

**Abstract: [TH-OR135] Response of Anti-PLA2R to Adrenocorticotrophic Hormone (ACTH) Gel in Membranous Nephropathy**

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5:06 PM - 5:18 PM

**Background:** Autoantibodies to the phospholipase A2 receptor (PLA2R) define most cases of primary membranous nephropathy (MN); their presence correlates with clinical disease activity. We analyzed anti-PLA2R in patients treated with long-acting ACTH gel (H.P. Acthar® Gel, repository corticotropin; Questcor) to better understand its potential mechanism of action. **Methods:** Samples were collected from 14 patients in 2 pilot studies (Mayo Clinic, n=9; Columbia, n=5) that treated MN patients with ACTH gel for 6 mo. Longer term follow-up samples were available in 11 cases. Serum was assayed for anti-PLA2R by immunoblotting and subsequent densitometry. **Results:** 86% of patients were anti-PLA2R positive at baseline (Mayo Clinic, n=8; Columbia, n=4). Two patients with undetectable baseline anti-PLA2R rapidly achieved clinical remission and may have already entered immunologic remission prior to treatment. All 12 patients experienced a reduction in anti-PLA2R (17-100%) by 6 mo with disappearance of anti-PLA2R in 5 cases. There were 5 partial remissions at 6 mo: 3 in patients who cleared their anti-PLA2R and 2 in those lacking baseline anti-PLA2R. Another patient later achieved a 96% reduction in anti-PLA2R without further treatment while 2 others, after receiving rituximab for perceived failure of ACTH gel, fully cleared anti-PLA2R. With long term (12-18 mo) follow-up of those with undetectable anti-PLA2R at baseline or after ACTH gel ± rituximab, there were 4 complete and 2 partial remissions, one non-responder, and a final patient who achieved partial remission but relapsed coincident with a return of anti-PLA2R. Two other patients also showed an increase in anti-PLA2R after discontinuing treatment with ACTH gel. **Conclusions:** Measurement of anti-PLA2R provides useful information relating immunological and clinical disease activity in MN patients treated with new agents such as ACTH gel. This study suggests that ACTH gel may work in part by suppressing autoantibody production; the duration and degree of this response need further study.

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**Room:** 108

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**Abstract: [TH-PO114] Adrenocorticotropin (ACTH) Gel Suppresses Renal Tubulointerstitial Inflammation and Injury by Direct Stimulation of the Melanocortin 1 Receptor (MC1R)**

**Rujun Gong, , Lance D. Dworkin, MD, FASN. Brown Medical School, Providence, RI. .**

**Background:** ACTH is a pituitary neuro-immuno-endocrine hormone and a prototype agonist of the melanocortin system. Clinical and experimental evidence demonstrates that ACTH has beneficial actions in chronic kidney disease; however, the mechanism(s) remain uncertain. This study examined the effect of ACTH gel (Acthar Gel, Questcor Pharmaceuticals, Inc.) on progressive renal tubulointerstitial injury. **Methods:** Following unilateral ureteral obstruction (UUO) surgery with or without simultaneous adrenalectomy, rats were administered ACTH gel (10 IU/kg) or saline (CON) every other day for 2 weeks. Renal histology was assessed. Expression of cognate receptors of ACTH was evaluated *in vivo* and in cultured murine renal tubular epithelial cells (TEC). **Results:** Compared to CON, ACTH gel prevented enlargement of the obstructed kidney as assessed by the increase in kidney to body weight ratio ( $1.13 \pm 0.14$  vs  $0.67 \pm 0.09$  g/100g wt,  $P=0.02$ ). Morphologically, renal interstitial fibrosis and tubular atrophy were significantly ameliorated by ACTH gel. In addition, renal inflammation, marked by ED-1 positive macrophage infiltration, and UUO induced expression of chemokines MCP-1 and RANTES in tubules, were also attenuated by ACTH gel treatment. Although somewhat diminished, the beneficial effects of ACTH gel were still evident in UUO rats that underwent adrenalectomy, suggesting a steroid independent mechanism. Consistently, abundant expression of MC1R was observed in renal tubules of rat kidneys and in cultured TEC. *In vitro*, ACTH gel markedly suppressed TNF- $\alpha$  induced proinflammatory events in cultured TEC, including NF $\kappa$ B activation and downstream target gene expression. This effect was significantly diminished in TEC in which MC1R expression was silenced by RNAi, demonstrating that ACTH gel induced anti-inflammatory signaling in TEC requires MC1R. **Conclusions:** ACTH gel markedly suppresses tubulointerstitial inflammation, tubular atrophy and fibrosis in progressive chronic kidney disease due, at least in part, to direct, anti-inflammatory effects on TEC. By silencing MC1R expression for the first time in kidney cells, we have also shown that these effects are mediated *via* the MC1R.

