

# Adrenocorticotrophic hormone analog use for podocytopathies

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**Background:** Adrenocorticotrophic hormone is being increasingly studied for treatment of various glomerulopathies, most notably membranous nephropathy. Less data are available regarding its use in idiopathic nephrotic syndrome (INS) secondary to minimal change disease (MCD) or focal segmental glomerulosclerosis (FSGS). We report here our experience with H.P. Acthar® Gel (repository corticotropin injection) as first-line or subsequent therapy in patients with INS.

**Methods:** Data were taken from three patients with MCD and ten patients with FSGS from around the US, who were treated with Acthar Gel as initial or subsequent therapy. Treatment was solely at the discretion of the primary nephrologist without a specific protocol. A complete response (CR) was defined as final urine protein-to-creatinine ratio <500 mg/g and a partial response (PR) as 50% decrease without rise of serum creatinine. Side effects and tolerability were noted.

**Results:** All three patients with MCD received Acthar Gel as second-line or later immunosuppressive (IS) therapy and all responded (one CR and two PRs). Two of the ten patients with FSGS received Acthar Gel as first-line IS therapy, while the other eight had failed multiple agents. Four of the ten patients with FSGS had responses, including two CRs and two PRs. The three patients with MCD tolerated therapy well without side effects. Five patients with FSGS tolerated therapy well, while five had various steroid-like side effects, resulting in therapy discontinuation in two patients.

**Conclusion:** Acthar Gel is a viable alternative IS agent for treatment of INS in patients intolerant or resistant to conventional therapy. More data are needed to better define its appropriate place.

**Keywords:** nephrotic syndrome, minimal change disease, focal segmental glomerulosclerosis, adrenocorticotrophic hormone, ACTH, Acthar Gel

## Introduction

Primary podocytopathies underlying idiopathic nephrotic syndrome (INS) include minimal change disease (MCD) and a group of histologic lesions collectively referred to as focal segmental glomerulosclerosis (FSGS). Despite similarities between the two (eg, generalized foot process effacement, circulating permeability factors, and response to corticosteroids), MCD and FSGS are considered distinct disease processes.<sup>1</sup> Five histologic subtypes of FSGS that have variable responses to treatment, overall prognoses, and probably different pathogeneses are recognized in the recent Columbia classification.<sup>2</sup>

The initial immunosuppressive (IS) treatment of both MCD<sup>3</sup> and the FSGS group<sup>4</sup> involves corticosteroids. In MCD patients who are intolerant to steroids or

with frequently relapsing disease (either steroid dependent or steroid resistant), other IS agents have been used; these include alkylating agents, as well as calcineurin inhibitors (CNIs), mycophenolate mofetil (MMF), and rituximab.<sup>4-6</sup> Although recommended by guidelines,<sup>4</sup> no randomized controlled trials (RCTs) support steroid use in FSGS. In FSGS patients resistant or intolerant to steroids, RCTs do support CNIs<sup>7,8</sup> and possibly dexamethasone with MMF.<sup>9</sup> Rituximab has also been used.<sup>10</sup>

Adrenocorticotrophic hormone (ACTH) has been known since the 1950s to decrease both proteinuria and hyperlipidemia in INS.<sup>11,12</sup> ACTH fell out of favor with the development of oral corticosteroids, presumably due to the need for multiple injections. Interest in ACTH for INS was renewed in 1999, when synthetic ACTH was found to effectively reduce proteinuria in patients with membranous nephropathy (MN).<sup>13</sup> Subsequently, one small RCT in MN,<sup>14</sup> as well as multiple case series and cohort studies in that and various other glomerulopathies, including MCD and FSGS, confirmed the efficacy of ACTH (porcine or a synthetic preparation).<sup>15-24</sup> We report here our experience with 13 cases of INS (three MCD and ten FSGS) treated with H.P. Acthar® Gel (repository corticotropin injection; Mallinckrodt ARD Inc., Hazelwood, MO, USA).

