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CLINICAL RESEARCH

An Open-Label Pilot Study of Adrenocorticotrophic Hormone in the Treatment of IgA Nephropathy at High Risk of Progression

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Introduction: IgA nephropathy (IgAN) is the most common glomerulonephritis with high risk of progression to end-stage renal disease in patients with proteinuria >1 g/24 hours. There are no known effective treatments in patients with IgAN.

Methods: We conducted a prospective open-label pilot study in patients with IgAN using adrenocorticotrophic hormone (ACTH) (Acthar Gel, Mallinckrodt Pharmaceuticals, Bedminster, NJ) at a dosage of 80 units subcutaneously twice weekly for a total of 6 months and followed patients for a total of 12 months. Patients had to have urinary protein >1 g/24 hours despite adequate renin-angiotensin-aldosterone system (RAAS) blockade and estimated glomerular filtration rate (eGFR) >30 ml/min at enrollment.

Results: A total of 19 patients were recruited and followed for 1 year. At baseline, the mean age was 34.9 ± 10.5 years with 11 men and 8 women, and 14 Caucasian and 5 Asian individuals. At 12 months, there was a statistically significant decline in 24-hour urinary protein from 2.6 to 1.3 g ($P = 0.007$) and significant increase in serum albumin (3.79 to 3.93, $P = 0.02$). There was no significant change in eGFR (65.5 to 61.1 ml/min, $P = 0.1$). There were 0 complete remissions and 8 partial remissions (42%). There were a total of 6 infections: 2 were viral and 4 required antibiotic therapy (2 sinusitis, 1 pneumonia, 1 otitis media). The most common adverse events included acne, hot flashes, soreness, and anxiety.

Conclusion: In summary, patients with IgAN with >1 g/24-hour urinary protein and eGFR >30 ml/min had a significant reduction in 24-hour urinary protein with stable eGFR at 12-month follow-up after being treated with 6 months of ACTH.

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IgAN is the most common glomerulonephritis worldwide and carries a high risk of progression to end-stage renal disease.[1–3] Patients with proteinuria >1 g/24 hours are particularly at risk of renal deterioration, with up to 50% progressing to end-stage renal disease over 15 years.[4–6] RAAS blockade has been shown to be protective and delay progression of the disease[7,8]; however, patients with sustained high-grade proteinuria continue to have progressive disease despite RAAS blockade. Presence of immune complexes in the kidney and the associated inflammatory response and presence of IgG-IgA complexes in the blood suggests that the immune system plays a role in the pathogenesis of the disease and immunosuppressive therapy may help delay the progression of the disease.[9] Even though several retrospective studies have suggested a role for corticosteroid therapy, a recent prospective randomized controlled trial did not show any added benefit from use of immunosuppression.[10] In addition to corticosteroids, other immunosuppressive therapies have been tried, including mycophenolate mofetil, azathioprine, and rituximab, without any proven success.[11–13]

Acthar Gel (Mallinckrodt Pharmaceuticals, Bedminster, NJ) is obtained from the porcine pituitary gland and a

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major component in the formulated complex mixture is N-25 deamidated porcine ACTH (1-39). ACTH is naturally synthesized by proteolytic cleavage from pre-pro-opiomelanocortin, which in turn stimulates the adrenal glands to generate cortisol. In addition to its steroidogenesis effect, ACTH also acts as an agonist of the melanocortin receptors (MCRs) MC1R to MC5R.[14] The MCRs are expressed in the kidneys and, in particular, in the glomerular podocytes, and receptor stimulation has been demonstrated to reduce oxidative stress and improve glomerular morphology by diminishing podocyte apoptosis, injury, and loss in animal models.[14–16] Human studies also have supported the antiproteinuric effect of ACTH in multiple different diseases, including membranous nephropathy, minimal change disease, and primary focal segmental sclerosis.[17–19] Indeed, ACTH remains the only drug approved by the Food and Drug Administration for treatment of patients with nephrotic syndrome. Considering that IgAN is an inflammatory glomerular disease, we hypothesized that ACTH therapy in the form of Acthar Gel might reduce glomerular inflammation, improve podocyte survival, and provide an effective therapy in patients with IgAN and heavy proteinuria.

