

Repository corticotropin injection in a patient presenting with focal segmental glomerulosclerosis, rheumatoid arthritis, and optic neuritis: a case report

Arvind Madan

Nephrology Associates of Central
Florida, PA, Orlando, FL, USA

Background: Focal segmental glomerulosclerosis (FSGS) causes scarring or sclerosis of glomeruli that act as tiny filters in the kidneys, damage to which results in diminished ability to properly filter blood, resulting in the urinary loss of plasma proteins and subsequent proteinuria.

Case presentation: A 60-year-old, white female with a history of intermittent proteinuria was referred by her primary care physician for renal dysfunction. Biopsy confirmed FSGS and she was treated with an angiotensin-converting enzyme inhibitor. She also had rheumatoid arthritis (RA) but no active synovitis and was maintained on prednisone 5 mg/d. She also complained of worsening vision in her right eye and was diagnosed with optic neuritis (ON). She remained stable for about 8 months when examination indicated FSGS relapse, and she reported painful RA flares. She was treated with Acthar® Gel (40 mg biweekly) for 6 months, after which proteinuria and urine protein-to-creatinine ratio decreased to about half. Her ON improved, and she reported that she had fewer RA flares and pain improved by 50%. This case of confirmed FSGS showed an improved response to treatment with Acthar Gel for FSGS with concomitant RA and ON.

Conclusion: This referral case is relevant to primary care practitioners who treat disorders that may be responsive to corticosteroid therapy. The antiproteinuric effects and ancillary improvement in RA and ON symptoms during treatment with Acthar Gel are not entirely explained by its steroidogenic actions. ACTH is a bioactive peptide that, together with α -melanocyte-stimulating hormone, exhibits biologic efficacy by modulating proinflammatory cytokines and subsequent leukocyte extravasation and may have autocrine/paracrine effects in joints. While Acthar Gel was primarily administered in this case to treat proteinuria, it also showed ancillary benefits in patients with concomitant inflammatory disease states.

Keywords: adrenocorticotrophic hormone, nephrotic syndrome, proteinuria, Acthar Gel

Background

Focal segmental glomerulosclerosis (FSGS) is named for the characteristic scarring or sclerosis of glomeruli that act as tiny filters in the kidneys. “Focal” relates to the fact that only some of the filters are damaged, whereas “segmental” conveys the fact that only parts of the glomeruli are scarred. Damage to the glomeruli results in a diminished ability to properly filter blood, resulting in the urinary loss of plasma proteins (ie, proteinuria), which is a hallmark of nephrotic syndrome (NS). The etiology of FSGS is often unknown, but known risk factors include infection, drug toxicity, and systemic diseases such as diabetes, hypertension, and obesity.¹ FSGS is a relatively

Correspondence: Arvind Madan
3885 Oakwater Circle, Orlando,
FL 32806-6296, USA
Tel +1 407 851 5600
Fax +1 407 438 9561
Email amadan@nacfla.com

common form of kidney disease in the United States and is now one of the most common patterns of glomerular injury encountered in human kidney biopsies, as well as the most common cause of proteinuria in the African American and US Hispanic populations.¹

In 2012, a clinical practice guideline from the organization Kidney Disease: Improving Global Outcomes (KDIGO) was published based on a systematic literature review conducted in January 2011, and supplemented by additional evidence through November 2011.¹ The recommended initial treatment of idiopathic FSGS associated with clinical features of the NS is immunosuppressive therapy that usually begins with prednisone given at high dose for a minimum of 4 weeks to a maximum of 16 weeks as tolerated, to achieve remission, with subsequent tapering over 6 months.¹ KDIGO recommends consideration of calcineurin inhibitor as first-line therapy for patients with a relative contraindication to high-dose corticosteroids (CS).¹

Rheumatoid arthritis (RA) is classified according to the 2010 American College of Rheumatology and European League Against Rheumatism classification criteria. The current classification focuses on features at earlier stages that are associated with persistent/erosive disease.² Historically, treatment for most patients started with CS or nonsteroidal anti-inflammatory drugs. However, emerging evidence indicates that early and aggressive targeted-treatment strategies that provide consistent suppression of RA disease activity is linked to better long-term outcomes.^{3,4}

Optic neuritis (ON) is an inflammatory, demyelinating condition that is highly associated with multiple sclerosis (MS), and it may be the presenting feature in 15% to 20% of patients with MS.⁵ ON typically affects young adults, and women are affected more often than men. ON is second only to glaucoma as the most common acquired optic nerve disorder in persons younger than age 50.⁶ ON usually improves on its own and although intravenous CS may speed recovery, it does not appear to provide long-term benefit and undergoing no treatment for acute ON is an option.^{6,7} A meta-analysis of randomized controlled clinical trials using CS or adrenocorticotrophic hormone (ACTH) showed that either modality produced significant improvement of visual disability and is therefore effective in accelerating short-term recovery.⁸

The author is not aware of a previous case that highlights an improved response to treatment with Acthar® Gel (repository corticotropin injection) in a patient having these multiple disorders that are usually treated with CS therapy.