## Methods

We herein report a retrospective case series, collected from the USA, of patients with either MCD or idiopathic FSGS treated with the ACTH analog Acthar Gel. The Office of Human Research Institutional Review Board, Sidney Kimmel Medical College at Thomas Jefferson University, deemed this study exempt from ethical approval. Due to the retrospective nature of this study, no patient consent was required. Various nephrologists directed the care of these patients, and there was no set protocol for treatment. All patients received prior renin-angiotensin system (RAS) blockade or IS therapy at the discretion of the treating nephrologist. Baseline clinical data obtained include demographics (age, sex, and race), comorbidities, degree of proteinuria (24-hour urine or spot urine protein-to-creatinine ratio [UPCR] in milligrams per gram), serum creatinine, serum albumin, and lipid levels when available. In cases of FSGS, the histologic variant was noted if available. These biopsies were interpreted locally and were not centrally reviewed.

Patients were followed for variable periods of time. Follow-up data included serum creatinine and albumin, urine protein, and lipid levels. Minimum criteria for remission were >50% proteinuria reduction, with stability of renal function (rise of serum creatinine <25%). A limited remission

(LR) had residual proteinuria still in the nephrotic range, whereas a partial remission (PR) resulted in subnephrotic levels (<3,500 mg/24 hours or <3,500 mg/g of creatinine). Complete remission (CR) was defined as 24-hour urine protein <500 mg or spot urine protein <500 mg/g creatinine, again with stable renal function. All others were considered to have no response (NR). Results are merely descriptive, as no formal statistical analysis was performed, owing to the small numbers.

## Results

We identified a total of 13 patients, including three with MCD and ten with FSGS. The latter included one with glomerular tip lesion, three with collapsing FSGS, and two patients with FSGS not otherwise specified (NOS). The other four cases were not further categorized. Baseline data are detailed in Table 1. Age of onset ranged from 6 years to 73 years (mean of 39 years; median of 38 years). Eight were female and eight were Caucasian, four African American, and one Asian.

Two MCD patients were initially treated with oral prednisone (60 mg/d). One was responsive but relapsed, and the other failed to respond, in association with intolerance (worsening edema). The third MCD patient had a long history of MCD (16 years). Most recently, he was refractory to a combination of prednisone, cyclophosphamide, and MMF.

Of the ten FSGS patients, two were treated only with RAS blockade prior to Acthar Gel. Seven were treated with prednisone – either alone (patients 10 and 13) or in combination with various other IS agents (Table 1), and one was treated with only MMF. The dose of Acthar Gel ranged from 40 U weekly to 80 U twice weekly, with most receiving 80 U twice weekly (Table 2). Therapy duration ranged from 1 month to 10 months, with the exception of two patients who remained on ongoing therapy, one with MCD receiving 80 U weekly for a total duration of 17 months and one FSGS patient receiving 40 U weekly for a total duration of 7 months. The other eleven patients received Acthar Gel with a median duration of 7 months (mean: 5.9 months) and a total dose ranging from 640 U to 7,000 U (mean: ~3,800 U; median: ~4,800 U) for that group. Two patients with MCD received concomitant RAS blockade, as did eight of ten patients with FSGS. Vitamin D (ergocalciferol: 50,000 U weekly) was concomitantly given to three FSGS patients, as was a statin to two MCD patients and three FSGS patients.

## MCD results

All three patients with MCD had a response. Patient 1 initially responded to 60 mg/d of oral prednisone with a decrease in proteinuria from ~16,000 mg/d to 400 mg/d. Upon tapering