METHODS

The protocol was reviewed and approved by the institutional review board. Informed consent was obtained from all study participants at each participating institution before any study procedure. The study was registered with clinicaltrials.gov (NCT02282930). Study recruitment began in January 2015 through June 2017, and follow-up was continued through June 2018.

Study Subjects

Adults (>18 years of age) with biopsy-proven IgAN (within 5 years) were included in the study. All biopsies were initially reviewed at the 3 centers from which patients were recruited and then reviewed by a fourth pathology at Mayo Clinic, Rochester, MN, to confirm the diagnosis. Oxford classification (MEST-C score: mesangial hypercellularity [M], endocapillary hypercellularity [E], segmental glomerulosclerosis [S], and tubular atrophy/interstitial fibrosis [T]–crescent [C]) was recorded for all patients. S1 lesion was not subclassified. Those with more than 50% glomerular senescence or cortical scarring were not eligible. Patients had to have at least 1 g of proteinuria over 24 hours despite maximal RAAS blockade (with either an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker) and adequate blood pressure control (>75% of the readings <130/80 mm Hg) for at least 3 months to be eligible. They had to have an eGFR (by Chronic Kidney Disease–Epidemiology Collaboration) or quantified 24-hour creatinine clearance >30 ml/min per 1.73 m^2 and serum creatinine ≤3 mg/dl. Patients with secondary forms of IgAN secondary to cirrhosis, inflammatory bowel disease, celiac sprue, or IgA-predominant lupus nephritis were excluded. Patients with IgA vasculitis were eligible for the study. All participants had to have negative infectious workup for hepatitis B and C and HIV. Those with active systemic infections, or major episode of infection requiring hospitalization or i.v. antibiotic treatment within 4 weeks of screening or oral antibiotics within 2 weeks of screening, positive pregnancy tests, or breast feeding were not eligible. Subjects were excluded if receiving glucocorticoid therapy in the 3 months preceding the trial or immunosuppressive therapy (including cyclophosphamide, mycophenolate mofetil, cyclosporine, tacrolimus, azathioprine, or rituximab) within 6 months of the trial. Individuals had to have hemoglobin ≥8.5 g/dl, platelets ≥100,000/μl, and aspartate aminotransferase and alanine aminotransferase <2.5 times the upper limit of normal. Previous exposure to ACTH, receiving live vaccine within 28 days of the study enrollment, or exposure to another investigational drug (within 30 days), concomitant or previous malignancies (with the exception of nonmelanoma skin cancer and carcinoma in situ of cervix) were other exclusion criteria.

Treatment and Follow-up

This was an open-label trial. All patients received Acthar Gel at the dosage of 80 units subcutaneously twice weekly for a total of 6 months. Subjects were trained on the study medication dosing and had to exhibit proficiency with the proper technique before leaving the injection 1 teaching session. After initiation of the ACTH, patients were seen at months 1, 3, 6, 9, and 12. During these visits, a comprehensive physical examination, evaluation for adverse events, routine complete blood count, serum chemistry, hemoglobin A1C, urine analysis with microscopy, and timed urine studies for evaluation of proteinuria and creatinine clearance were completed. A serious adverse event was defined as an event that resulted in death, was life-threatening, required prolonged inpatient hospitalization, was disabling, resulted in congenital anomaly or birth defect (in a child or fetus of a patient exposed to the trial drug before conception or during pregnancy), or jeopardized the patient and required medical or surgical intervention. The subjects also were required to keep a log of their injections and bring the log with all their medication vials to each visit. At each visit, the subject's log was reviewed and the medication vials were counted to ensure compliance.

Outcomes

The primary efficacy endpoint was the change in proteinuria and eGFR from baseline to 12 months. The

rate of complete and partial remission was evaluated. Complete remission was defined as proteinuria <300 mg/24 hours and no more than 10% reduction in eGFR (based on the Chronic Kidney Disease–Epidemiology Collaboration) from baseline. Partial remission was defined as >50% reduction in proteinuria and no more than 25% reduction in eGFR from baseline. The primary safety endpoint was incidence of infections (pneumonia, urinary tract infections, and pyelonephritis), and rate of developing diabetes. Secondary endpoint evaluated improvement in hematuria.