**Funding:** Pharmaceutical Company Support

**Course:** Annual Meeting: Abstract Sessions

**Session:** Basic/Experimental Inflammation

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**Abstract: [SA-PO2864] Treatment of Resistant Glomerular Diseases with ACTH Gel: A Prospective Trial**

**Andrew S. Bomback, MD, Pietro A. Canetta, MD, Jai Radhakrishnan, MD, FASN, Gerald B. Appel, MD, FASN. Columbia University Medical Center, New York, .**

**Background:** Adrenocorticotrophic hormone (ACTH) has shown promising results as second- and third-line therapy for idiopathic glomerular diseases resistant to conventional therapies, but the data reported to date has solely been from retrospective, observational studies. **Methods:** In this prospective, open-label, pilot study (NCT01129284), 15 patients with resistant glomerular diseases were treated with ACTH gel (80 units SC twice weekly) for 6 months. Resistant membranous nephropathy (MN) was defined as failure to achieve sustained remission with at least 2 immunosuppressive regimens, resistant MCD/FSGS was defined as failure to achieve sustained remission with corticosteroids and at least 1 other immunosuppressive regimen, and resistant IgA nephropathy was defined as  $\geq 1$  g/day proteinuria despite effective renin angiotensin system blockade. Complete remission was defined as stable or improved renal function with proteinuria falling  $< 500$  mg/day. Partial remission was defined as stable or improved renal function with  $\geq 50\%$  reduction in proteinuria and final proteinuria 500-3500 mg/day. **Results:** The study included 5 patients with resistant MN, 5 patients with resistant MCD(n=2)/FSGS(n=3), and 5 patients with resistant IgA nephropathy. Two resistant MN patients were in partial remission at the end of 6 months of therapy, although 3 achieved immunologic remission of disease (PLA2R antibody disappeared by 4 months of therapy). One patient with resistant FSGS achieved complete remission at 6 months; one patient with resistant MCD achieved a partial remission at 6 months but relapsed within 4 weeks of stopping ACTH. Three of 5 patients with resistant IgA nephropathy demonstrated  $\geq 50\%$  reductions in proteinuria while on ACTH, with proteinuria consistently  $< 1$  g/day by 6 months. Three of 15 patients reported significant steroid-like adverse effects with ACTH, including weight gain and hyperglycemia, prompting early termination of therapy without any signs of clinical response. **Conclusions:** ACTH gel is a promising treatment for resistant glomerular diseases. This therapeutic option should be studied further in randomized, controlled trials against currently available therapies for resistant disease.

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**Course:** Annual Meeting; Abstract Sessions

**Session:** Glomerular Disease: Pathology and Management - II

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# Treatment of nephrotic syndrome with adrenocorticotrophic hormone (ACTH) gel

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**Purpose:** A synthetic adrenocorticotropin (ACTH) analog has shown efficacy in Europe as primary and secondary therapy for nephrotic syndrome, but there is no published experience using the natural, highly purified ACTH gel formulation, available in the United States, for nephrotic syndrome. We therefore investigated the use of ACTH gel for nephrotic syndrome in the United States.

**Patients and methods:** Twenty-one patients with nephrotic syndrome treated with ACTH gel outside of research settings in the United States, with initiation of therapy by December 31, 2009, allowing a minimum 6 months follow-up. We defined complete remission as stable renal function with proteinuria falling to  $\leq 500$  mg/day, and partial remission as stable renal function with  $\geq 50\%$  reduction in proteinuria from 500 to 3500 mg/day.

**Results:** Twenty-one patients with nephrotic syndrome were treated: 11 with idiopathic membranous nephropathy (IMN), 4 with membranoproliferative glomerulonephritis (MPGN), 1 with focal segmental glomerulosclerosis (FSGS), 1 with minimal change disease (MCD), 1 with immunoglobulin A (IgA) nephropathy, 1 with class V systemic lupus erythematosus (SLE) glomerulonephritis, 1 with monoclonal diffuse proliferative glomerulonephritis, and 1 with unbiopsied nephrotic syndrome. ACTH was used as primary therapy for 3 patients; the remaining patients had previously failed a mean 2.3 immunosuppressive regimens. Eleven patients achieved a complete or partial remission, with 4 (19%) in complete remission. Of the 11 patients who achieved remission, 9 had IMN, 1 had FSGS, and 1 had IgA nephropathy. Of the 11 patients with IMN, 3 (27%) achieved complete remission and 6 (55%) achieved partial remission despite having previously failed a mean 2.4 therapies. Five patients reported steroid-like adverse effects, but there were no severe infections. The limitations were retrospective data analysis with short-term follow-up.

