Use of Repository Corticotropin Gel (Acthar) in Progressive Nephrotic Syndrome Secondary to Transplant Glomerulopathy: A Report of Three Cases

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Transplant glomerulopathy is a feared complication of kidney transplantation, often resulting in rapid loss of kidney function and ultimate graft failure. The underlying cause is unclear, with both antibody and cell-mediated immune mechanisms postulated, as well as intrinsic glomerular factors. At the present time, there is no known therapy. We report here 3 cases in which corticotropin gel (Acthar) was used with varying response of proteinuria and stabilization of graft function with continued graft survival as long as 10 years following the diagnosis. Future randomized controlled trials are warranted to examine the efficacy and safety of ACTH gel therapy in nephrotic patients with transplant glomerulopathy.

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INTRODUCTION

Transplant glomerulopathy is a morphologic lesion of renal allografts that is characterized histologically by duplication or multilayering of the glomerular basement membrane (GBM). Advanced transplant glomerulopathy presents with proteinuria that can be in the nephrotic range, with rapid and progressive loss of kidney function. The exact cause of transplant glomerulopathy is unclear, with theories ranging from late autoantibody-mediated injury to primary podocytopathy in susceptible organs resulting from “podocyte stress” and detachment following donor nephrectomy and insertion into a recipient dependent on the single kidney for function. Currently, there are no known effective therapies for transplant glomerulopathy.

Corticotropin gel has recently been used for the treatment of recurrent focal segmental glomerulosclerosis (FSGS) following kidney transplantation. In addition to its steroidogenic effects, corticotropin acts as an agonist of the melanocortin system, which plays a role in melanin synthesis, immunomodulation, anti-inflammation, stimulation of lipolysis, and modulation of exocrine function. During the last 2 decades, corticotropin has re-emerged as a possible therapy for nephrotic syndrome, particularly for patients who have not responded to therapies that are more conventional.

We report 3 cases in which corticotropin gel was used for refractory nephrotic syndrome in patients with transplant glomerulopathy.

CASE 1

A woman with a history of end-stage kidney disease secondary to medullary cystic disease received a living related donor kidney transplant from her mother at age 30 years. She developed non-Hodgkin lymphoma associated with de novo Epstein-Barr virus infection 3 years later, which was successfully treated with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone). Six months following her last CHOP treatment, she became pregnant. During the first trimester, she developed biopsy-proven acute cell-mediated rejection and her first allograft failed 5 years later. She then received a second living related donor kidney transplant from her sister as a pre-emptive transplant. Induction therapy included antithymocyte globulin followed by tacrolimus (level of 5–8 ng/dL) and prednisone tapered to 5 mg. Her lowest creatinine level was 1.5 mg/dL.

Six years later, she reported bilateral leg edema and had proteinuria with protein excretion of 12 g and creatinine level of 1.9 mg/dL. Six months following her last CHOP treatment, she became pregnant. During the first trimester, she developed biopsy-proven acute cell-mediated rejection and her first allograft failed 5 years later. She then received a second living related donor kidney transplant from her sister as a pre-emptive transplant. Induction therapy included antithymocyte globulin followed by tacrolimus (level of 5–8 ng/dL) and prednisone tapered to 5 mg. Her lowest creatinine level was 1.5 mg/dL.

During the last 2 decades, corticotropin has re-emerged as a possible therapy for nephrotic syndrome, particularly for patients who have not responded to therapies that are more conventional.

We report 3 cases in which corticotropin gel was used for refractory nephrotic syndrome in patients with transplant glomerulopathy.
Corticotropin gel was continued at 80 mg twice weekly for 6 months. Because most regimens for nephrotic syndrome in the literature had followed a 6-month course, we suggested discontinuing therapy. However, the patient requested to continue therapy. One year after the initial biopsy, a repeat biopsy was performed. Eleven glomeruli were sampled, of which 5 were globally sclerotic. The rest showed mesangial hypercellularity, sclerosis, and GBM duplication. Findings were similar to the initial biopsy, with findings suggestive of chronic rejection with transplant glomerulopathy with evidence of antibody-mediated rejection. Using a solid-phase optical bead microarray assay, DSA for HLA antigen class 1 were negative and HLA class 2 were positive for DQB0202/DQA0201 (8904 mean fluorescence intensity).

The patient’s proteinuria decreased to protein excretion of 3.2 to 3.5 g. Corticotropin gel treatment was decreased to 80 mg once a week.

Eighteen months after the second allograft biopsy, the patient’s creatinine level was 2.4 mg/dL, with protein-creatinine ratio of 2.4 g/g. Corticotropin gel treatment was decreased to 80 mg once a week.