Determination of Serum Levels of Total IgA, IgG, Galactose-Deficient-IgA1, and IgG Autoantibody Specific for Gd-IgA1

The serum levels of total IgA and IgG were measured by enzyme-linked immunosorbent assay (ELISA) and expressed in mg/ml serum, as described previously.[20] Galactose-deficient-IgA1 (Gd-IgA1) was measured by lectin ELISA, as described,[21,22] except that *N*-acetylgalactosamine (GalNAc)-specific lectin from *Helix aspersa* was replaced with a lectin from *Helix pomatia* (Human Protein Atlas; Sigma-Aldrich, St. Louis, MO).[23] Human Protein Atlas reactivity of IgA1 in each sample was expressed as Units of Gd-IgA1 per specific amount of IgA1. A Gd-IgA1 myeloma protein (Ale) purified from plasma of a patient with IgA myeloma was used as the standard. Optical density at 490 nm for 12.5 ng neuraminidase-treated IgA1 (Ale) was defined as 100 U of Gd-IgA1. Serum levels of IgG autoantibodies specific for Gd-IgA1 were measured by ELISA with standard Gd-IgA1 coated in the ELISA-plate wells.[11,24] One Unit of IgG autoantibody was defined as binding of IgG to ELISA-coated Gd-IgA1 resulting in the optical density at 490 nm of 1.0.

Statistical Analysis

Data were stored securely in a central database. This was a pilot study and power calculation was not performed. Outcome variables were expressed as mean with SD if normally distributed and median with ranges (minimum–maximum) for nonnormally distributed data. Changes in proteinuria and eGFR were analyzed by paired *t* test comparing 12-month follow-up versus baseline. Logistic regression modeling was used when evaluating association between baseline clinical and histological findings and outcome (response status). A *P* value of <0.05 was considered significant.

RESULTS

This was a prospective open-label trial with total of 4 centers recruiting patients (Mayo Clinic in Rochester and Jacksonville in addition to Columbia and Stanford Universities). Twenty-five patients underwent screening. Four patients were screen failures due to proteinuria <1 g/24 hours and 1 patient withdrew from the study before receiving any treatment. Of the 20 patients who were started on ACTH, 1 patient was withdrawn from the study at month 3 because of positive hepatitis B surface antigen. The remaining 19 patients were included in the analysis. One patient was withdrawn from the study because of progression of the disease at 6 months but was included in the final analysis. All patients were on maximally tolerated RAAS blockade with either angiotensin-converting enzyme inhibitor or angiotensin receptor blocker and had to have adequate blood pressure control (<130/80 mm Hg) before enrollment. Twelve patients did not receive any prior immunosuppressive therapy before enrollment in the study. Of the 7 who did receive prior therapy, 6 were treated with corticosteroids only (all use stopped 3 months before enrollment in the study) and one received cyclophosphamide and mycophenolate mofetil, in addition to corticosteroids before this study (all use stopped 6 months before enrollment in the study).

Table 1. Patients' demographics and renal biopsy findings

Baseline characteristics	*n* = 19
Age, yr	34.9 ± 10.5
Race (Caucasian/Asian)	14/5
Sex (M/F)	11/8
Oxford classification	
M (0,1)	1, 18
E (0,1)	8, 11
S (0,1)	3, 16
T (0,1,2)	8, 11, 0
C (0,1,2)	12, 5, 2

F, female; M, male; MESTC, mesangial hypercellularity, endocapillary hypercellularity, segmental glomerulosclerosis, tubular atrophy/interstitial fibrosis, crescent.

All patients had biopsy-proven IgAN with 50% or less scarring on renal biopsy. The Oxford classification findings are summarized in Table 1. The mean global sclerosis was 23.0% ± 16.5%, and the mean interstitial fibrosis and tubular atrophy were 21.3% ± 16.4%. The mean time from the renal biopsy to enrollment in the study was 13.5 ± 11.6 months and most patients (17 of 19) had biopsy performed within 2 years of the start of the study.

There were 11 men and 8 women, and 14 Caucasian and 5 Asian individuals with an overall mean age of 34.9 ± 10.5 years. Average blood pressure at the beginning of the trial was 124/76 ± 20/8 mm Hg. Mean baseline creatinine was 1.40 ± 0.49 mg/dl with an associated eGFR (Chronic Kidney Disease–Epidemiology Collaboration) of 65.5 ± 28.8 ml/min and a median 24-hour urinary protein of 2635 mg (range, 1230–5243 mg). Other baseline characteristics are shown in Table 2.

