Membranous glomerulopathy and treatment with Acthar®: a case study

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Abstract: Treatment options for refractory membranous nephropathy are limited. Herein we describe the case of a 46-year-old white male with membranous nephropathy who progressed during 3 years of treatment with antihypertensive agents (specifically angiotensin-converting enzyme inhibitors and angiotensin receptor blockers), diuretics, simvastatin, prednisone, cyclosporine A, and mycophenolate mofetil. Prior to initiation of treatment with H.P. Acthar® Gel, his proteinuria level was 9,520 mg/dL (952.0 g/L) but it decreased to 2,948 mg/dL (294.8 g/L) after 10 months of Acthar therapy. After 13 months, treatment with Acthar was halted as his 24-hour urinary protein was 1,628 mg/dL (162.8 g/L); by 15 months, it was 407 mg/dL (40.7 g/L). The patient has remained free of signs and symptoms of membranous nephropathy for 1.5 years. These results support the use of Acthar as an effective and safe therapy for patients with refractory membranous nephropathy.

Keywords: membranous glomerulopathy, membranous nephropathy, ACTH, proteinuria, nephrotic syndrome

Introduction
Membranous nephropathy is an immune-mediated glomerular disease that is the most common form of nephrotic syndrome in adults. Membranous nephropathy has the potential to progress to end-stage renal failure; however, it also spontaneously resolves in about 30% of patients. Its onset is insidious, with edema being the most common presenting symptom. Patients may also complain of anorexia, malaise, and fatigue. The primary sign of membranous nephropathy is proteinuria, with higher levels of urine protein correlated with greater risk of disease progression.

Initial treatment of membranous nephropathy involves management of the accompanying edema, hypertension, and often hyperlipidemia, most commonly through the use of diuretics, angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers, and statins, respectively. Such treatments, along with dietary management of proteinuria, may be sufficient in patients with disease at low risk of progressing. However, immune suppression via corticosteroids, cyclosporine, and alkylating agents is generally required for patients with higher-risk disease (characterized by persistent/high-grade proteinuria and/or deteriorating renal function). Unfortunately, such therapies can be associated with significant toxicity, and many patients experience recurrence or develop resistance to treatment.

Synthetic adrenocorticotropic hormone (ACTH) analogs have been used in Europe with some success for the treatment of nephrotic syndrome of various etiologies,
including idiopathic membranous nephropathy. In the United States, the natural ACTH, H.P. Acthar\textsuperscript{®} Gel (Acthar; Questcor Pharmaceuticals, Inc., Union City, CA, USA) has recently been shown to induce remission, defined as stabilization or improvement of renal function (by estimated glomerular filtration rate) and resolution of proteinuria, in patients with idiopathic membranous nephropathy. Herein, we describe a case in which 13 months of treatment with Acthar resulted in a sustained remission of membranous nephropathy in a patient with refractory disease.

Case report
At an initial visit in September 2006, a 46-year-old white male presented with edema, blood pressure indicative of hypertension (144/94 mmHg), heart rate of 76 beats per minute, and creatinine of 1.4 mg/dL (123.76 \(\mu\)mol/L). He had experienced sudden onset of edema in his feet and legs 5 weeks prior to this initial visit, which caused him serious concern. At a height of 5 feet 8 inches (172.72 cm) and weighing 235 lbs (105.75 kg; up about 35 lbs [15.75 kg] from his usual weight), his body mass index was 35.7. He had not been on any medication regimen. Laboratory values included 24-hour urinary protein at >7,500 mg/dL (750.0 g/L) and cholesterol at 307 mg/dL (7.9513 mmol/L; low-density lipoprotein, 224 mg/dL [5.8016 mmol/L]). He was negative for cancer screening, hepatitis B and C panel, antinuclear antibody, rheumatoid factor, and rapid plasmid reagin. He was started on olmesartan medoxomil-hydrochlorothiazide 40/25 mg for hypertension and proteinuria and simvastatin 40 mg for elevated cholesterol.