**Conclusion:** ACTH gel may be a viable treatment option for resistant nephrotic syndrome due to membranous nephropathy. Short-term data suggest that remission rates may approach 80%.

**Keywords:** nephrotic syndrome, membranous nephropathy, chronic kidney disease

## Introduction

Patients with nephrotic syndrome often require immunosuppression to achieve remission, yet many patients either relapse after remission or are resistant to therapy. For example, while up to 90% of adults with minimal change disease (MCD) will respond to initial therapy with prednisone, approximately one-third of these same patients will relapse within 6 months and require further immunosuppression.<sup>1,2</sup> With diseases such as idiopathic membranous nephropathy (IMN) and focal segmental glomerulosclerosis (FSGS), for which first-line therapies produce substantially lower

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response rates than for MCD, physicians are often compelled to use second-, third-, and even fourth-line therapies to achieve remission.<sup>3-8</sup>

In several European studies, tetracosactide, a synthetic adrenocorticotropic hormone (ACTH) analog, has shown efficacy as primary and secondary therapy for nephrotic syndrome. The initial reports came in a case series of patients with various etiologies of nephrotic range proteinuria, including MCD, iMN, FSGS, and membranoproliferative glomerulonephritis (MPGN).<sup>9</sup> Subsequently, a randomized, controlled study by Ponticelli et al reported similar remission rates in patients with iMN randomized to synthetic ACTH or to therapy with alternating months of steroids and cyclophosphamide.<sup>10</sup> These reports have generated renewed interest in using ACTH as treatment for nephrotic syndrome, particularly in patients who are resistant to conventional therapies. Synthetic ACTH is not currently available for use in the United States, but a natural, highly purified ACTH gel formulation (H.P. Acthar<sup>®</sup> Gel [repository corticotropin injection], Questcor Pharmaceuticals, Inc, Union City, CA, USA; abbreviated ACTH gel) is both available and approved for use in nephrotic syndrome.

To date, however, there is no modern published experience on using ACTH gel in nephrotic patients. We therefore explored the initial use of ACTH gel for nephrotic syndrome in nonresearch settings (ie, by prescription), collecting data from treating nephrologists of all known patients in the United States whose treatment with this agent was initiated by the end of 2009. We describe their clinical course before and after treatment with ACTH gel.

## Material and methods

In this retrospective case series, we evaluated all known cases of idiopathic, nondiabetic nephrotic syndrome treated with ACTH gel outside of research settings (ie, by prescription) with initiation of therapy by December 31, 2009, allowing a minimum of 6 months' follow-up. Questcor Pharmaceuticals, the drug's manufacturer, provided contact information for nephrologists whose patients had ACTH gel prescriptions filled during this time period. Treating nephrologists were asked to provide data on patients' demographics, diagnoses, previous immunosuppressive regimens, indications for ACTH gel therapy, dosing of ACTH gel, clinical response to therapy (creatinine, proteinuria, serum albumin, cholesterol), and adverse events from initiation of therapy to most recent clinical encounter.

We defined complete remission as stable or improved renal function (estimated glomerular filtration rate, eGFR

[eGFR], based on serum creatinine) with final proteinuria falling to <500 mg/day; partial remission as stable or improved renal function with  $\geq 50\%$  reduction in proteinuria and final proteinuria 500 to 3500 mg/day; and limited response as stable or improved renal function with  $\geq 50\%$  reduction in proteinuria but final proteinuria >3500 mg/day. Failure to meet the above criteria was classified as no response. Given the small number of patients and the observational nature of this study, the data are presented descriptively, and no formal statistical analyses were performed.

## Results

### Patient characteristics

In the United States, 25 patients with nondiabetic nephrotic syndrome began treatment with ACTH gel before December 31, 2009. Data were not available for 4 patients with unknown diagnoses. Full data were available for 21 patients with the following diagnoses (Table 1): iMN (n = 11), MPGN (n = 4), FSGS (n = 1), MCD (n = 1), immunoglobulin A (IgA) nephropathy (n = 1), class V systemic lupus erythematosus (SLE) glomerulonephritis (n = 1), monoclonal diffuse proliferative glomerulonephritis (n = 1), and unbiopsied nephrotic syndrome (n = 1).

