did not meet remission criteria. Another patient (patient 8) achieved partial response in proteinuria with ACTH but relapsed during the last month of treatment. The mean follow-up time for all patients was 70±31 weeks (48±29 weeks after stopping ACTH).

During the follow-up period, five of seven patients who achieved remission with ACTH had a sustained remission, with a median follow-up time of 90 (range, 23–104) weeks for these patients (median follow-up, 66 weeks after stopping ACTH) (Figure 1). Two of these long-term responders were taking additional immunosuppressive medications during the follow-up period (patient 3: MMF plus tacrolimus; patient 12: MMF). Two patients (patients 15 and 23) who achieved partial remission with ACTH therapy experienced relapse during the follow-up period. After relapse, patient 23 was treated with cyclosporine without response, then achieved partial remission with a second course of Stanford protocol ACTH; on last follow-up, however, this patient did not meet criteria for remission because of an elevated serum creatinine.

Five of the seven patients who experienced remission were women, five were white non-Hispanic, and all were either steroid resistant (n=5) or steroid dependent (n=2) before starting ACTH therapy (Table 4). In comparing those who experienced remission versus those did not, remitters had lower serum creatinine levels at baseline, but no such trend was observed for baseline age, ethnicity, prior steroid response category, FSGS subtype, the use of additional immunosuppression during ACTH treatment, the cumulative ACTH dose, or duration of treatment (Table 4).

Fifty-two adverse events were recorded during ACTH therapy in 21 patients (Table 5). Twenty-three corticosteroid-like adverse effects were reported, including one episode of new-onset diabetes that resolved with cessation of ACTH. Four patients required hospitalization during treatment: patient 5, for volume overload and a transudative pleural effusion that was attributed to nephrosis; patient 8, who had a history of cerebrovascular disease and was hospitalized with an ischemic stroke; patient 16, who experienced reversible new-onset diabetes; and patient 23, who experienced two episodes of AKI while receiving ACTH (also attributed to nephrosis), both of which resolved. One patient was diagnosed clinically (*i.e.*, without imaging) with pneumonia and was treated with azithromycin, and four other patients experienced symptoms of an upper respiratory tract infection during therapy. No other serious infections occurred. Body mass index did not significantly change with ACTH treatment (pre-ACTH, 29.8±5.5 kg/m^2; post-ACTH,

Table 3. Treatment regimens, data pre- and post-adrenocorticotropic hormone, and outcome category for patients with FSGS treated with adrenocorticotropic hormone

Patient	Treatment Regimen	IMD during ACTH Therapy	Duration of ACTH Therapy (wk)	Change in Laboratory Values before/after ACTH Treatment			Outcome
				Variable	Initial	Final	
Columbia patients							
1	Columbia	Tacrolimus, mycophenolic acid[a,b]	15	Scr (mg/dl)	2.7	3.7	Failed
				Proteinuria (mg/g)	7000	2841	
				Albumin (g/dl)	3.7	3.7	
2	Columbia	None	24	Scr (mg/dl)	2.3	1.3	Partial
				Proteinuria (mg/g)	5046	963	
				Albumin (g/dl)	2.1	3.4	
3	Individual	Tacrolimus	36	Scr (mg/dl)	1.1	0.7	Partial
				Proteinuria (mg/g)	5200	1500	
				Albumin (g/dl)	1.9	3.4	
4	Columbia	None	24	Scr (mg/dl)	1.2	1.4	Complete
				Proteinuria (mg/g)	2100	272	
				Albumin (g/dl)	3.7	4.0	
5	Individual	Cyclosporine	34	Scr (mg/dl)	2.6	1.1	Failed
				Proteinuria (mg/g)	11,200	7789	
				Albumin (g/dl)	1.3	2.3	
6	Columbia	None	12	Scr (mg/dl)	3.2	2.9	Failed
				Proteinuria (mg/g)	16,800	25,000	
				Albumin (g/dl)	1.6	1.4	
7	Individual	None	56	Scr (mg/dl)	1.6	1.2	Failed
				Proteinuria (mg/g)	10,300	5380	
				Albumin (g/dl)	2.0	3.3	
8	Columbia	None	28	Scr (mg/dl)	2.3	1.7	Failed
				Proteinuria (mg/g)	2300	5620	
				Albumin (g/dl)	2.9	3.6	
9	Columbia	None	23	Scr (mg/dl)	1.0	1.0	Failed
				Proteinuria (mg/g)	1600	1900	
				Albumin (g/dl)	3.6	3.8	
10	Columbia	Cyclosporine	19	Scr (mg/dl)	0.8	0.9	Failed
				Proteinuria (mg/g)	2200	3847	
				Albumin (g/dl)	2.9	2.4	
11	Individual	MMF	36	Scr (mg/dl)	3.4	1.5	Failed
				Proteinuria (mg/g)	8800	9500	
				Albumin (g/dl)	2.3	1.6	
12	Individual	None[b]	36	Scr (mg/dl)	3.6	1.3	Partial
				Proteinuria (mg/g)	15,200	891	
				Albumin (g/dl)	2.1	3.4	
Stanford patients							
13	Stanford	None	16	Scr (mg/dl)	2.2	2.2	Failed
				Proteinuria (mg/g)	2020	1620	
				Albumin (g/dl)	3.8	3.9	