**Table 1** Baseline characteristics and previous therapy

	Patient number	Age, years	Race	Duration prior to Acthar Gel	Sex	Proteinuria, mg/g or mg/d	Serum creatinine, mg/dL	Serum albumin, g/dL	Serum TC, mg/dL	Initial IS therapy	Response to initial therapy
MCD	1	32	Asian	6 months	F	16,465 mg/d	0.84	0.8	506	Prednisone 60 mg/d	CR
	2	73	C	6 months	M	4,060 mg/d; 3,100 mg/g	1.2	4.1	159	Prednisone 60 mg/d	NR
	3	6	C	16 years	M	12,400 mg/g	1.3	2.2	NA	Prednisone Azathioprine MMF Cyclophosphamide	NR
FSGS	4 Tip	44	C	6 months	F	8,430 mg/d	0.84	2.3	290	Acthar Gel	NR
	5 Coll	33	C	10 months	F	7,920 mg/d	0.99	1.9	404	Prednisone 60 mg/d PE/Dexa/MMF Abatacept	NR NR PR
	6	38	C	10 years	F	5,800 mg/d	1.2	3.3	NA	Acthar Gel	NR
	7 Coll	17	AA	10 months	M	36,000 mg/g	1.79	1.2	359	Prednisone 60 mg/d Cys A 150 mg bid	NR
	8 NOS	65	C	4 years	M	7,700 mg/g	1.93	3.6	189	MMF 1,500 mg bid	NR
	9 NOS	19	AA	3 years	F	16,100 mg/g	1.48	2.2	251	Prednisone 60 mg/d Cys A 150 mg bid	CR CR
	10 Coll	54	AA	8 months	F	11,090 mg/g	1.34	2.2	289	Prednisone 60 mg/d Prednisone 80 mg/d	PR Initial PR, then side effects
	11	52	AA	9 years	F	6,700 mg/g	6.3	1.2	NA	Prednisone Cyclophosphamide Cys A MMF Tacrolimus Rituximab	NR
	12	33	C	10 years	F	3,100 mg/g	0.9	3.3	NA	Prednisone Cyclophosphamide MMF Azathioprine Pentoxifylline	NR
	13	43	C	4 years	M	5,900 mg/g	0.9	4.2	NA	Prednisone	PR

**Note:** The laboratory values in this table are those obtained prior to any IS therapy.

**Abbreviations:** AA, African American; bid, twice daily; C, Caucasian; Coll, collapsing FSGS; CR, complete remission; Cys A, cyclosporine A; Dexa, dexamethasone; F, female; FSGS, focal segmental glomerulosclerosis; IS, immunosuppressive; M, male; MCD, minimal change disease; MMF, mycophenolate mofetil; NA, not available; NOS, FSGS not otherwise specified; NR, no response; PE, plasma exchange; PR, partial remission; TC, total cholesterol; Tip, glomerular tip lesion.

the prednisone, a marked relapse in proteinuria occurred, ultimately increasing to 84,000 mg/d, which was unresponsive to increasing prednisone dosage. Twice-weekly administration of Acthar Gel, 80 U, was initiated and followed within 6 months by treatment with 80 U weekly (which is ongoing), along with MMF 1,000 mg twice daily (bid). She remained in PR (1,860 mg/d) at her last follow-up 17 months after starting Acthar Gel. Patient 2 with MCD was initially treated with oral prednisone 60 mg/d but did not respond after 8 weeks and was intolerant (weight gain and worsening edema). Acthar Gel initiation at 80 U twice weekly produced a PR with 6 months of therapy. Patient 3 had a 16-year history of MCD since age 6. As an adult, he was unresponsive to a regimen of prednisone, azathioprine, cyclophosphamide, and MMF. Twice-weekly administration of Acthar Gel,

80 U, was initiated, and MMF was continued at 1,000 mg bid for 8 months. Proteinuria decreased from 12,400 mg/g to 270 mg/g for a CR. He remains on MMF.

## FSGS results

Of the ten patients with FSGS, two had a CR and two a PR. Patient 5, a 33-year-old Caucasian woman, had severe nephrosis with proteinuria values that became markedly elevated (UPCR >30,000 mg/g), anasarca, hypoalbuminemia (<2.0 g/dL), and hypercholesterolemia (404 mg/dL). She initially received 6 weeks of daily prednisone (60 mg/d) without response. Subsequently, plasma exchange (×5) and dexamethasone/MMF were used for 4 months but were ineffective and discontinued because of side effects. Following a several-month hiatus, she began abatacept, 750 mg every