Table 2. Patients' characteristics at baseline and at 12-month follow-up

Parameters	Baseline (n = 19)	Follow-up (n = 19)	P value
sBP (mm Hg)	124.2 ± 20.2	119.2 ± 10.7	0.28
dBP (mm Hg)	76.0 ± 8.2	77.3 ± 9.8	0.66
BMI (kg/m^2)	27.7 ± 7.4	28.5 ± 7.0	0.18
Creatinine (mg/dl)	1.40 ± 0.49	1.55 ± 0.64	0.1
$eGFR_{CKD-EPI}$ (ml/min)	65.5 ± 28.8	61.1 ± 31.1	0.1
HgbA1C	5.1 ± 0.36	5.1 ± 0.32	0.7
Serum albumin (g/dl)	3.79 ± 0.54	3.93 ± 0.39	0.02
24 h UP (mg)	2635 (1230–5243)	1274 (344–6228)	0.007
Hematuria (RBC/HPF)	22.9 ± 36.5	10.6 ± 23.6	0.06

BMI, body mass index; CKD-EPI, Chronic Kidney Disease–Epidemiology Collaboration; dBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HgbA1C, hemoglobin A1C; RBC/HPF, red blood cell/high-power field; sBP, systolic blood pressure; UP, urinary protein.

At the end of the trial (month 12), the blood pressure was not significantly changed compared with baseline (119/77 ± 11/9 mm Hg, $P = 0.28/0.66$). Serum creatinine similarly remained stable at 1.55 ± 0.64 with an associated eGFR (Chronic Kidney Disease–Epidemiology Collaboration) of 61.1 ±31.1 mm Hg compared with baseline ($P = 0.1$). Twenty-four–hour urinary protein, however, did decrease significantly to a median of 1274 mg (344–6228 mg) ($P = 0.007$) with an expected significant increase in the serum albumin from 3.79 ± 0.54 to 3.93 ± 0.39 ($P = 0.02$). There was a trend toward significance with hematuria going down from 23 red blood cells per high-powered field to 11 red blood cells per high-powered field ($P = 0.06$). At 6-month follow-up, corresponding to completion of ACTH gel injections, the median proteinuria was 1125 mg (444–5317 mg), which was significantly reduced compared with baseline ($P = 0.007$), but not significantly different compared with urinary protein at 12 months ($P = 0.9$) (Figure 1). None of the patients in this study achieved complete remission, defined as proteinuria less than 300 mg/24 hours and no more than 10% drop in eGFR. However, 8 of 19 (42%) achieved partial remission (PR), defined as more than 50% reduction in proteinuria and no more than 25% drop in eGFR. Of the 8 patients who achieved PR, 7 had a proteinuria less than 1 g at 12 months. The median 24-hour urinary protein in partial responders was 625 mg (344–1458 mg). In patients who achieved PR at 12 months, the median 24-hour urinary protein at 6 months was 732 mg (444–2094) and not significantly changed compared with 12 months. The serum creatinine in the responders was 1.45 ± 0.54 mg/dl in follow-up. None of the patients developed end-stage renal disease, defined as need for dialysis, transplantation, or eGFR <15 ml/min.

There were no associations between the MEST-C score, percentage of global glomerulosclerosis, or interstitial fibrosis with tubular atrophy and response to therapy. Similarly, lack of response to previous therapy was not predictive of response to ACTH therapy (data not shown).

We also evaluated serum levels of Gd-IgA1 and IgG autoantibodies against Gd-IgA1. The results are shown in Table 3. There was no significant change in the Gd-IgA1 or the IgG autoantibody levels at follow-up compared with baseline. When specifically evaluating the patients who achieved PR, there was no significant change in the levels of Gd-IgA1 or IgG autoantibodies either (Table 4).

There were 53 adverse events reported in this study and none met the criteria for serious adverse events (Table 5). There were 6 infections. Two were viral (1 zoster and 1 upper respiratory tract infection that were treated conservatively) and 4 bacterial infections, all of which were treated effectively with antibiotics (2 sinusitis, 1 pneumonia, and 1 otitis media). There were 7 injection-related reactions, all of which occurred after the first injection; none resulted in discontinuation of the ACTH. One patient had polycythemia that was attributed to ACTH, and the drug was held for 4 weeks and then resumed again thereafter without recurrence of polycythemia. The most common reported adverse events related to the ACTH were acne, hot flashes, soreness, anxiety, and insomnia. None of the patients discontinued the study drug due to side effects. None developed hyperglycemia. The average hemoglobin A1C remained unchanged in follow-up compared with baseline (5.1%, $P = 0.7$). One patient was withdrawn from the study at month 3 because of hepatitis B positivity. After further review, it was noted that the patient already had a positive hepatitis B status (positive hepatitis B surface antigen testing) before enrollment in the study and should not have been eligible to be included. This patient was therefore withdrawn from the study and was not included in the analysis.