Table 3. (Continued)

Patient	Treatment Regimen	IMD during ACTH Therapy	Duration of ACTH Therapy (wk)	Change in Laboratory Values before/after ACTH Treatment			Outcome
				Variable	Initial	Final	
14	Stanford	None	16	Scr (mg/dl)	2.7	2.9	Failed
				Proteinuria (mg/g)	3170	2240	
				Albumin (g/dl)	2.9	NA	
15	Stanford	None	16	Scr (mg/dl)	1.0	1.1	Partial
				Proteinuria (mg/g)	7240	1940	
				Albumin (g/dl)	NA	3.3	
16	Stanford	None	16	Scr (mg/dl)	3.0	2.7	Failed
				Proteinuria (mg/g)	2200	2240	
				Albumin (g/dl)	4.8	NA	
17	Stanford	None	16	Scr (mg/dl)	2.2	2.1	Failed
				Proteinuria (mg/g)	3550	4580	
				Albumin (g/dl)	4.3	3.6	
18	Stanford	None	16	Scr (mg/dl)	3.3	3.9	Failed
				Proteinuria (mg/g)	23,800	18,600	
				Albumin (g/dl)	1.7	2.8	
19	Stanford	None	16	Scr (mg/dl)	0.6	NA	Lost to follow-up
				Proteinuria (mg/g)	4860	NA	
				Albumin (g/dl)	2.4	NA	
20	Stanford	None	16	Scr (mg/dl)	1.1	1.1	Failed
				Proteinuria (mg/g)	2320	1570	
				Albumin (g/dl)	3.4	3.8	
21	Stanford	None	16	Scr (mg/dl)	1.7	2.0	Failed
				Proteinuria (mg/g)	1710	3230	
				Albumin (g/dl)	3.2	3.9	
22	Stanford	None	16	Scr (mg/dl)	0.6	0.7	Complete
				Proteinuria (mg/g)	4330	270	
				Albumin (g/dl)	1.7	3.6	
23	Stanford	None	16	Scr (mg/dl)	1.1	1.2	Partial
				Proteinuria (mg/g)	6560	2120	
				Albumin (g/dl)	2.2	2.1	
24	Stanford	None	16	Scr (mg/dl)	1.0	1.7	Failed
				Proteinuria (mg/g)	2000	6100	
				Albumin (g/dl)	3.3	NA	

Patient 19 was lost to follow-up. Columbia protocol: 80 units subcutaneously (SC) twice weekly for 24 weeks. Stanford protocol: 40 units subcutaneously weekly for 2 weeks, 80 units SC weekly for 2 weeks, then 80 units SC twice weekly to complete 16 weeks of therapy. Individual treatment regimens: Patient 3: 80 units twice weekly for 18 weeks, then 80 units weekly for 18 weeks; patient 5: 80 units twice weekly for 16 weeks, then three times weekly for 18 weeks; patient 7: 80 units twice weekly for 24 weeks, then 50 units twice weekly for 10 weeks, then 50–80 units weekly for 22 weeks; patient 11: 80 units twice weekly for 20 weeks, then 40 units twice weekly for 16 weeks; patient 12: 80 units twice weekly for 13 weeks, then 80 units weekly for 21 weeks. IMD, immunosuppressive drugs; ACTH, adrenocorticotropic hormone; Scr, serum creatinine, MMF, mycophenolate mofetil; NA, not applicable.

[a]Patient 1 had undergone four prior renal transplants for recurrent FSGS and was diagnosed with another recurrence 2 months before starting ACTH.