**Table 2** Response to Acthar Gel

Patient	Acthar Gel regimen	Acthar Gel duration	Follow-up after Acthar Gel initiation	Concomitant therapy	Serum creatinine, pre-/post-Acthar Gel initiation, mg/dL	Proteinuria, pre-/post-Acthar Gel initiation	Outcome	Adverse events
1	80 U twice weekly, then weekly	Ongoing	17 months	RASB Statin MMF 1,000 mg bid	0.7/0.51	84,300 mg/d/ 1,860 mg/d	PR	None
2	80 U twice weekly	6 months	16 months	Statin	1.2/1.39	3,119 mg/g/ 918 mg/g	PR	None
3	80 U twice weekly	10 months	26 months	RASB MMF	1.3/1.2	12,400 mg/g/ 270 mg/g	CR	None
4	40 U twice weekly	5 months	18 months	RASB	0.84/0.9	8,430 mg/d/ 10,825 mg/d	NR	Weight gain, myalgia, worsening diabetes, and hypertension
5	80 U twice weekly	9 months	16 months	RASB Abatacept	3.05/0.83 <sup>a</sup>	Albumin/ creatinine: >30,000 mg/g/ 255 mg/g <sup>a</sup>	CR	Weight gain
6	80 U twice weekly	2 months	16 months	RASB	2.4/ESRD	NA	NR	None but noncompliant
7	80 U twice weekly	10 months	15 months	Vitamin D Statin	2.44/3.61	15,700 mg/g/ 2,700 mg/g	NR (rise in creatinine)	None
8	80 U twice weekly	1 month	7 months	RASB Vitamin D Statin	3.02/2.3	8,400 mg/g/ 15,600 mg/g	NR	Weight gain, hypertension, edema, and fatigue
9	80 U twice weekly	3 months	20 months	Vitamin D	1.01/1.01	1,100 mg/g/ 67 mg/g	CR	None
10	40 U twice weekly, then weekly	Ongoing	7 months	RASB Statin	1.55/1.71	2,700 mg/g/ 624 mg/g	PR	Myalgia, weakness, and hyperpigmentation
11	80 U twice weekly	7 months	14 months	RASB	6.3/6.5	6,700 mg/g/ 12,800 mg/g	NR	Skin pigmentation, weight gain, worsening diabetes, and Cushingoid features
12	80 U twice weekly	7 months	17 months	RASB	0.9/1.2	3,100 mg/g/ 2,100 mg/g	NR	None
13	80 U twice weekly	7 months	18 months	RASB	0.9/1.0	5,900 mg/g/ 1,700 mg/g	PR	None

**Note:** <sup>a</sup>Post-Acthar Gel initiation laboratory values for this patient are from her 7-month follow-up.

**Abbreviations:** CR, complete remission; ESRD, end-stage renal disease; MMF, mycophenolate mofetil; NA, not available; NR, no response; PR, partial remission; RASB, renin-angiotensin system blockade; U, units.

other week, with significant diuresis (biopsy noted to be B7-1 negative). Acthar Gel 80 U twice weekly was added 2 months later, with serum creatinine at 3 mg/dL. Diuresis continued with this combination. Serum creatinine decreased to <1.0 mg/dL repeatedly, with a urine albumin/creatinine ratio of 766 by 2 months of combined therapy and 254 by 7 months. Weight loss was ~20 kg. She took Acthar Gel for 9 months. Sixteen months after starting Acthar Gel and having been off it for several months, she continued to do well; abatacept had been tapered to every other month and was being discontinued.

Patient 9, a 19-year-old African American woman, initially responded to 6 months of 60 mg/d oral prednisone (UPCR decreased from 10,000 mg/g to 210 mg/g) and subsequently to 150 mg bid cyclosporine (UPCR down to 58 mg/g). When this was discontinued after 2 years because of abdominal pain, she relapsed (UPCR 16,000 mg/g), which partially responded to 60 mg/d oral prednisone (UPCR of 1,100 mg/g). After 2 months, prednisone was stopped and Acthar Gel begun, 80 U twice weekly for 3 months, with a CR (UPCR of 67 mg/g). She has remained in CR on tacrolimus 3.5 mg bid for >1 year.

As noted, two patients had a PR. Patient 10, a 54-year-old African American woman, with a UPCr of 11,000 mg/g, initially had a PR to 4 weeks of 80 mg/d oral prednisone (UPCr of 2,700 mg/g). Due to side effects (mood changes and facial puffiness), Acthar Gel was substituted (40 U twice weekly) for 6 months, with further response (UPCr of 624 mg/g). Therapy remains ongoing. Patient 13 is a 43-year-old Caucasian man with a 4-year history of nephrotic-range proteinuria (5,900 mg/g) without nephrotic syndrome (albumin 4.2 g/dL). Although refractory to high-dose oral steroids, he had a near-CR with Acthar Gel (UPCr of 600 mg/g).