DISCUSSION

This is the first prospective study to evaluate the efficacy of ACTH in reducing proteinuria in patients with IgAN who are at high risk of progression. Overall, ACTH resulted in a significant reduction in proteinuria from a median of 2.6 to 1.1 g/24 hours at 6 months, which was sustained at 12 months (1.3 g/24 hours). When specifically evaluating patients who responded to ACTH, the proteinuria continued to improve from 6 to 12 months. In patients who were nonresponders, proteinuria increased further from 6 months to 12 months. This was associated with a significant rise in serum albumin and a trend toward reduction in hematuria, whereas the serum creatinine and eGFR remained unchanged over the 12-month period. Eight

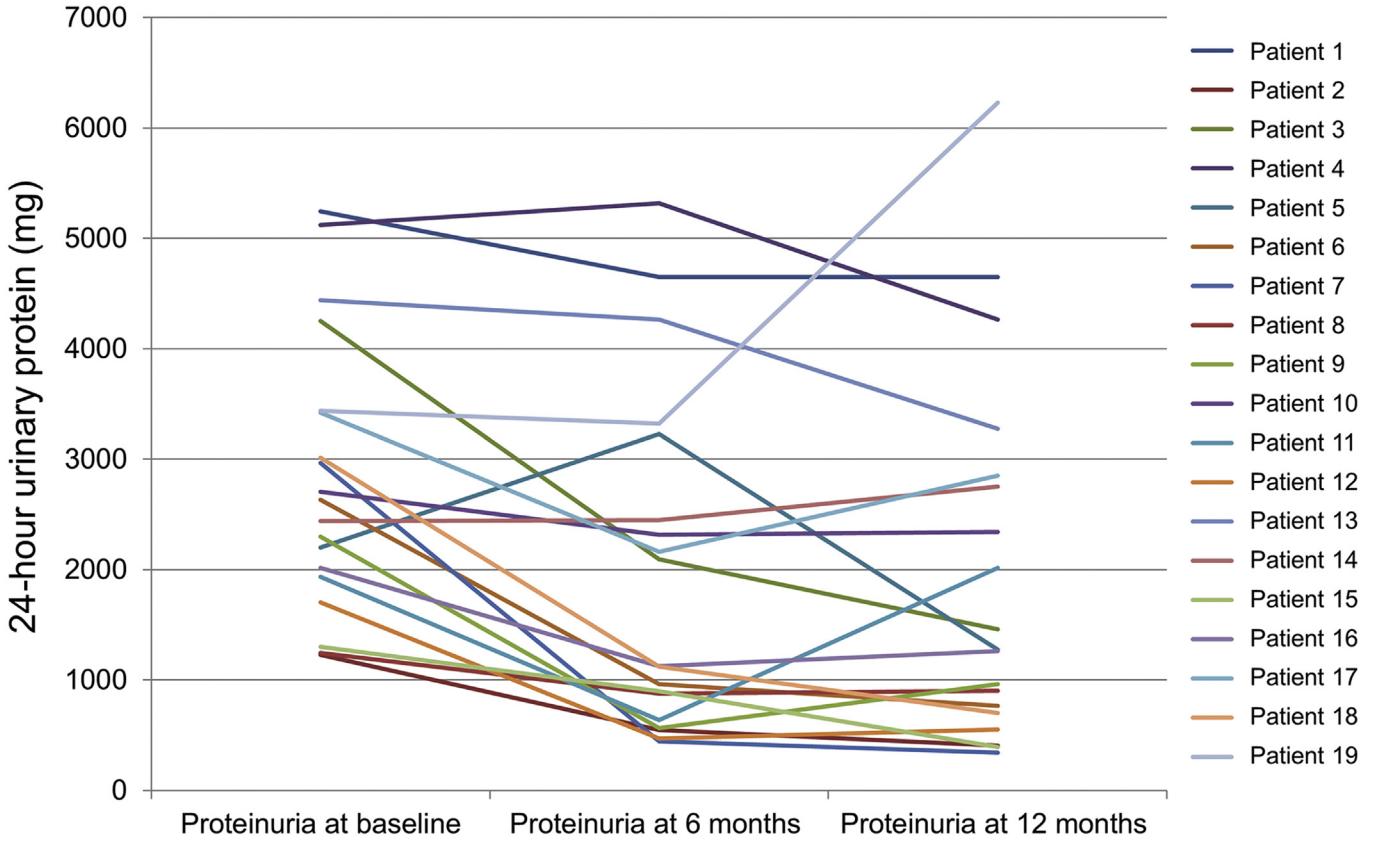

Figure 1. Proteinuria at baseline and 6-month and 12-month follow-up.

patients achieved PR and, of those, 7 reached a proteinuria less than 1 g in follow-up. The drug was well-tolerated and no patient discontinued the drug because of side effects.

The patients with IgAN in this trial were at particularly high risk of progression. Even though the enrollment criterion was proteinuria more than 1 g despite maximal conservative measures, 14 patients (74%) had proteinuria more than 2 g and 7 (37%) had proteinuria more than 3 g/24 hours. In addition, 14 (74%) had hematuria at the time of renal biopsy. This type of patient population has been shown to be at very high risk of progression, with 30% reaching end-stage renal disease in 5 years.[25,26] Indeed, most IgAN trials exclude patients with heavy proteinuria. In the STOP-IgAN trial, patients with proteinuria >3.5 g/24 hours were excluded from the study; average proteinuria of those who were randomized to treatment was 1.8 g/24 hours versus the 2.8 g/24 hours in our cohort. Despite the high risk of progression in this patient population, 42% achieved PR.

In this study, we also evaluated the findings of renal biopsy and response to therapy. Even though the non-responders had a higher degree of interstitial fibrosis with tubular atrophy compared with responders (25% vs. 17.5%), this did not reach statistical significance.