[b]Patient 1 underwent plasma exchange therapy; patient 12 completed plasma exchange therapy during week 1 of ACTH therapy.

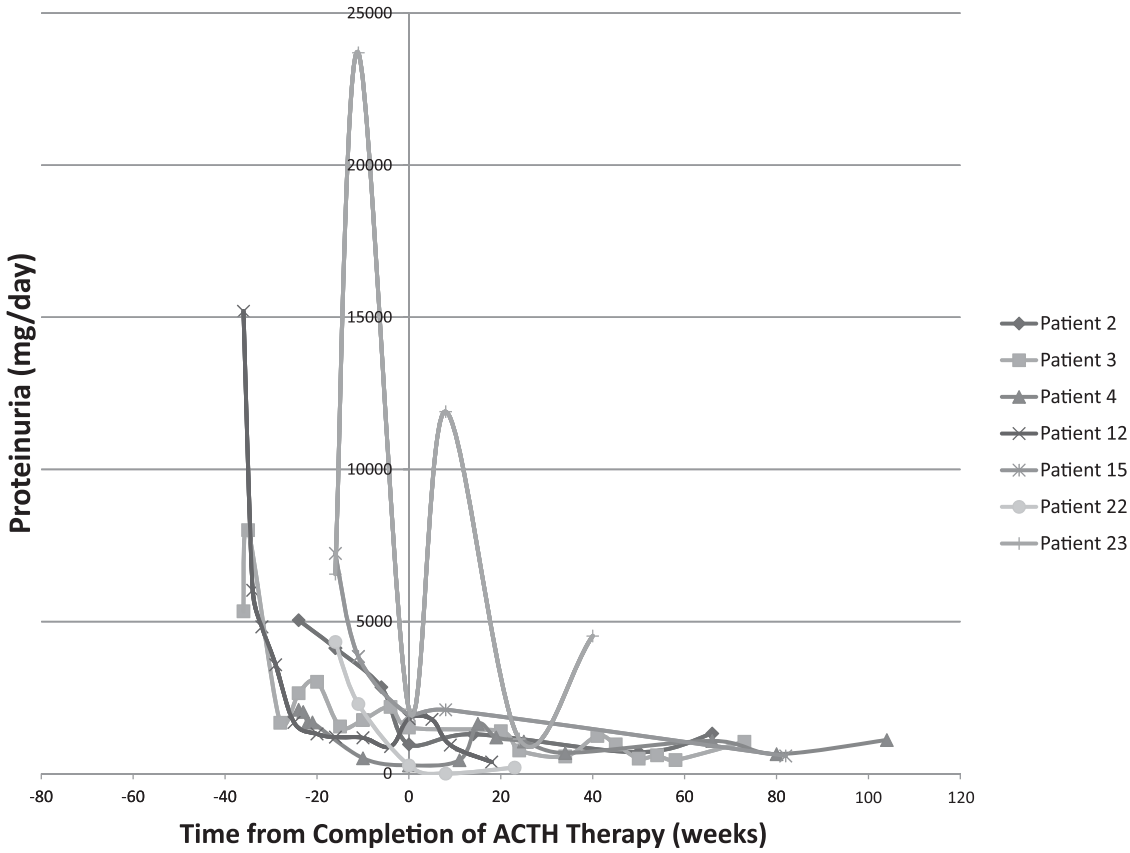

Figure 1. | **Proteinuria trend versus time for seven patients who achieved remission with adrenocorticotropic hormone (ACTH).** Time zero demarcates the end of the ACTH treatment course for each patient. Patients 15 and 23 experienced relapse after ACTH therapy, with patient 15 not meeting remission criteria because of worsened renal function, and patient 23 attaining remission in proteinuria with a repeat course of Stanford Protocol ACTH but not meeting criteria for remission based on serum creatinine. Additional immunosuppressive therapy used during follow-up period: patient 3, mycophenolate mofetil and tacrolimus; patient 12, mycophenolate mofetil; patient 23, cyclosporine and ACTH.

29.9±5.6 kg/m^2; P=0.93), and ACTH had no discernable effect on BP.