Six FSGS patients had NR. Patient 4 is a 44-year-old Caucasian female with glomerular tip lesion (GTL). Acthar Gel was the initial IS treatment at 40 U twice weekly for 5 months. Treatment was discontinued due to side effects (myalgia, weight gain, and worsening diabetes) without remission. Repeat biopsy confirmed GTL, and subsequent treatments with MMF 1,000 mg bid followed by cyclosporine 50 mg bid were also ineffective. Patient 6, a 38-year-old Caucasian female, presented with a 10-year history of nephrosis. After noncompliance with oral steroids, she received 80 U Acthar Gel twice weekly, which was stopped after 2 months due to declining glomerular filtration rate. Dialysis was initiated 1 month later. Patient 7, a 17-year-old African American man, presented with collapsing FSGS. He was treated initially with prednisone 60 mg/d, with reduction of UPCr from 36,000 mg/g to 12,800 mg/g after 4 months. This was followed by cyclosporine 150 mg bid, with no improvement in proteinuria (UPCr increased to 15,700 mg/g). Acthar Gel was then prescribed at 80 U twice weekly, with proteinuria decreasing to a UPCr of 2,700 mg/g, but the case was deemed an NR due to rising serum creatinine (from 2.44 mg/dL to 3.61 mg/dL). Patient 8 was a 65-year-old Caucasian man with FSGS NOS. Initial IS treatment was MMF 1,500 mg bid for 10 months, with no improvement in UPCr (7,700 mg/g to 8,400 mg/g), although serum creatinine was reduced from 3.02 mg/dL to 2.3 mg/dL. A twice-weekly dose of Acthar Gel, 80 U, was initiated and continued for 1 month, with NR. Treatment was discontinued due to side effects (worsening edema and hypertension). Patient 11, a 52-year-old African American female, presented with advanced disease (serum creatinine 6.3 mg/dL). There was NR to 7 months of the ACTH preparation (serum creatinine 6.5 mg/dL; UPCr increasing from 6,700 mg/g to 12,800 mg/g). Patient 12, a 33-year-old Caucasian female, had a reduction of proteinuria after 7 months of Acthar Gel, from a UPCr of 3,100 mg/g to 2,100 mg/g, a reduction of <50%.

Acthar Gel was reasonably well tolerated. The three patients with MCD had no side effects. Four patients with FSGS had no side effects, as did another who was noncompliant, however, with a short course (2 months) prior to end-stage renal disease. The other five patients had various, predominantly steroid-like, adverse effects, including weight gain (n=4), myalgias (n=2), worsening diabetes (n=2), increased skin pigmentation (n=2), and hypertension (n=2), as well as edema and fatigue (n=1 each). Two patients discontinued Acthar Gel because of the side effects.

## Discussion

This retrospective case series confirms the potential utility of Acthar Gel in patients with INS from a primary podocytopathy (MCD or FSGS) when resistant or intolerant to conventional therapy. All three patients with MCD responded (two PR and one CR), as did four of ten patients with FSGS (two CR and two PR).

Acthar Gel remains the only US Food and Drug Administration-approved ACTH preparation for remission of proteinuria in nephrotic syndrome, with >50 years of history. Originally used for pediatric INS in the 1950s, this practice was supplanted with the development of oral steroids. Currently, two long-acting ACTH preparations are available.<sup>25</sup> In Europe, synthetic ACTH (*N*-terminal peptide ACTH<sub>1-24</sub>) is available, while in the USA, the only available preparation, Acthar Gel, is a highly purified, porcine-derived whole ACTH (Mallinckrodt ARD Inc., Hazelwood, MO, USA); Acthar Gel contains ACTH<sub>1-39</sub>, along with other proopiomelanocortin (POMC) peptides.<sup>25,26</sup> The synthetic preparation lacks the *C*-terminal 15 amino acids, which are included in the ACTH<sub>18-39</sub> fragment. These two preparations also differ in their half-lives, as well as in posttranslational modifications.<sup>26</sup> They have not been compared in any trial.