ACTH gel was used as primary therapy for only 3 patients, one each with diagnoses of iMN, IgA nephropathy, and nonbiopsied nephrotic syndrome. The remaining 18 patients had failed a mean 2.3 immunosuppressive regimens prior to ACTH gel therapy, of which 9 patients had failed at least 3 prior therapies. Nine of 21 patients were female, all but 3 patients were white, and there was a wide range of ages (24 to 81 years). Most patients had impaired baseline renal function (eGFR range from 0.2 to >1.0 mL/s/1.73 m<sup>2</sup> [11 to >60 mL/min/1.73 m<sup>2</sup>]) with 12 patients demonstrating stage 4 or 5 chronic kidney disease (eGFR  $\leq 0.5$  mL/s/1.73 m<sup>2</sup> [ $\leq 30$  mL/min/1.73 m<sup>2</sup>]). Pretreatment proteinuria ranged from 1340 mg/day to 18,553 mg/day; only 3 patients had proteinuria <4000 mg/day, while 11 had proteinuria >8000 mg/day (Table 2). The 3 patients whose baseline proteinuria was in subnephrotic range exhibited other signs of nephrotic syndrome (hypoalbuminemia, hyperlipidemia, and edema). Mean pretreatment albumin (data available for 19 patients) was 29 g/L (2.9 g/dL), and mean pretreatment total cholesterol was 6.10 mmol/L (236 mg/dL) (data available for 12 patients).

The most common treatment regimen was 80 units subcutaneously (SC) twice weekly for 6 months, which was used in 13 of 21 patients (Table 2). All but 6 were treated for a minimum

**Table 1** Characteristics of patients in the United States treated with ACTH gel for nephrotic syndrome through December 31, 2009

Patient	Age	Gender	Race/ ethnicity	Diagnosis	Previous Immunosuppression	eGFR (mL/min/1.73 m <sup>2</sup> )	Proteinuria (mg/day)
1	59	Male	White	IMN	MMF, CNI	>60	485
2	77	Male	Hispanic	IMN	MMF, CNI	21	6749
3	58	Male	White	IMN	Steroids + CTX, CNI, MMF	58	4598
4	55	Male	White	iMN	Steroids + CTX, CNI, MMF	57	8153
5	27	Male	White	iMN	Steroids, MMF, CNI	30	9000
6	24	Female	White	IMN	None	>60	8900
7	75	Female	White	IMN	Steroids + CTX	>60	3469
8	49	Male	White	iMN	Steroids, CNI	25	9150
9	46	Male	White	iMN	Steroids + CTX	20	11,911
10	53	Male	White	IMN	Steroids, Steroids + CTX	>60	5700
11	70	Female	White	iMN	Steroids, CNI, CTX	40	2625
12	81	Male	White	MPGN	Steroids, MMF, rituximab	25	13,073
13	28	Female	White	MPGN	Steroids, MMF, rituximab	23	5500
14	53	Female	White	MPGN	Steroids, MMF	11	12,398
15	47	Female	White	MPGN	MMF	21	10,244
16	57	Female	White	MCD	Steroids, MMF, CNI	15	18,553
17	63	Female	Hispanic	FSGS	Steroids, MMF, CNI	33	10275
18	75	Male	Black	IgA nephropathy	None	22	4952
19	32	Female	White	SLE class V	Steroids + MMF + CNI	>60	1340
20	36	Male	White	Monoclonal DPGN	Steroids, rituximab, MMF, CNI	19	8560
21	74	Male	White	NS*	None	12	5805

Notes: Conversion factor for eGFR: mL/min/1.73 m<sup>2</sup> to mL/s/1.73 m<sup>2</sup>,  $\times 0.01667$ ; \*Patient with nephrotic syndrome who did not undergo biopsy for specific diagnosis. Abbreviations: CNI, calcineurin inhibitor; CTX, cyclophosphamide; DPGN, diffuse proliferative glomerulonephritis; eGFR, estimated glomerular filtration rate; FSGS, focal segmental glomerulosclerosis; IgA, immunoglobulin A; iMN, idiopathic membranous nephropathy; MCD, minimal change disease; MMF, mycophenolate mofetil; MPGN, membranoproliferative glomerulonephritis; NS, nephrotic syndrome; SLE, systemic lupus erythematosus.

of 6 months. Five patients treated for fewer than 6 months were taken off therapy as a result of clear lack of response: 1 patient discontinued therapy due to weight gain but had achieved a temporary response while on therapy. The longest treatment duration was 14 months, of which the last 2 months included a taper of the dose from 40 units twice weekly to 40 units once weekly. Most patients stopped treatment without a taper, however, and without obvious rebound in proteinuria.