Discussion

This report represents the largest experience of treating idiopathic FSGS with ACTH. Most of these patients were steroid resistant (n=15) or steroid dependent (n=6), and in most of them at least two previous immunosuppressive agents had failed. The cumulative remission rate with ACTH therapy was 29%. A nonsignificant decrease in median proteinuria was observed (P=0.08), and neither mean serum creatinine (P=0.34) nor mean eGFR (P=0.69) changed. Two responders experienced relapse during the follow-up period, one of whom experienced a partial remission in proteinuria with a repeat course of Stanford protocol ACTH but did not meet criteria for remission at last follow-up because of an elevated serum creatinine. Adverse events were reported in 21 of 24 patients, including a high rate of steroid-like adverse effects. However, most adverse events were mild and transient.

There is limited published literature on the use of ACTH for FSGS. ACTH was first used for the nephrotic syndrome in children in the 1950s and was reintroduced as a treatment of nephrotic syndrome in last two decades, initially in Europe with a synthetic ACTH depot and then in the United States with natural ACTH gel (26–30,32). The patients in these studies had high (50%–90%) rates of remission, but most successes were seen in patients with the nephrotic syndrome due to idiopathic membranous nephropathy. To date, only five patients treated with ACTH for FSGS have been described (27,30,32).

Although only 7 of 24 patients experienced remission in this series, the refractory nature of these patients' disease to previous therapies, the relatively favorable safety profile of ACTH, the improved prognosis of patients with FSGS who experience remission, and the limited available treatment options for resistant disease may prompt physicians to consider ACTH in cases of FSGS refractory to steroids and second-line therapies. As a comparison, in the recent National Institutes of Health clinical trial in children and young adults with steroid-resistant FSGS, cyclosporine led to 46% remission versus 33% with MMF/dexamethasone (12). The decreased response rates observed in our study compared with previous studies using ACTH for the nephrotic syndrome may be due to heterogeneity in the pathogenesis to FSGS, genetic causes of FSGS that may not be responsive to treatment, and the treatment-resistant nature of FSGS compared with idiopathic membranous nephropathy. Moreover, because all patients who underwent

Table 4. Baseline characteristics and treatment regimen, organized by response category during adrenocorticotropic hormone therapy

Variable	Steroid Response Category (*n*)	Age (yr)	Sex (*n*)	Race/ Ethnicity (*n*)	FSGS Morphology (*n*)	Time from Diagnosis to Treatment (mo)	Previous IMD (*n*)	Creatinine (mg/dl)	eGFR (ml/min per m^2)	Proteinuria (mg/d)	IMD use during ACTH (*n*)	Treatment Regimen (*n*)
Complete remission (*n*=2)	SR: 2	55 (40–69)	M: 1 F: 1	WNH: 2	Tip: 2	95 (94–96)	2: 1 4: 1	0.9 (0.6–1.2)	82 (71–93)	3215 (2100–4330)	Yes: 0 No: 2	Stanford (1) Columbia (1)
Partial remission (*n*=5)	SR: 3 SD: 2	43 (21–64)	M: 1 F: 4	WNH: 3 BNH:1 BH: 1	NOS: 2 Tip: 2 Cellular: 1	12 (2–56)	1: 2 2: 1 3: 2	1.8 (1.1–3.6)	49 (17–76)	7849 (5046–15,200)	Yes: 2 No: 3	Stanford (2) Columbia (1) Individual (2)
Failed (*n*=17)	SR: 9 SD: 5 NA: 3	44 (18–66)	M: 12 F: 5	WNH: 8 BNH: 2 WH: 7	NOS: 6 Tip: 7 Cellular: 3 Collapsing: 1	31 (2–132)	0: 2 1: 3 2: 5 3: 4 4: 3	2.1 (0.6–3.4)	49 (17–124)	3170 (1600–23,800)	Yes: 2 No: 15	Stanford (9) Columbia (5) Individual (3)

Values with ranges in parentheses are medians and interquartile ranges. IMD, immunosuppressive therapy; ACTH, adrenocorticotropic hormone; SR, steroid resistant; SD, steroid dependent; M, male; F, female; WNH, white non-Hispanic; BNH: black non-Hispanic; BH, black Hispanic; NOS, not otherwise specified; WH: white Hispanic.

remission had steroid-dependent or steroid-resistant FSGS, our results support recent research that ACTH may have actions beyond a corticosteroid-like effect, possibly *via* anti-inflammatory mechanisms or by acting directly on podocytes *via* the melanocortin 1 receptor (26,31). Although our study had a high percentage of steroid-dependent and -resistant patients, these are the patients often seen at our referral centers and for whom data on therapies such as ACTH are needed.