Long-acting ACTH has a well-known lipolytic effect when given to people with normal kidney function or patients with kidney disease (as documented in studies by Berg and Nilsson-Ehle<sup>27,28</sup> with synthetic ACTH). Berg et al<sup>13</sup> studied 14 patients with hyperlipidemia and nephrotic syndrome from MN using synthetic ACTH. Surprisingly, proteinuria was markedly reduced, with improved serum albumin and glomerular filtration rate.<sup>13</sup> Subsequently, ten more case series/cohort studies<sup>15-24</sup> of ACTH use in various glomerulopathies have been published, along with one RCT<sup>14</sup> and four case reports<sup>29-32</sup> (Table 3); overall, ~100 patients with MN received ACTH, with well >50% responding. Most had failed ≥2 prior therapies. Approximately 60% were treated with synthetic ACTH and 40% with Acthar Gel. More than



**Table 3** Case series, cohort studies, and case reports of various glomerulopathies treated with ACTH preparations

Study	Preparation	MN	FSGS	MCD	DN	IgAN	MPGN	Other	Discontinued due to AEs
Berg et al <sup>13</sup>	T	9/5 <sup>a</sup> (5) <sup>b</sup>							0/5
Berg and Arnadottir <sup>16</sup>	T	10 (10)	1 (1)	2 (2)	2 (2)		6 (6)	2 (1)	0/23
Picardi et al <sup>15</sup>	T	7 (5)							2/7
Ponticelli et al <sup>14</sup>	T	16 (14)							2/16
Rauen et al <sup>17</sup>	T	4 (4)							0/4
Lindskog et al <sup>18</sup>	T	5 (4)							0/5
Bomback and Radhakrishnan <sup>19</sup>	Gel	11 (9)	1 (1) <sup>c</sup>	1 (0)		1	4 (0)	3	0/21
Bomback et al <sup>20</sup>	Gel	5 (2)	3 (1) <sup>c</sup>	2 (1)		5			3/15
Hogan et al <sup>21</sup>	Gel		24 (7)						0/24
Tumlin et al <sup>22</sup>	Gel				14 (8)				9 of 23 initially randomized <sup>d</sup>
Hladunewich et al <sup>23</sup>	Gel	20 (12)							0/20
Lorusso et al <sup>24</sup>	T	9 (4)	2 (2)	2 (1)			2 (1)		1 of 18 initially randomized
Gigante et al <sup>29,e</sup>	T	1 (1)							
Watson <sup>30,e</sup>	Gel	1 (1)							
Anwar et al <sup>31,e</sup>	Gel		1 (1)						
Madan <sup>32,e</sup>	Gel		1 (1)						
This study	Gel		10 (4)	3 (3)					2/13
Total		94	39	10	16	6	12	5	
Overall response		67 (71%)	16 (41%)	7 (70%)	10 (63%)		7 (58%)		

**Notes:** <sup>a</sup>Five were treated for 1 year and are included in the overall total, nine just for the short term; <sup>b</sup>overall number attaining complete or partial remission in parentheses; <sup>c</sup>included among the study of Hogan et al<sup>21</sup> and not counted separately in total; <sup>d</sup>includes one withdrawing due to need for injections and two with scheduling conflicts; <sup>e</sup>isolated case reports.

**Abbreviations:** ACTH, adrenocorticotropic hormone; AEs, adverse events; DN, diabetic nephropathy; FSGS, focal segmental glomerulosclerosis; Gel, Acthar Gel; Ig, immunoglobulin; IgAN, IgA nephropathy; MCD, minimal change disease; MN, membranous nephropathy; MPGN, membranoproliferative glomerulonephritis; T, tetracosactide (long-acting), ACTH<sub>1-24</sub>.

30 patients with FSGS were given ACTH (mostly Acthar Gel), with ~40% responding. Only seven with MCD have been reported, culled from four separate series.

Hogan et al<sup>21</sup> described in detail the response to Acthar Gel in 24 patients with FSGS (eleven with tip variant) at two academic centers, using predominantly a 16-week course (2,160 U total) in 12 patients or a 24-week course (3,840 U) in seven patients; five others were heterogeneously treated. A trend (not significant) to reduced proteinuria (median of 4,595 mg/g reduced to 2,243 mg/g creatinine) was seen, with no change in serum creatinine or estimated glomerular filtration rate. Seven patients responded, two CR and five PR, with median times to proteinuria reduction of 5 weeks (range: 2–16 weeks) and to remission of 16 weeks (range: 5–18 weeks). Five had sustained remission, and two relapsed, although two nonrelapsers were on additional IS therapy. This response rate of 29% is similar to that obtained in an FSGS RCT conducted by the National Institutes of Health (NIH),<sup>33</sup> which compared CNI with MMF/dexamethasone in patients with resistant FSGS (with at least a PR obtained by 1 year in 46% of patients on cyclosporine and 33% of patients on MMF). Our overall response rate in FSGS was 40%, similar to the results of Hogan et al<sup>21</sup> and the NIH trial.<sup>33</sup>