## Outcomes

Overall, 11 of 21 patients (52%) achieved a complete or partial remission, with 4 (19%) in complete remission (Table 2). One patient achieved a limited response, while 9 patients had no overall response to therapy. The patient with class V SLE glomerulonephritis transiently responded to therapy (proteinuria declining to <500 mg/day) but relapsed as soon as therapy was stopped, thus not meeting criteria for remission. Of the 11 patients who achieved complete or partial remission, 9 had iMN, 1 had FSGS, and 1 had IgA nephropathy. Of the 11 patients with iMN (Figure 1), 3 achieved complete remission and 6 achieved partial remission despite having previously failed a mean 2.4 therapies. Of the 10 patients with nephrotic syndrome diagnoses other than iMN (Figure 2), 1 patient with IgA nephropathy achieved complete remission,

1 patient with FSGS achieved partial remission, and 1 patient with MPGN had a limited response to therapy.

Follow-up time for patients ranged from 6 to 14 months. Five patients reported steroidlike adverse effects with therapy: 2 patients had impaired blood glucose control, 2 patients had significant weight gain, and 1 patient showed evidence of accelerated bone loss on bone densitometry not observed prior to ACTH gel therapy (Table 3). In addition, 1 patient with monoclonal diffuse proliferative glomerulonephritis developed acute renal failure within 1 month of starting therapy, with creatinine rising from 327.1  $\mu\text{mol/L}$  (3.7 mg/dL) to 751.4  $\mu\text{mol/L}$  (8.5 mg/dL). The drug was stopped along with the patient's diuretics and angiotensin-converting enzyme inhibitor; after intravenous fluid hydration, the creatinine returned to 353.6  $\mu\text{mol/L}$  (4.0 mg/dL). Six months after starting ACTH gel, the patient's creatinine ranged between 442.0 and 530.4  $\mu\text{mol/L}$  (5.0 and 6.0 mg/dL), with transplant evaluation underway. The other 15 patients reported no adverse events. No severe infections were reported in the entire cohort.

## Discussion

We present here a retrospective case series evaluating the initial experience of 21 patients in the United States treated

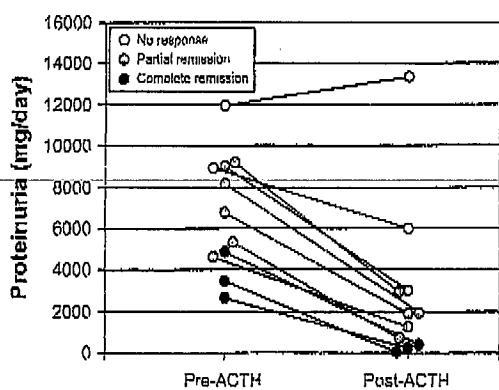
**Table 2** Dosing, duration, and outcomes of ACTH gel therapy for nephrotic syndrome

Patient	Diagnosis	ACTH gel dose (units)	Duration of ACTH therapy	Follow-up time	Pre-ACTH proteinuria (mg/day)	Last proteinuria (mg/day)	Outcome
1	iMN	80 SC twice weekly	6 months	8 months	4851	400	Complete remission
2	iMN	80 SC twice weekly	6 months	6 months	6749	1540	Partial remission
3	iMN	80 SC twice weekly	6 months	6 months	4598	1242	Partial remission
4	iMN	80 SC twice weekly	6 months	6 months	8153	1935	Partial remission
5	iMN	80 SC twice weekly	6 months	6 months	9000	3000	Partial remission
6	iMN	80 SC twice weekly	5 months	12 months	8900	6000	No response
7	iMN	40 SC twice weekly	12 months	14 months	3469	34	Complete remission
8	iMN	80 SC q 72 hrs	11 months	11 months	9150	2948	Partial remission
9	iMN	40 SC thrice weekly	6 months	7 months	11911	13,338	No response
10	iMN	40 SC thrice weekly	6 months	6 months	5700	694	Partial remission
11	iMN	80 SC twice weekly	12 months	13 months	2625	240	Complete remission
12	MPGN	80 SC twice weekly	4.5 months	8 months	13073	3741	No response
13	MPGN	80 SC twice weekly	4 months	6 months	5500	4825	No response
14	MPGN	40 SC thrice weekly	6 months	6 months	12398	4560	Limited response
15	MPGN	80 SC twice weekly	6 months	6 months	10244	3878	No response
16	MCD	80 SC twice weekly	4 months	8 months	18553	18,557	No response
17	FSGS	80 SC twice weekly	6 months	6 months	10275	2970	Partial remission
18	IgA nephropathy	40 SC q 72 hrs	8 months	8 months	4952	42	Complete remission
19	SLE class V	40 SC thrice weekly	5 months	8 months	1340	2290	No response
20	Monoclonal DPGN	80 SC twice weekly	1 month	6 months	8560	8500	No response
21	NS	40 SC q 72 hrs	6 months	9 months	5805	8708	No response

