



The Use of ACTH Gel in Membranous Nephropathy

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Abstract

Membranous Nephropathy (MN) is one of the most common causes of nephrotic syndrome characterized by insidious onset, nephrotic range proteinuria, reduced renal function, and can lead to end stage renal disease. Treatment regimens for MN have been described including steroids treatment in combination with cyclophosphamide or calcineurin inhibitors, cyclosporine or tacrolimus. Adrenocorticotropin (ACTH) has been increasingly studied for various glomerulopathies, most notably MN and growing evidence suggesting that ACTH maybe an effective treatment option.

Keywords: ACTH gel; Adrenocorticotropin; Membranous nephropathy; Nephrotic syndrome; Nephrotic-range proteinuria

Abbreviations: MN: Membranous Nephropathy; ACTH: Adrenocorticotropin; GFR: Glomerular Filtration Rate; PLA2R: Phospholipase A2 Receptor; ACEI: Angiotensin-Converting Enzyme; ARB: Angiotensin II Receptor Blockers; FSGS: Focal Segmental Glomerulosclerosis; MCD: Minimal Change Disease

Introduction

MN is the most common cause of nephrotic syndrome in non-diabetic Caucasian adults over 40 years of age. The estimated incidence is 8-10 cases per 1 million. 50% of patients diagnosed with primary MN continue to have nephrotic syndrome and 30% progress towards end-stage renal disease. Continuous studies have helped increase our understanding of the pathogenesis and treatment in last decade [1]. In 20-30% of cases, MN is secondary and is associated with solid tumors of breast, lung and colon, infections like hepatitis B, malaria and schistosomiasis, and rheumatological disorders like lupus, rheumatoid arthritis, IgG4 disease or drug exposure. In Idiopathic MN, 70% of cases have autoantibodies against the M- type phospholipase A2 receptor which circulate and bind to the PLA2R on human podocytes, producing characteristic deposits [2].

Case Presentation

We report a case of 51-year-old Caucasian male with history of hypertension who presented to us after referral from his primary care physician with weakness, leg edema, and frothy looking urine. On examination, patient looked tired and bilateral leg edema

was noticed. After performing renal biopsy, he was diagnosed with idiopathic MN. He was started with cyclophosphamide and prednisolone for three months, but he did not respond to the treatment. Then he was tried on a course of cyclosporine and prednisolone for three months with only partial response. ACTH gel treatment was discussed with the patient and it was agreed upon by the physician and patient to begin treatment with ACTH (H.P Acthar® gel 80 U/mL). At that time, his Glomerular Filtration Rate (GFR) was 38 ml/min, creatinine 2.0 mg/dL and proteinuria with urine protein to creatinine ratio in the range of 3000 mg/dL. Three months after the start of ACTH treatment, significant decrease of proteinuria and protein to creatinine ratio of 800 mg/dL was noted, along with improvement of GFR to 58 ml/min and creatinine 1.3 mg/dL. No adverse effects were noted. Bilateral leg edema and fatigue resolved. His proteinuria decreased gradually over the next 6 months reaching 75 mg/dL and normalized after 12 months to 20 mg/dL.

Discussion

ACTH has an important protective role on podocytes and decreasing proteinuria. Gene expression of melanocortin receptor MC1R is discovered in podocytes, glomerular endothelial cells, mesangial cells, and tubular epithelial cells. It was found that treatment with MC1R agonists such as ACTH improved podocyte morphology and reduced oxidative stress hence reducing proteinuria [3]. On a study on rats where the podocytes were subjected to the nephrotic-inducing agent puromycin amino nucleoside, activation of MC1R promoted an increase of catalase activity and reduced oxidative stress, which resulted in the dephosphorylation of p190RhoGAP and formation of stress fibers through RhoA. In addition, MC1R agonists protect against

apoptosis. Together, these mechanisms protect the podocyte against puromycin [4] (Table 1).

	Reference values	Before starting ACTH	3 months post- ACTH use	12 months post- ACTH use
GFR (ml/min)	>60	38	58	53
Cr (mg/dL)	0.6 – 1.2	2.0	1.3	1.4
UP/C (mg/dL)	<30	3047	808	20
BUN (mg/dL)	7 - 20	40	24	29

ACTH: Adrenocorticotrophic Hormone; GFR: Glomerular Filtration Rate; Cr: Creatinine; UP/C: Urine Protein/Creatinine Ratio; BUN: Blood Urea Nitrogen

Table 1: Renal function measurements after ACTH use in comparison to normal values.