It is not certain how both Acthar Gel and synthetic ACTH exert their beneficial effect in glomerulonephritis. Following a single injection of synthetic ACTH, there is a bolus of endogenous cortisol production equivalent to 50 mg of cortisol given orally three times over 24 hours.<sup>34</sup> It is unlikely that this degree of steroid exposure twice weekly would be efficacious in a disease such as MN, which is not responsive to corticosteroid monotherapy<sup>35</sup> or in resistant FSGS. Perhaps there is a differential effect of endogenously produced corticosteroids compared to that of exogenous agents,<sup>13</sup> although no substantial proof to support this concept is available.

ACTH is derived from the cleavage of POMC produced by the anterior pituitary.<sup>26</sup> Other cleavage products of POMC, or of ACTH itself, include three melanocyte-stimulating hormones (MSHs):  $\alpha$ ,  $\beta$ , and  $\gamma$ . ACTH and these MSHs are collectively called melanocortins and are capable of activating at least five known melanocortin receptors (MCRs), termed MC1R to MC5R. Only ACTH can activate MC2R on adrenal cells to produce corticosteroids. The other four MCRs are widely expressed in various tissues, including the skin (melanocytes), kidneys, brain, exocrine glands, and various inflammatory cells, such as monocytes and lymphocytes.

ACTH is capable of stimulating all five MCRs and hence may have anti-inflammatory effects through various

mechanisms beyond enhanced cortisol production.<sup>26</sup> In general, activation of the four MCRs other than MC2R is anti-inflammatory. MCRs are expressed on human leukocytes, including monocytes and macrophages, as well as B-lymphocytes, CD4+ T-helper cells, and natural killer cells.<sup>36,37</sup> Hence, melanocortins may affect cytokine production, including the potential permeability factors proposed to underlie FSGS and MCD. Melanocortins downregulate nuclear factor (NF)- $\kappa$ B activation, which is relevant to treatment of podocytopathies.<sup>25,38</sup> The peripheral blood mononuclear cells of MCD patients in relapse have been shown to have increased nuclear NF- $\kappa$ B binding, with reduction of both mRNA and protein expression of the inhibitory I $\kappa$ -B.<sup>39</sup> Furthermore, stimulation of MCRs by ACTH in the brain may activate the anti-inflammatory pathway that is mediated by the release of acetylcholine due to vagal nerve stimulation.<sup>40</sup> Nicotinic acetylcholine receptor activation on tissue macrophages inhibits release of inflammatory mediators, eg, tumor necrosis factor- $\alpha$  (which produces potent NF- $\kappa$ B stimulation) and interleukin-1.<sup>41</sup>

Importantly, MCRs are expressed in the kidney, and ACTH and other melanocortins may have direct podocyte-protective effects. Lindskog et al<sup>18</sup> demonstrated *MC1R* mRNA expression in all three cell types in normal human glomeruli as well as in tubules, which contrasts with prior work demonstrating strong *MC5R* complementary DNA kidney expression.<sup>42</sup> Lindskog et al<sup>18</sup> also showed that MC1R protein was expressed in glomeruli, specifically in podocytes, by colocalization with synaptopodin, although not in endothelial cells. Furthermore, in the passive Heymann nephritis (PHN) model of MN in rats, synthetic ACTH, as well as  $\alpha$ -MSH and the specific MC1R agonist MS05, ameliorated proteinuria, hypoalbuminemia, and hypertension.<sup>18</sup> Ultrastructural podocyte morphology was improved, and oxidative stress was reduced. In a subsequent study, Lindskog Jonsson et al<sup>43</sup> confirmed the benefit of MS05 in PHN, with reduction of proteinuria and improved podocyte morphology.