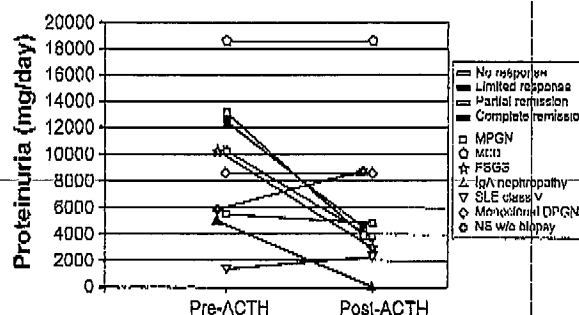
**Notes:** \*Drop in proteinuria occurred in the setting of significant (>25%) decline in eGFR, thus not meeting criteria for response to therapy; <sup>b</sup>While on ACTH gel therapy, proteinuria dropped from 1340 mg/day to 420 mg/day; after patient discontinued therapy due to concerns of weight gain, her proteinuria rebounded to 2290 mg/day.  
**Abbreviations:** ACTH, adrenocorticotropic; DPGN, diffuse proliferative glomerulonephritis; FSGS, focal segmental glomerulosclerosis; IgA, immunoglobulin A; iMN, idiopathic membranous nephropathy; MCD, minimal change disease; MPGN, membranoproliferative glomerulonephritis; NS, nephrotic syndrome without biopsy; SC, subcutaneous; SLE, systemic lupus erythematosus.

with ACTH gel for nephrotic syndrome. The majority of these patients received ACTH as second-, third-, or fourth-line therapy for resistant nephrotic syndrome. Idiopathic membranous nephropathy was the leading diagnosis among these patients and also showed the greatest benefit of therapy, with 9 of 11 patients (82%) achieving either complete or

partial remission. Adverse events associated with therapy were relatively minor and included no significant infections. Although 3 patients with other etiologies of nephrotic syndrome demonstrated response to therapy, the early clinical data suggest that the drug's greatest potential benefit may be in treating refractory iMN.



**Figure 1** Changes in proteinuria with ACTH gel therapy in 11 patients with nephrotic syndrome due to membranous nephropathy.  
**Abbreviation:** ACTH, adrenocorticotropin.



**Figure 2** Changes in proteinuria with ACTH gel therapy in 10 patients with nephrotic syndrome due to etiologies other than membranous nephropathy.  
**Abbreviations:** ACTH, adrenocorticotropin; FSGS, focal segmental glomerulosclerosis; IgA, immunoglobulin A; MCD, minimal change disease; MPGN, membranoproliferative glomerulonephritis; NS, nephrotic syndrome without biopsy; SLE, systemic lupus erythematosus

Table 3 Reported adverse events of ACTH gel therapy

Patient	Diagnosis	ACTH gel dose (units)	Duration of ACTH therapy	Adverse events
1	iMN	80 SC twice weekly	6 months	None
2	iMN	80 SC twice weekly	6 months	None
3	iMN	80 SC twice weekly	6 months	None
4	iMN	80 SC twice weekly	6 months	None
5	iMN	80 SC twice weekly	6 months	Hyperglycemia
6	iMN	80 SC twice weekly	6 months	None
7	iMN	40 SC twice weekly	5 months	Weight gain
8	iMN	40 SC twice weekly	12 months	Bone demineralization
9	iMN	80 SC q 72 h	11 months	None
10	iMN	40 SC thrice weekly	6 months	None
11	iMN	80 SC twice weekly	12 months	None
12	MPGN	80 SC twice weekly	4.5 months	Hyperglycemia
13	MPGN	80 SC twice weekly	4 months	None
14	MPGN	40 SC thrice weekly	6 months	None
15	MPGN	80 SC twice weekly	6 months	None
16	MCD	80 SC twice weekly	6 months	None
17	FSGS	80 SC twice weekly	4 months	None
18	IgA nephropathy	40 SC q 72 h	6 months	None
19	SLE class V	40 SC thrice weekly	8 months	None
20	Monoclonal DPGN	80 SC twice weekly	5 months	Weight gain
21	NS	40 SC q 72 h	1 month	Acute renal failure <sup>a</sup>
			6 months	None