In one cohort study done on twenty patients with idiopathic MN treated with 40 or 80 IU of ACTH twice weekly for 3-6 months, resulted in significant improvement in proteinuria and greater than 50% decrease in proteinuria in 65% of the patients. All patients developed significant improvement in both serum albumin and total LDL cholesterol. There was a statistically significant correlation between the percentage change in anti-PLA2R antibodies and improvement in proteinuria after completion of the ACTH therapy. No adverse effects were noted during the course of the study [5].

Patients diagnosed with MN should receive conservative treatment directed toward decreasing blood pressure, reducing edema, and limiting the risks for cardiovascular events and thromboembolism. Angiotensin-Converting Enzyme (ACEI) inhibitors or Angiotensin II Receptor Blockers (ARB) are recommended for controlling blood pressure. ACEI and ARB have a Reno-protective effect on the kidneys through decreasing intraglomerular pressure and decreasing proteinuria. Patients with hypercholesterolemia should receive statin therapy for prevention against cardiovascular risks. Prophylactic anticoagulant might be considered in some patients particularly those with albumin <2.2 g/dL and high risk for thromboembolic events. If patient not fully responsive to conservative treatment other approaches have been employed [6].

Multiple studies have been conducted on membranous nephropathy patients and treatment options used including conservative treatment of angiotensin-converting enzyme inhibitors or angiotensinogen receptor blocker in addition to immunosuppressive therapy including steroid therapy alternatingly with alkylating agents. Calcineurin inhibitors could be use as first line in patient who refuse or contraindicated to treatment with steroids and alkylating agent. Other treatment options suggested including rituximab, mycophenolate mofetil, adrenocorticotrophic hormone, intravenous immunoglobulin, and azathioprine. Rituximab demonstrated beneficial outcome with limited toxicity. Evidence was limited regarding mycophenolate use and no role for azathioprine or intravenous immunoglobulin use in patients with Idiopathic MN [7]. Using ACTH in idiopathic MN has been described in multiple studies [8-10]. One study conducted on 21 patients with nephrotic syndromes, 11 of them with idiopathic MN

were treated with ACTH gel and were followed up for 6 months. 9 of the 11 patients with MN achieved complete remission suggesting viable role of ACTH and high remission rates approaching 80% [8].

According to the KDIGO practice guideline on glomerulonephritis, Cyclical regimen of alkylating agents (Cyclophosphamide rather than chlorambucil in the initial therapy) and Corticosteroids for a period of six months was effective in achieving remission [11]. However, this approach can lead to the development of opportunistic infections, reactivation of viral hepatitis, hemorrhagic cystitis, neoplasia, and toxic hepatitis [6]. Alternate regimens include cyclosporine or tacrolimus which can be used for at least 6 months for patients who have contraindications, or partial response to cyclophosphamide/steroid regimen. Patients who receive Calcineurin inhibitors could have nephrotoxicity resulting in Acute kidney injury and rarely thrombotic microangiopathy, hence should be monitored closely [11].

Based on a meta-analysis done in 2016 data from patients with MN, Focal Segmental Glomerulosclerosis (FSGS), and Minimal Change Disease (MCD) were collected. The rate of complete remission in MN after ACTH treatment course was 80% in 0-6 months, 69% at >6-12 months, 90% at >12-24 months and 95% beyond 24 months of follow-up. Individuals with primary FSGS and MCD treated with ACTH were in remission at 6 months, however the relapse rate was high after ACTH discontinuation (17%) [12].

Conclusion

MN is the most common cause of nephrotic syndrome and treatment modalities targeting immune suppression have been documented like corticosteroids, cyclophosphamide and calcineurin inhibitors. Some recent studies showed the efficacy of ACTH gel use in treatment MN patients. Based on our experience in the use of ACTH gel in this patient with idiopathic MN, we find that ACTH treatment has led to significant improvement in both proteinuria and renal function during the course of the treatment and maintaining GFR in stable values without relapse after discontinuing the medication. While on the contrary, completion of a course of cyclophosphamide

with steroids and subsequently cyclosporine with steroids resulted in only minimal effects. Based on this experience, we suggest that ACTH is a well-tolerated therapy and may play a viable role in the treatment of membranous nephropathy.

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