In contrast, Qiao et al<sup>44</sup> found a nonsteroidogenic melanocortin pan agonist to be equally effective in reducing proteinuria and ameliorating podocyte ultrastructural changes in *MC1R*-mutant and wild-type mice exposed to lipopolysaccharide or adriamycin. They also reported complete remissions with ACTH in two patients with mutated *MC1R* (congenital red hair) and refractory MN.<sup>44</sup> In a mouse model of experimental FSGS (adriamycin nephrosis), neither a MC1R agonist nor  $\alpha$ -MSH had any beneficial effect on proteinuria or morphology.<sup>43</sup> In comparison, a significant beneficial effect of Acthar Gel was found in a model of

secondary FSGS (nephron reduction),<sup>45</sup> even though corticosteroids are known to exacerbate injury in this model.<sup>46</sup> Hence, the exact mechanism of action of ACTH in MN and other glomerulopathies remains uncertain.

In an analogous manner, a direct effect on podocytes, apparently independent from immunosuppression, may also be obtained with other agents effective in INS, including steroids, cyclosporine, and rituximab. Studying differentiated human podocytes in vitro, Xing et al<sup>47</sup> demonstrated that dexamethasone upregulated glucocorticoid receptor expression, accelerated podocyte maturation, increased the production of nephrin and tubulin- $\alpha$ , and prolonged podocyte survival. Faul et al<sup>48</sup> showed that cyclosporine A directly inhibits the dephosphorylation and degradation of synaptopodin, which is mediated by podocyte calcineurin, a requirement for the maintenance of the normal actin cytoskeleton. Fornoni et al<sup>49</sup> demonstrated reduced sphingomyelin phosphodiesterase acid-like 3b (SMPDL-3b) mRNA and protein expression in podocytes of transplant patients with recurrent FSGS compared to those with nonrecurrent disease. Rituximab restored this expression compared to nontreated patients, resulting in a reduction of stress fiber disruption, an effect that correlated with the degree of proteinuria. In vitro, rituximab reduced apoptosis of podocytes that were exposed to the serum of recurrent FSGS patients. Rituximab was shown to specifically bind to SMPDL-3b in the absence of any detectable podocyte CD20,<sup>49</sup> indicating a direct effect independent from CD20 binding or B-cell depletion.

Acthar Gel was reasonably well tolerated in our patients. The majority of side effects were steroid related and not severe. Two patients, however, discontinued Acthar Gel due to side effects (patients 4 and 8). Similar adverse events (AEs) were noted in the other studies cited herein, with no obvious difference noted between synthetic ACTH and Acthar Gel. These include various central nervous system effects (mood change, insomnia, and tremulousness), worsening glucose and blood pressure control, weight gain, skin changes, and myalgias. A minority of patients could not complete the planned treatment course because of various reasons, including side effects: two of seven in the case series of Picardi et al,<sup>15</sup> two of 16 in the Ponticelli et al RCT,<sup>14</sup> three of 15 in the prospective study of Bomback et al,<sup>20</sup> and nine of 23 in the diabetic nephropathy trial<sup>22</sup> (Table 3). Hogan et al<sup>21</sup> reported 52 AEs (23 steroid-like) in 21 of 24 FSGS patients.

Our study has obvious limitations, especially the small size. It is a retrospective case series collected from various nephrology practices. Biopsies were not reviewed centrally, and the histologic subtype of FSGS was not available in some

cases. There was no specific protocol for either initial IS therapy or for the use of Acthar Gel (dose or duration), and concomitant therapy was variable. Follow-up was relatively short and also variable in length.

## Conclusion

In conclusion, our data add further support for the potential use of Acthar Gel in INS due to a primary podocytopathy (MCD or FSGS) in patients intolerant or resistant to, or reluctant to use, corticosteroids or other second- and third-line agents. Remission occurred in all three MCD patients and in four of ten FSGS patients. These results, along with those culled from the literature review, compare favorably with the effects of other available agents. Hopefully, RCTs using Acthar Gel will determine appropriate patients, regimens, and durations of therapy in terms of safety and effectiveness.

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## Disclosure

EJF has been on speakers' bureau/has received lecture fees from Mallinckrodt ARD Inc. SMU has received speaker honoraria from Mallinckrodt ARD Inc. The other authors report no conflicts of interest in this work.

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