**Note:** <sup>a</sup>Creatinine returned to baseline after IV hydration alongside cessation of ACTH gel, diuretics, and angiotensin converting enzyme-inhibitor.

**Abbreviations:** ACTH, adrenocorticotropic; DPGN, diffuse proliferative glomerulonephritis; FSGS, focal segmental glomerulosclerosis; IgA, immunoglobulin A; MN, idiopathic membranous nephropathy; MCD, minimal change disease; MPGN, membranoproliferative glomerulonephritis; NS, nephrotic syndrome without biopsy; SC, subcutaneous; SLE, systemic lupus erythematosus.

Our observations are concordant with previously published reports from Europe using a synthetic ACTH analog for nephrotic syndrome due to iMN. Berg and Arnadottir, in a seminal paper from 2004, reported the results of ACTH treatment in 23 cases of nephrotic syndrome of various etiologies, including 10 cases of iMN.<sup>9</sup> Half of these iMN patients had previously been treated with at least 1 prior immunosuppressive therapy, and all 10 achieved sustained remission of proteinuria. A more recent series from Germany reported the results of 8 months of synthetic ACTH therapy for 4 patients with iMN refractory to prior therapies of steroids, cyclosporine, cyclophosphamide, mycophenolate mofetil, or azathioprine.<sup>11</sup> Within the first year, 2 had achieved complete remission, and 2 had achieved partial remission. The most convincing data, however, come from the randomized trial by Ponticelli et al, in which 16 patients with iMN received steroids alternating with a cytotoxic drug for 6 months versus 16 patients with iMN treated with synthetic ACTH for 1 year.<sup>10</sup> Most of these patients were on renin angiotensin system blocking drugs, but none had previously received immunosuppression. After a median follow-up of 24 months, there were 4 complete and 8 partial remissions in the steroid/cytotoxic therapy group versus 8 complete and 6 partial remissions in the ACTH group.

The results presented here, on the other hand, do not wholly agree with the successful experiences of Berg and Arnadottir in treating nephrotic syndromes other than iMN.<sup>9</sup> Thirteen of the 23 cases presented in their series were nephrotic syndrome diagnoses other than iMN. Only 1 patient with MPGN did not respond to synthetic ACTH. The remaining 12 patients – with diagnoses of MPGN, MCD, FSGS, diabetic nephropathy, and hereditary nephritis – all experienced at least a 50% reduction in proteinuria during synthetic ACTH therapy, and 8 patients achieved sustained complete remission (proteinuria < 500 mg/day). In this case series, US patients treated with ACTH gel for diagnoses other than iMN did not fare as well: for example, only 1 of 4 MPGN patients demonstrated a limited response. In part, this may be due to these patients having worse baseline renal function and having failed more therapies than those reported by Berg and Arnadottir. Notably, 11 of the 21 patients reported here had advanced renal insufficiency (GFR < 0.5 mL/s/1.73 m<sup>2</sup> [30 mL/min/1.73 m<sup>2</sup>]) when prescribed ACTH. Eight of these 11 patients were diagnosed with diseases other than MN, and their response rate to ACTH was generally poor. The lack of response exhibited by these patients may reflect the degree of renal failure more than the specific diagnosis itself. Theoretically, the difference in response could also be explained by inherent

differences between the synthetic and natural formulations of ACTH.

Although encouraging, the initial results of ACTH gel therapy in the United States must be interpreted cautiously in light of the limitations of an observational series such as this. These patients were not randomized to therapy, and there is no comparison or control group against which to interpret these results. In some respects, however, the patients may serve as their own controls, having failed on average between 2 and 3 prior immunosuppressive regimens. We did not have detailed data on duration of time between prior immunosuppressive therapies and initiation of ACTH gel; conceivably, if this duration was short, some of the response could be attributed to a delay in response to prior agents. In addition, the data presented here reflect only short-term follow-up, most patients having less than 1 year of follow-up at the time of this report. Given that 1 of the patients presented here has relapsed off therapy, the follow-up period is likely too short to label the remissions as sustained. In previous reports of synthetic ACTH therapy, some patients have relapsed but responded to second courses of ACTH with good results.<sup>9,11</sup> The short duration of follow-up may also understate adverse events in this cohort, which thus far have been mild and mostly steroidlike in presentation. Finally, our report does not address cost analysis of the various agents available to treat the nephrotic syndrome.

