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Resistant Nephrotic Syndrome: Review of Trials Using ACTH and a Case Series of Six Patients Treated with ACTHar

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Authors' contributions

This work was carried out in collaboration between all authors. Authors JW and VP did the literature searches, wrote large sections of the manuscript and author RP helped with graphics and tables. Author GT oversaw all aspects and was involved in the care of all the subjects referenced in the cases series. All authors read and approved the final manuscript.

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Case Study

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ABSTRACT

Nephrotic syndrome (NS) is associated with edema, proteinuria, hyperlipidemia, and an increased risk for deep vein thrombosis. Therapy may include glucocorticoids, immunosuppressive therapy, and/or chemotherapy. Each is associated with significant toxicity. Adrenocorticotrophic hormone (ACTH) has been approved for treating NS since the 1950s. Both the synthetic form of ACTH (cosyntropin-ACTH 1-24) and ACTHar (ACTH1-39), a synthetic gel isolated from porcine pituitary extracts, have been used successfully in treating NS but fewer than 100 published cases of ACTHar therapy are available in the literature. Membranous nephropathy is the best studied entity. Our case series adds six new cases to the literature and strengthens the growing consensus that ACTHar may be effective in treating focal segmental glomerulosclerosis.

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1. INTRODUCTION

Nephrotic Syndrome (NS) is a relatively rare condition with an estimated incidence of 3 new diagnoses per 100,000 per year [1].

General principles of therapy include non-specific antiproteinuric therapy with angiotensin converting enzyme inhibitors, angiotensin receptor blockers, anti-hyperlipidemic therapy, and more specific therapy tailored to the specific medical entity being treated [1].

Targeted therapy may include glucocorticoids, immunosuppressives, or chemotherapy. Each carries its own risk over time: glucocorticoids causingamong other things diabetes, cataracts, and osteoporosis; immunosuppressives increasing infectious risk, de novo cancers, and cytopenias; and chemotherapy causing increased risk of infection, de novo cancers, and troublesome nausea, vomiting, and hair loss [1,2,3]. Therapy can range from 6 months up to 2 years. Furthermore, many forms of NS relapse necessitating repeat therapy which increases toxicity [1].

Adrenocorticotrophic hormone (ACTH) was approved by the Food and Drug Administration to treat NS in the 1950's, and was used largely in children [4]. A pituitary polypeptide hormone consisting of 39 amino acids, ACTH stimulates the adrenal cortex to produce cortisol in response to stress. ACTH can decrease plasma lipid levels and increase plasma insulin levels. The use of ACTH for treatment of NS has since largely been replaced by synthetic glucocorticoids, immunosuppressives, and or chemotherapy [3].

Studies show ACTH can decrease proteinuria in patients with NS previously refractory to treatment with glucocorticoids, indicating that the effects of ACTH cannot entirely be explained by itssteroidogenic effects. ACTH is believed to act via the melanocortin system. There are 5 G protein-coupled melanocortin receptors (MC1R-MC5R) present in kidney cells as well as other tissues of the body. All five show a strong affinity for ACTH and agonism of these receptors reduces proteinuria, improves glomerular morphology and reduces oxidative stress [5,6].

Histologically, ACTH administration in rats leads to reduction in foot-process effacement and podocyte apoptosis [5]. By binding to MCRs expressed on B lymphocytes, CD4+ T helper cells, NK cells, monocytes and granulocytes ACTH may have adirect effect in immune-complex-mediated glomerulopathies [7]. ACTH ameliorates many signs/symptoms of NS including decreasing proteinuria and dyslipidemia, and improving diuresis and edema. Generally well-tolerated, ACTH tends to cause side effects similar to those associated with glucocorticoids [8].

Over the last decade or so the use of ACTH 1-24 and 1-39 has surged and several clinical trials and cases series have been undertaken. Table 1 reviews these in detail.

2. METHODS

We performed a literature search of all available trials using ACTHar and synthetic ACTH.