Table 3. Serum levels of Gd-IgA1 and IgG autoantibody at baseline and 12-month follow-up

	Baseline (n = 19)	Follow-up (n = 19)	P value
Gd-IgA1 U/ml	1,931,734 (328,871–6,197,802)	2,584,870 (161,172–8,424,908)	0.62
Gd-IgA1 U/mg IgA	548,055 (70,787–1,087,726)	622,354 (42,759–1,523,776)	0.54
IgG autoantibody U/ml	1605 (55–4295)	1895 (390–3440)	0.17
IgG autoantibody U/mg IgG	100.5 (13.3–337.7)	146 (55.7–321.8)	0.17

Gd-IgA1, galactose-deficient IgA1.
Data are presented as median and then ranges from minimum to maximum.

Table 4. Serum levels of Gd-IgA1 and IgG autoantibody at baseline and 12-month follow-up in patients who achieved partial remission

	Baseline (n = 8)	Follow-up (n = 8)	P value
Gd-IgA1 U/ml	1,865,313.7 (328,871–2,464,944)	1,940,959 (161,172–3,335,793)	0.90
Gd-IgA1 U/mg IgA	440,519 (70,787–1,087,726)	639,409 (42,759–1,523,776)	0.81
IgG autoantibody U/ml	2067 (470–4295)	1975 (615–3360)	0.95
IgG autoantibody U/mg IgG	158.45 (51.6–337.7)	178.9 (55.7–321.8)	0.78

Gd-IgA1, galactose-deficient IgA1.
Data are presented as median and then ranges from minimum to maximum.

Table 5. Adverse events during the trial

Adverse events	Number
Related to the drug	
Infections	Total: 6
- Sinusitis	2
- Pneumonia	1
- Otitis media	1
- Shingles	1
- Viral upper respiratory infection	1
Injection reaction	Total: 7
- Rash/swelling at the site of injection	3
- Pressure behind the eye after injections	2
- Syncope from site of needle at the time of first injection	2
Muscle soreness	4
Acne	3
Hot flashes	3
Anxiety	3
Insomnia	3
Hypertension	2
Increased appetite	1
Face roundness	1
Polycythemia	1
Unrelated to the drug	Total 19
Rash	1
Fatigue	1
Blurred vision	1
Plantar fasciitis	1
Concentration impairment	1
Headache	1
Urinary frequency	1
Back pain	1
Diarrhea	1
Left foot pain	1
Jaw pain	1
Heart palpitation	1
Reflux	1
Tooth sensitivity	1
Increased thirst	1
Skin sensitivity	1
Lightheadedness	1
Congestion	1
Wisdom tooth extraction	1