The patient was scheduled for a kidney biopsy for nephrotic range proteinuria in October 2006, which resulted in a diagnosis of idiopathic membranous glomerulopathy. Lisinopril 40 mg twice daily was added to his medication regimen. At this time, his creatinine was at 1.3 mg/dL (114.92 \(\mu\)mol/L).

The patient’s membranous glomerulopathy progressed from October 2006 to July 2009, as revealed by laboratory results. During this period, he remained on an angiotensin receptor blocker (olmesartan medoxomil-hydrochlorothiazide)

\begin{table}[h]
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Urinary protein, mg/dL (g/L) & $>$300 & $>$30.0 & & & & & \\
Creatinine, mg/dL (\(\mu\)mol/L) & 1.4 & 1.6 & 3.8 & 2.1 & 1.9 & 1.8 & 1.9 \\
& (123.76) & (141.44) & (335.92) & (185.64) & (167.96) & (159.12) & (167.96) \\
Albumin, mg/dL (g/L) & 2.2 & 2.1 & 2.3 & 2.7 & 2.1 & 1.7 & 1.7 \\
& (0.22) & (0.21) & (0.23) & (0.27) & (0.21) & (0.17) & (0.17) \\
Pr/Cr ratio & & & & & & & \\
CrCl mL/min/1.73 m\(^2\) (mL/s/m\(^2\)) & 61 & & & & & & \\
Weight, lbs (kg) & 222.4 & 235.0 & & & & & \\
& (100.1) & (105.8) & & & & & \\
Dose of Acthar\textsuperscript{®} & & & & & & & \\
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\textbf{Laboratory values from August 2006–September 2011} & \textbf{April 2009} & \textbf{July 2009} & \textbf{September 2009\textsuperscript{a}} & \textbf{October 2009} & \textbf{December 2009} & \textbf{January 2010} & \textbf{February 2010} \\
\hline
Urinary protein, mg/dL (g/L) & 5,970 & $>$9,150 & $>$9,150 & 6,607 & & & \\
& (597.0) & ($>$915.0) & ($>$915.0) & (660.7) & & & \\
Creatinine, mg/dL (\(\mu\)mol/L) & 2.7 & 2.4 & 2.5 & 2.5 & 1.8 & 2.2 & 2.1 \\
& (238.68) & (212.16) & (221.00) & (219.00) & (159.12) & (159.12) & (185.64) \\
Albumin, mg/dL (g/L) & 3.1 & 2.8 & 3.5 & 3.5 & 3.3 & 3.5 & 2.9 \\
& (0.31) & (0.28) & (0.35) & (0.35) & (0.33) & (0.35) & (0.29) \\
Pr/Cr ratio & & & & & & & \\
CrCl mL/min/1.73 m\(^2\) (mL/s/m\(^2\)) & 42 & 48 & 77 & 77 & 60 & & \\
& (0.70) & (0.80) & (1.29) & (1.29) & (1.00) & & \\
Weight, lbs (kg) & 185.6 & 180.2 & 171.0 & 186 & 194.4 & 195 & \\
& (83.5) & (81.1) & (77.0) & (83.7) & (87.5) & (87.8) & \\
Dose of Acthar\textsuperscript{®} & 40 U & 40 U & 40 U & 40 U & 40 U & 80 U & 80 U \\
& q72h & q72h & q72h & q72h & q72h & q72h & q72h \\
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Notes: Initial visit following initiation of Acthar\textsuperscript{®} (Acthar started September 1, 2009, at 40 U every 72 hours); date of last dose of Acthar on October 5, 2010. \\
Abbreviations: Pr/Cr, protein/creatinine; CrCl, creatinine clearance; Acthar\textsuperscript{®}, H.P. Acthar\textsuperscript{®} Gel.
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and angiotensin-converting enzyme inhibitor (lisinopril) treatment regimen. Since no improvement was observed, he then received cyclosporine A for 6 months, to which he was relatively adherent. No improvement was observed 3 months after initiation of cyclosporine A, so prednisone was added. Three months later, he developed shingles and was admitted to the hospital due to what was felt to be complications of cyclosporine A plus prednisone. Both cyclosporine A and prednisone were tapered off after the patient requested all immunosuppressive medications be stopped. Three months later, he agreed to be treated with mycophenolate, which he received for approximately 12 months but only during the last 3 months did he take it as prescribed.