3. RESULTS

3.1 Review of Clinical Trials and Case Series

Berg et al. [9] studied synthetic ACTH (ACTH1-24) in the treatment of NS in Europe, renewing interest in this hormone. Fourteen subjects with NS from Membranous Nephropathy (iMN) received ACTH 1-24 for 8 weeks. Lipids fell by 30-60% and 5 of the 14 patients had remission of NS at 18 months. Proteinuria was reduced substantially in all subjects, and prompted further investigation with this agent [8].

In 2004 Berg studied the use of ACTH in NS more broadly, including cases of iMN, Minimal Change Disease (MCD), Diabetic Nephropathy, Focal Segmental Glomerulosclerosis (FSGS) and Mesangiocapillary Glomerulonephritis (MSGN). Therapy ranged from 2-11months, and many of the subjects had failed one or more traditional regimens. In all, 22 out of 23 patients responded, with a mean decrease in proteinuria of 90%. While 4 subjects relapsed after completion of ACTH 1-24, 3 were re-challenged and again responded with decreased proteinuria [9].

To measure response, Bomback proposed the following: Complete response occurred when proteinuria falls<500 mg/day, partial response as ≥50% reduction in proteinuria and final

proteinuria 500-3500 mg/day, and limited response a ≥50% reduction in proteinuria but final proteinuria >3500 mg/day [10].

In Bomback's 2011 case series of 21 patients treated with ACTHar gel, over half (52%) the patients responded with a complete or partial remission, the majority of whom had iMN. Among responders proteinuria improved on average by 82%. Whereas the therapy was not effective in subjects with Lupus Nephritis Class V, Membranoproliferative Glomerulonephritis (MPGN), Monoclonal Diffuse Proliferative Glomerulonephritis, MCD, or unclassified NS, one patient with IgA Nephropathy (IgAN) had a complete and one with FSGS had a partial response [10]. A year later Bomback, using ACTHAr prospectively treated15 patients with refractory glomerular disease (not all were nephrotic) who had previously failed ≥ 2 different therapies. Including subjects with iMN, FSGS, MCD, and IgAN, nearly half (46.7%) of these patients had complete or partial response [11].

By 2012 ACTHar was an established therapy in iMN, but was less well-studied in other forms of NS. Hogan et al, in 2013, prospectively studied 24 subjects with resistant FSGS treated with ACTHar Gel. The mean number of previous therapies was 2.2. A complete or partial response occurred in 29% [12].

Fervenza's series in 2014 measured proteinuria and lipid parameters in patients with iMN treated with ACTHar. 65% of patients responded to treatment (13/20 treated patients) with 10% showing complete remission and 50% with partial remission. Overall the mean improvement in proteinuria in both responders and non-responders was 57% (9.1±3.4 g/day to 3.9±4.2 at one year follow-up). Total cholesterol also fell by 39% (306±133 to 187±49) [13].

In the cases above, ACTHar or ACTH 1-24 was rarely a first-line therapy and was not compared with another agent or even placebo. The strength of the evidence that ACTHar or ACTH 1-24 is efficacious in NS rests of case series data which suffers from significant bias. In 2006, Ponticelli randomized 32 subjects with iMN and NS to a Prednisone and Chlorambucil or Cyclophosphamide (standard therapy) regimen versus ACTH1-24. At 24 month follow up, of 16 subjects treated with standard therapy 12 had a complete [4] or partial remission [8] of NS versus 8 complete and 6 partial remissions in the ACTH 1-24 group. The difference was not statistically significant but indicated relatively equivalent efficacy [14].

On the strength of the available literature, our center began using ACTHar regularly in 2013, particularly in resistant cases of NS. Our experience, listed in Table 2, draws from 6 patients who on average had been exposed to nearly 3 previous non-ACTHar based regimens (listed), and all having received at least one non-ACTHar therapy. All received standard RAAS blockers and were treated for hyperlipidemia with statin drugs. Three of the subjects experienced partial remissions, 2 had no response, and one withdrew due to significant fluid retention and hyperglycemia. As with prior literature, our patients did experience hyperglycemia and upper respiratory tractsymptoms. Mean reduction in proteinuria among responders was 68%.