Table 1. Trends in Creatinine and Protein-Creatinine Ratio From Baseline (at start of corticotropin therapy)

|       | Baseline       | 3 mo          | 6 mo          | 1 y           |
|-------|----------------|---------------|---------------|---------------|
| Cr, mg/dL | PCR, g/g Cr | Cr, mg/dL | PCR, g/g Cr | Cr, mg/dL | PCR, g/g Cr |
| Patient 1 | 1.9 | 12 | 2.1 | 4.7 | 2.2 | 4.1 | 2.3 | 3.2 |
| Patient 2 | 1.47 | 5.14 | 1.2 | 2.6 | 1.43 | 2.3 | 1.47 | 3.9 |
| Patient 3 | 1.65 | 10 | 1.37 | 2.1 | 1.05 | 2.18 | 1.24 | 2 |

Note: All patients were receiving angiotensin-converting enzyme inhibitors or angiotensin receptor blockers at the time of therapy and receiving maintenance immunosuppression.
Abbreviations: Cr, creatinine; PCR, protein-creatinine ratio.

Acthar therapy was discontinued in patient 3 because of worsening glucose tolerance and edema. This measurement was taken after discontinuation.

Case Report

**CASE 2**

A 69-year-old white woman with a history of non-nephrotic end-stage kidney disease secondary to unknown cause received a deceased donor kidney transplant in 1990 and a second deceased donor transplant in 1998. She also developed new-onset diabetes after transplantation and had a history of hypertension.

Sixteen years after the second kidney transplant, the patient was found to have proteinuria with protein excretion of ~5 g/d and creatinine level of 1.6 mg/dL. Renal allograft biopsy was performed. Eleven glomeruli were sampled; 4 were globally sclerotic. In the rest, there was extensive GBM duplication, mesangial expansion, and mild lymphocytic glomerulitis. Interstitial fibrosis and tubular atrophy were present in 25% of the biopsy sample. No tubulitis or isometric vacuolization was present. C4d immunostaining was negative in the peritubular capillaries. The findings were interpreted as chronic allograft nephropathy with transplant glomerulopathy. DSA for HLA class 1 were negative and class 2 was positive for DR11 (961) and DQB0301/DQA0302 (1432), respectively.

**Figure 1.** Kidney transplant biopsy specimen stained with periodic acid–Schiff shows hypercellularity and glomerular basement membrane (GBM) duplication with mild glomerulitis. No isometric vacuolization or tubulitis is present. Original magnification, (A) ×20; (B) ×40.
With the addition of valsartan, the patient’s protein-creatinine ratio transiently decreased to 3.6 g/g. However, during the following several months, it increased to 8 g/g of creatinine, creatinine level increased to 2.2 mg/dL, and serum albumin level decreased to 3.2 mg/dL. She was started on treatment with Acthar gel, 80 mg, twice weekly. After 3 months, corticotropin gel treatment was stopped due to fluid retention and worsening hyperglycemia. Table 1 shows the changes in creatinine and proteinuria values over time.

CASE 3

A 40-year-old woman with a history of end-stage kidney disease secondary to systemic lupus erythematosus received a deceased donor kidney transplant in 2013. Six months posttransplantation, she was noted to have an increase in serum creatinine level from 1.08 to 1.54 mg/dL and a protein-creatinine ratio of 5 g/g per day.

A kidney biopsy was performed. Seventeen glomeruli were available, with no glomerulitis, no interstitial inflammation, no tubulitis, and no peritubular vasculitis. Electron microscopy showed normal foot processes and a normal GBM. No immune complex deposits were identified. Immunofluorescence for C1q, C3, C4, immunoglobulin A (IgA), and IgM was negative, suggestive of no evidence of recurrent lupus nephritis. DSA was negative. The patient was continued on treatment with tacrolimus (trough level, 3.5–8 ng/mL), mycophenolate mofetil, prednisone, and hydroxychloroquine with the addition of telmisartan, 40 mg, daily.

Three months later, the patient’s creatinine level continued to be elevated, with protein-creatinine ratio increasing to >10 g/g. She underwent a repeat kidney biopsy with focal tubular atrophy, interstitial fibrosis, mild lymphocytic infiltration (<10%), mild arteriosclerosis, and no tubulitis, intimitis, or vacuolization seen. Immunostains were negative. She was started on treatment with Acthar gel, 80 mg, twice weekly. Over 4 months, her protein-creatinine ratio decreased to 2.1 g/g. She was continued on treatment with corticotropin gel and was switched to enalapril treatment. During the next year, the patient’s proteinuria and symptoms remained stable, with protein excretion of 2 g/g, and corticotropin gel treatment was reduced to once weekly. Subsequently, creatinine level increased to 2.31 mg/dL without an increase in proteinuria. She underwent a kidney biopsy that again showed chronic rejection (tubular atrophy and interstitial fibrosis of 15%). C4D immunostain was negative. DSA results were negative. The patient remains on treatment with corticotropin gel, 80 mg, once weekly with stabilization of kidney function (Table 1).