This study represents the largest experience regarding the use of ACTH for idiopathic FSGS. Although four of our patients have previously been described (30,32), we present longer follow-up data for these patients, including a median follow-up of 90 weeks (66 weeks after stopping ACTH) in patients who responded to treatment. These patients reflect a difficult-to-treat group: Twenty-one of 24 patients had steroid-dependent or steroid-resistant disease, 10 patients had not responded to or had relapsed after at least three prior therapies, and, on average, they had used more than two immunosuppressive therapies before ACTH. On average, they had substantial proteinuria and significant renal dysfunction. This is a challenging patient population at substantial risk for progression of renal disease and with limited treatment options. Given the limited data in treating resistant FSGS and the high treatment cost of ACTH, referral to major institutions for enrollment in protocols and clinical trials that evaluate new treatments such as ACTH should be considered.

This study also helps to guide therapy with ACTH. The median time to proteinuria decline was 5 weeks (range, 2–16 weeks), and the median time to remission was 16 weeks (range, 5–18 weeks) after initiation of ACTH therapy. On the basis of these data, we recommend that ACTH be discontinued for patients with FSGS who have not demonstrated any significant decline in proteinuria by 12–16 weeks. This approach may obviate the prolonged and futile use of a drug that has potentially important adverse effects and high treatment costs. This study also provides useful information on adverse events with ACTH gel in patients with FSGS. We noted more adverse events than prior reports of using this dosing regimen of ACTH gel, one of which was retrospective (six adverse events in 21 patients) (30) and one of which was prospective (12 adverse events noted in 15 patients) (32).

Our findings are subject to important limitations. The data combine retrospective observational data with prospective data of patients who were not randomly assigned to therapy. We have no comparison group against which to interpret these results. Twenty-two of 24 patients were previously receiving immunosuppression, and it is possible that these prior therapies had a lingering effect that influenced clinical outcomes in these patients. The dosing regimens and follow-up times varied, and additional immunosuppression was used in some patients both during and after ACTH therapy. Lack of a control group means we cannot definitively attribute responses to the effect of ACTH, although this is unlikely in a patient population in which spontaneous remissions are exceedingly rare (9). Likewise, lack of controls also means we cannot be certain which of the many adverse events were due to ACTH versus other drugs or associated comorbid conditions. No cost-benefit analysis has been performed, an

Table 5. Adverse events observed during adrenocorticotropic hormone therapy

Steroid-like Adverse Events	Events (*n*)	Patients Experiencing Event (*n*)
Swelling/edema/volume overload/weight gain	5	5
Increased energy	4	4
Mood alteration/anxiety/increased energy	4	4
Elevated BP	3	3
Acne	2	2
Dyspepsia/bloating	2	2
Increased appetite	1	1
Face swelling	1	1
Hyperglycemia/diabetes (reversible)	1	1
Other reported adverse events		
Sinus congestion/rhinorrhea/upper respiratory tract symptoms	4	4
Muscle cramps	4	4
AKI	2	1
Pain/bruising at injection site	2	2
Tanning of skin	2	2
Rash	2	2
Fatigue	1	1
Vertigo	1	1
Pneumonia[a]	1	1
Slow wound healing	1	1
Redness of face on injection days	1	1
Nausea	1	1
Headache	1	1
Polyuria	1	1
Palpitations	1	1
Intermittent chest discomfort	1	1
Loose stools	1	1
Shortness of breath after injection	1	1
Total events (*n*)	52	

[a]Patient 6 was clinically diagnosed with pneumonia and treated empirically with azithromycin. No chest radiography was performed.

important note of caution given the very high costs of ACTH treatment regimens. The percentage of patients with tip lesion FSGS was high, which may be responsible for increased responsiveness to treatment. Moreover, post-treatment biopsies were not performed, and no biomarkers were measured to shed light on the mechanism of action of ACTH. Lastly, we were unable to predict ACTH response in any subgroup of patients with FSGS.

In conclusion, we present the largest cumulative experience of using ACTH therapy for idiopathic FSGS in a group of predominantly steroid-dependent or steroid-resistant patients. Complete or partial remission with ACTH therapy was achieved in 7 of 24 patients, all of whom had steroid-dependent or steroid-resistant disease, and two relapses were observed during the follow-up period. ACTH may be a useful therapy in some patients with refractory or relapsed FSGS. These results highlight the need to further evaluate ACTH in the treatment of FSGS, particularly in the setting of resistant or relapsed disease.

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