4. DISCUSSION

Nearly 50 years after its approval to treat NS, ACTH-based therapies have experienced a renaissance. While over 3700 patients have been treated with ACTHar, the available clinical trial and case series data is sparse. As such we acknowledge the limitations of this study. We were only able to show partial responses, somewhat inconsistent with successes such as those published by others [9-11]. Our experience with the previous standard of care, the Ponticelli Regimen, was generally positive, allowing in some cases for extended periods of remission [3]. Several subjects received more than one course of this therapy. Ultimately, however, we chose to transition to an ACTHar-based therapy for fear of cumulative toxicity of Cyclophosphamide and steroids. With this change in therapy, we were still able to induce partial responses in subjects with resistant and/or recurrent forms of NS. We believe any reduction in proteinuria in otherwise hopeless cases is cause for some sober optimism. Therapy for NS is aimed at inducing a remission. Arbitrary definitions of complete and partial remission obscure the benefit of reducing proteinuria which is an established predictor of progressive renal disease. In the literature a patient's whose urine protein falls from 20 g/d down to 2 g/d is classified as achieving a partial remission but has had a 90% decline in proteinuria, but a patient whose proteinuria falls from 2500 mg/d to 450 mg/d achieves a complete remission. Both represent dramatic outcomes.

Table 1. ACTH and ACTHar trials in resistant nephrotic syndrome

Study	Total number of patients studied	% of patients to respond to treatment	Mean % reduction in proteinuria in patients who responded to treatment	Mean % reduction in proteinuria overall	Pts that had been refractory to prior tx
Berg, 2004 [9]	23	100%	90.0%	--	11 (47.8%)
Bomback, 2011 [10]	21	52% - 19% complete - 33 % partial	81.9%	48.1%	18 (85.7%)
Bomback, 2012 [11]	15	46.7% -13.3% complete - 33.3% partial	66.2%	11.4%	15/15 (100%)
Hogan, 2013 [12]	24	29% - 5 partial - 2 complete	76.1%	23.4%	22/24
Hladunewich, 2014 [13]	20	65% - 50% partial - 10% complete	--	57.1%	0 (ineligible)

Table 2. Lankenau medical center, single center experience with ACTHar in resistant nephrotic syndrome

Patient #	Age	DX	Previous drug regimens	Pre-ACTHar proteinuria (mg/day)	Post-ACTHar proteinuria (mg/day)	Response
1	64	MN-NSAID	3	5100	6600	None
2	57	FSGS	3	2500	1246	Partial
3	41	SLE NEPH CLASS III	1	19890	2454	Partial
4	72	FSGS	2	3600	1270	Partial
5	63	FSGS	1	2800	N/A	Withdrew/ Side effects
6	49	FSGS	5	13000	13000	None

**All subjects were treated with Renin-Angiotension-Alodosterone Antagonists and Statin; Subject 1: Received Ponticelli regimen three separate times; Subject 2: Received Steroids, Cyclosoprine and Mycophenolate Mofetil; Subject 3: Received Cyclophospahmide and Prednisone; Subject 4: Received Prednisone and Cyclosporine; Subject 5: Received Cyclosporine; Subject 6: Received Prednisone, Cyclosporine, and Mycophenolate Mofetil*

We propose that a decline in proteinuria by over 50% and a final level < 1000 mg/d should represent a complete remission, and a decline in proteinuria by 50% with residual protein excretion > 1 g/d be referred to as a partial remission. In cases of resistant NS, any decline in proteinuria is progress. We believe ACTHar and ACTH1-24 are underutilized therapeutic options in NS and promote further investigation in these efficacious agents.

5. CONCLUSION

ACTHar and ACTH-based therapies offer hope for treating resistant forms of NS. The side effect profile is generally less severe than other more common therapies. Our experience adds to the growing body of literature promoting ACTHar use in NS.

DISCLOSURES

Dr. Teehan is a paid speaker for Questcor Pharmaceuticals.

CONSENT

Not applicable-IRB waived review process.

ETHICAL APPROVAL

Not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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