These data also do not provide any further understanding of the mechanism of action by which ACTH ameliorates proteinuria in the nephrotic syndrome. Speculatively, its better performance in iMN than other causes of nephrotic syndrome might point to a target of action; eg, antibodies against the phospholipase A2 receptor.<sup>12</sup> However, a recent study using rats with passive Heymann nephritis, an animal model of membranous nephropathy, proposes that ACTH may work at the melanocortin receptor MC1R in podocytes to reduce proteinuria, improve glomerular morphology, and reduce oxidative stress.<sup>13</sup> This finding suggests that ACTH should be equally, if not more, effective in podocytopathies such as MCD and FSGS than in iMN. As only 2 of our patients had MCD or FSGS, further study of ACTH gel in these conditions is clearly warranted.

## Conclusion

In conclusion, we present a case series on the initial experience in the United States of using ACTH gel as treatment of nephrotic syndrome. Overall, 11 of 21 patients – including 10 of 18 patients who could be classified as treatment resistant – achieved either complete or partial remission

with at least 6 months of follow-up. Further, 9 of 11 patients with refractory nephrotic syndrome due to iMN achieved remission despite having previously failed at least 2 prior immunosuppressive regimens. Adverse events were relatively few, with no associated infections. This retrospective data analysis suggests that further studies are warranted to evaluate ACTH gel in the treatment of nephrotic syndrome.

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## Disclosure

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## Anti-phospholipase A2 receptor antibody in membranous nephropathy.

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### Abstract

The M-type phospholipase A2 receptor (PLA2R) is a target autoantigen in adult idiopathic membranous nephropathy (MN), but the prevalence of autoantibodies against PLA2R is unknown among Chinese patients with MN. Here, we measured anti-PLA2R antibody in the serum of 60 patients with idiopathic MN, 20 with lupus-associated MN, 16 with hepatitis B (HBV)-associated MN, and 10 with tumor-associated MN. Among patients with idiopathic MN, 49 (82%) had detectable anti-PLA2R autoantibodies using a Western blot assay; an assay with greater sensitivity detected very low titers of anti-PLA2R in 10 of the remaining 11 patients. Using the standard assay, we detected anti-PLA2R antibody in only 1 patient with lupus, 1 with HBV, and 3 with cancer, producing an overall specificity of 89% in this cohort limited to patients with secondary MN. The enhanced assay detected low titers of anti-PLA2R in only 2 additional samples of HBV-associated MN. In summary, these results suggest that PLA2R is a major target antigen in Chinese idiopathic MN and that detection of anti-PLA2R is a sensitive test for idiopathic MN.

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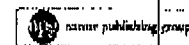
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Kidney Int. 2010 May;77(5):765-70. Epub 2010 Feb 24.

### Membranous nephropathy: recent travels and new roads ahead.

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#### Abstract

Insights from experimental studies have been recently translated into substantial advances in understanding the pathogenesis of human membranous nephropathy (MN). These include identification of neutral endopeptidase (NEP) as the target antigen in alloimmune MN resulting from fetomaternal immunization in NEP-deficient mothers, and our demonstration that a high proportion of patients with idiopathic MN (IMN) have circulating antibodies to the M-type phospholipase A2 receptor (PLA2R), a transmembrane protein located on podocytes. Here we highlight the studies that led to these discoveries and our current knowledge about the possible role of anti-PLA2R autoantibodies in the pathogenesis of IMN. Given that the sensitivity and specificity of anti-PLA2R for IMN are >75 and 100%, respectively, we foresee that a widely available assay for anti-PLA2R will prove to be valuable for diagnosing IMN, distinguishing it from secondary MN, and evaluating response to therapy. We suggest reasons why 25% of patients with IMN have tested negative for anti-PLA2R, and propose possible explanations for the presence of complement deposits in IMN despite the fact that immunoglobulin G4 (IgG4), the predominant anti-PLA2R IgG subclass, is incapable of activating the classical complement pathway. Finally, we point out avenues to be explored, including the events that induce production of anti-PLA2R, their ability to cause podocyte injury, the role of complement, and the nature of the antibodies in secondary forms of MN.

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