DISCUSSION

Transplant glomerulopathy is a feared complication of kidney transplantation, with no known effective therapy at present. It is characterized on light microscopy by capillary wall widening and double contours with a pale expanded mesangium. On electron microscopy, the thick double glomerular capillary walls are due to flocculent material on the subendothelial aspect with an underlying layer of new basement membrane material.

Corticotropin has re-emerged as a possible therapy for nephrotic syndrome, particularly for patients who have not responded to more conventional therapies.

The antiproteinuric effect of corticotropin has been observed in diverse glomerulopathies, implying that the effect might not simply be due to corticosteroid effects, but may result in part from direct melanocortin binding altering a pathogenic pathway common to all proteinuric kidney diseases. A number of studies suggest that the beneficial effect of melanocortin therapy is likely due to a direct action on podocytes. Podocytes are a critical component of the glomerular filtration barrier controlling glomerular permeability, and podocytopathy is thought to underlie the massive proteinuria observed in diverse glomerular diseases. Melanocortin receptors are expressed in glomerular podocytes and it has been shown that receptor stimulation can reduce oxidative stress and improve glomerular morphology by diminishing podocyte apoptosis, injury, and loss in the remnant kidney animal model.

Corticotropin has been demonstrated to bind to all 5 melanocortin receptors (MC1R, MC2R, MC3R, MC4R, and MC5R) found throughout the body, including those found in the kidneys, and is shown to improve glomerular morphology, podocyte ultrastructure, and tubulointerstitial fibrosis in multiple animal models. In an animal model of progressive renal tubulointerstitial injury, corticotropin gel showed suppression of tubulointerstitial inflammation, tubular atrophy, and fibrosis through anti-inflammatory effects mediated by MC1R on tubular epithelial cells. Evidence suggests that corticotropin also has potent immunomodulatory, antiapoptotic, and protective effects on dysregulation of the podocyte cytoskeleton induced by various immune- or non-immune-mediated injuries.

Corticotropin performed comparably to steroids and alkylating agents in a randomized study of patients with idiopathic membranous nephropathy, and 11 of 21 patients achieved complete or partial remission in a study of patients with nephrotic syndrome of various causes.

In kidney transplant recipients, there are limited data for Acthar use. It has most commonly been used to treat recurrent FSGS. Vaitla et al described use of corticotropin gel in patients for whom conventional therapy failed after recurrence of FSGS post-transplantation. The addition of corticotropin gel induced remission of nephrotic syndrome in all 6 patients who developed biopsy-proven recurrent FSGS at 12.5 (range, 0.1–42) months posttransplantation.
Khalil et al. retrospectively reviewed the available data and outcomes of the 19 transplant recipients who underwent treatment with corticotropin. Median treatment duration was 6.1 (range 1.6-20.8) months. Forty-seven percent of patients showed a ≥50% reduction in proteinuria, 41.1% showed <50% reduction, and the remaining patients showing no change or worsening of proteinuria. Data for adverse events were not reported.

Madan et al., in a multicenter retrospective case series with 44 adult patients with nephrotic syndrome, reported that 7 (15.9%) patients had discontinued treatment with corticotropin gel due to adverse events, including weight gain, hypertension, edema, fatigue, and seizures. Similar adverse events have been reported in other small retrospective or case studies in patients with nephrotic syndrome.

In corticotropin gel use in kidney transplantation, authors reported cushingoid features in 2 patients, transient BK viremia (n=1), pneumonia (n=1), and line sepsis (n=1) in a case series of 6 patients with biopsy-proven recurrent FSGS. Average hemoglobin A1c levels during the study period did not change from baseline. Because we found that 2 of the patients developed fluid retention with worsening edema on the full dose, it may be advisable to start severely nephrotic patients on a half dose or lower of corticotropin gel.

Our data may not be representative of outcomes in all patients with transplant glomerulopathy because this is a case report, with the third case not representative of classic transplant glomerulopathy. Changes in proteinuria in these cases cannot be attributed to Acthar gel alone; however, in all cases, the patients had been on a stable dose of renin-angiotensin-aldosterone system inhibitor with worsening proteinuria before initiation of Acthar treatment and received no other therapy. Future randomized controlled trials with extended follow-up are warranted to examine the appropriate dose, long-term efficacy, and safety of corticotropin gel therapy in nephrotic patients with chronic allograft nephropathy and transplant glomerulopathy because at this time, there is no treatment available to prevent allograft loss when this disease manifests.

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