Similarly, 28.5% of patients who had failed previous therapy responded to ACTH compared with 50% who had no previous therapy, but this was not statistically significant. It is possible that patients who have a higher degree of fibrosis on their biopsy and have failed previous therapy are less likely to respond to ACTH therapy; however, the number of patients in this study was too small to reach any definitive conclusions.

We also measured serum levels of Gd-IgA1 and IgG autoantibodies specific for Gd-IgA1 in these patients before and after ACTH treatment and at the end of the study, and despite the improvement in the proteinuria, there was no significant change in the antibody levels. Similarly, when evaluating the responders only, there still was no change in the levels of these antibodies. The pathogenesis of IgAN is thought to be a multi-hit process starting with development of Gd-IgA followed by IgG autoantibodies against the Gd-IgA–forming immune complexes, followed by deposition of the IgA complexes in the kidney, which results in activation of the complement cascade and podocyte injury.[27,28] Given that ACTH is thought to reduce proteinuria primarily through its action on the MCR on the podocytes, it is possible that this drug does not change the production of the Gd-IgA or the autoantibody but rather exerts its effect downstream on the podocyte. Activation of MC1R has been shown to promote an increase of catalase activity and reduce oxidative stress. This in turn results in deactivation of p190RhoGAP activity and increased formation of stress fibers through RhoA. In addition, MC1R agonists protect against apoptosis and has been shown to lower proteinuria.[29,30] Systemic immunomodulation through MCR and anti-inflammatory effects on peripheral white blood cells through MCR 1, 3, and 5 may be other mechanisms by which ACTH exerts its effects.[31,32]

ACTH gel was overall well-tolerated over 6 months, with reversible polycythemia in 1 patient and 6 infections, none resulting in hospitalization. Four were treated with antibiotics and all resolved. Injection-related reactions occurred primarily following the first injection and were overall mild.

This study has several limitations. Being a pilot study, the number of patients in this study was small and the study also lacked a placebo group for comparison. This limits our power to detect associations between clinical outcomes and potential predictors, as well as limiting our ability to definitively implicate ACTH as the cause for improvement. It should, however, be noted that the patients in this study were of particularly high risk of progression with heavy proteinuria, and many would not have qualified for clinical trials based on previous protocols. Last, the duration of follow-up is too short, and the long-term outcome of these patients is unknown. This particularly limits our ability to accurately measure changes in eGFR, which may occur over a longer period. It is, however, reassuring to see that even though the ACTH injection was stopped at 6 months, the effect on proteinuria was sustained at 12 months. Whether the effect on the proteinuria would be sustained past 12 months is at this point unclear. It is possible that intermittent therapy with ACTH would be a more effective way to treat IgAN while minimizing the toxicity associated with prolonged use of ACTH. Future studies are needed to evaluate this approach further. The positive signal in the current study with the low toxicity observed supports proceeding with a properly conducted

randomized controlled trial to further evaluate the effectiveness of ACTH against current therapies.

In conclusion, this is the first prospective trial to evaluate the efficacy and safety of ACTH in treatment of patients with IgAN and proteinuria >1 g/24 hours. Overall, the drug was well-tolerated without any major adverse events, and 6 months of therapy was associated with a clinically significant reduction in proteinuria at 6 months, which was sustained up to 12 months.

DISCLOSURES

JN reports his current funding from the National Institutes of Health and sponsored research agreements with Retrophin and Alexion, is a co-inventor on US patent applications US08/230,473 and US14/318,082 (assigned to University of Alabama at Birmingham Research Foundation), and is a co-founder of Reliant Glycosciences, LLC. RL has received advisory fees from Mallinckrodt, Omeros, Calliditas, Retrophin, and Otsuka, Inc, and has received research grant support from Mallinckrodt Medical Inc, Apellis, Omeros, Calliditas, and Otsuka. FCF received an unrestricted research grant from Mallinckrodt Medical Inc. All the other authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

Supplementary File (MS Word)

CONSORT Checklist.

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