The patient was agreeable to trying Acthar (80 USP U/mL) and received treatment from September 2009 to October 2010; his laboratory values during this period are summarized in Table 1. Acthar was self-administered subcutaneously at an initial dose of 40 U every 72 hours. After 3 months, the dose was increased to 80 U every 72 hours. In April 2010, his urinary protein levels rose to 9,520 mg/dL (952.0 g/L), and he required additional antihypertensive therapy. By July 2010, his urinary protein had dropped to 2,948 mg/dL (294.8 g/L). Thus, it took approximately 10 months of Acthar treatment to improve his urinary protein levels. By October 2010, his urinary protein levels had decreased further to 1,628 mg/dL (162.8 g/L). As shown in Table 1, in addition to the decline in urinary protein levels, the patient experienced decreases in creatinine and albumin levels, an increase in creatinine clearance, and modest weight gain while receiving treatment with Acthar.

Acthar treatment was stopped in October 2010 for several reasons. First, one year of ACTH treatment has been shown in European studies to be sufficient for resolving proteinuria. In addition, the patient’s laboratory results indicated clinically significant improvement in his signs of membranous nephropathy. Finally, the patient reported that his quality of life had improved, and he was not experiencing any symptoms of membranous nephropathy. He felt well and was able to return to his previous lifestyle.

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*Acthar was self-administered subcutaneously at an initial dose of 40 U every 72 hours. After 3 months, the dose was increased to 80 U every 72 hours.
The laboratory results since halting Acthar are also shown in Table 1. Urinary protein levels continued to decline overall, from 407 mg/dL (40.7 g/L) in December 2010, with slight elevation to 451 mg/dL (45.1 g/L; still within normal range) in March 2011, to 189 mg/dL (18.9 g/L) in September 2011. His protein to creatinine ratio was 0.58 in January 2012, and at that time his medications were limited to an angiotensin-converting enzyme inhibitor (lisinopril) and angiotensin receptor blocker (olmesartan medoxomil-hydrochlorothiazide). As of May 1, 2012, his blood pressure was 124/78 mmHg, he weighed 199 lbs (89.55 kg), his heart rate was 81 beats per minute, and there was no evidence of edema. Current medications include olmesartan medoxomil-hydrochlorothiazide 40/12.5 mg once daily, lisinopril 40 mg once daily, and simvastatin 40 mg once daily.

**Conclusion**

At the time of diagnosis of membranous nephropathy, this patient had serious health concerns. However, after 10 months of Acthar treatment, his proteinuria resolved and several other signs and symptoms of membranous nephropathy improved. Since treatment with Acthar was halted, this patient has remained stable and has not required any additional treatment for 1.5 years. In conclusion, the results described in this case report suggest that, in agreement with the data obtained during previous studies, Acthar appears to be an effective treatment strategy for patients with refractory membranous nephropathy.

**Disclosure**

The author reports no conflicts of interest and did not receive funding or financial support while treating this patient or writing this manuscript. The author alone is responsible for the content of this paper.

Writing support was provided by Aric Fader and Diana Talag of MedVal Scientific Information Services, LLC, and funded by Questcor Pharmaceuticals, Inc. This manuscript was prepared according to the International Society for Medical Publication Professionals’ “Good Publication Practice for Communicating Company-Sponsored Medical Research: The GPP2 Guidelines.”

**References**