Case presentation

A 60-year-old, white, obese woman was referred by her primary care physician for renal dysfunction. The patient, who has a history of intermittent proteinuria, had normal renal biopsy findings 14 years ago, and would likely benefit from another biopsy. She also has a history of hypertension, hyperlipidemia, hypothyroidism, peptic ulcer, chronic obstructive pulmonary disease, RA, and type 2 diabetes mellitus. Her joint exam revealed some deformities related to RA but no active synovitis. Proteinuria was 2.5 g at presentation, serum creatinine was at a normal level, and C-reactive protein level was elevated. A biopsy confirmed the diagnosis of FSGS. Light microscopy examination of tissue samples revealed glomerular scarring. Intracapillary hyaline dense deposits were identified in sclerotic segments. No glomerular inflammatory cellular infiltrates or foci of capillary thrombosis or necrosis were present. Glomerular immunofluorescence was uniformly negative for immunoglobulins IgG, IgA, complement C3, C1q, and light chains. One glomerulus was examined by electron microscopy. The quality of glomerular tissue preservation was adequate, with no evident cellular or proliferative changes or entrapment of immune complexes at any capillary or mesangial foci. Foot processes of the visceral epithelial cells and capillary basement membranes were intact and free of defects.

The patient was treated with an angiotensin-converting enzyme (ACE) inhibitor for FSGS and was maintained on her current dosage of prednisone for RA. She also complained of worsening vision in her right eye and of seeing “water bubbles.” An exam with an ophthalmologist showed that the patient had orbital inflammation and ON hyperemia and she was diagnosed with ON. The patient’s FSGS remained stable for approximately 8 months after presentation when examination showed worsening edema and highly probable FSGS relapse. Serum creatinine concentration was 1.54 mg/dL, and she had 4+ proteinuria (319 mg/dL) and a urine protein-to-creatinine ratio (UPCR) of 9.3 g/g. The patient also experienced painful RA “flares” during ongoing treatment with 5 mg of prednisone once daily. She began treatment with a 6-month regimen of Acthar Gel (40 U twice weekly) in April 2013 for FSGS. At her initial follow-up visit in September 2013, proteinuria and UPCR had decreased to about one-half (159 mg/dL and 4.3 g/g, respectively) and serum albumin was 3.4 g/dL. At a follow-up visit later in September, spot urine UPCR was 1.78 g/g and serum albumin was 3.7 g/dL. She also had 2+ bilateral pitting edema. In addition, ophthalmic follow-up showed a decrease in orbital

inflammation and reduction in swelling and thickness of the optic nerve in both eyes.

Although approved by the Food and Drug Administration (FDA) for treatment of ON, there are limited data demonstrating the efficacy of Acthar Gel (a highly purified preparation of ACTH) for this condition. The patient reported that after starting treatment with Acthar Gel, she experienced fewer RA flares and pain had decreased by about 50%. She was also instructed to call in the case of worsening symptoms or adverse effects to medications. The patient has a history of hypertension and is receiving blood pressure medication. The patient did experience an elevation of her blood pressure and vitreous seeding was observed.

Discussion

This patient had a confirmed diagnosis of FSGS of unknown etiology but had a history of risk factors associated with FSGS. Although less responsive than minimal-change NS, FSGS appears to respond to CS and treatment with CS is specifically recommended in KDIGO guidelines.¹ Although not specifically studied in primary or secondary FSGS, ACE inhibitors or angiotensin-receptor blockers (ARBs) also reduce proteinuria and slow progression in proteinuric kidney disease, and patients with FSGS should receive renin-angiotensin system blockade and instructions to restrict dietary sodium.⁹ This patient was initially treated with the ACE inhibitor lisinopril 20 mg and later switched to the ARB telmisartan 80 mg. The empirical results shown in the patient in this case appear to support further consideration of Acthar Gel for treatment of FSGS.

The role of Acthar Gel has not been adequately studied in RA, and it is FDA-approved in RA only for short-term use. However, ACTH stimulates the adrenal cortex to produce cortisol in response to stress and also is an important physiologic agonist of the melanocortin (MC) system.¹⁰ The rationale for its use in RA is related to a study showing increased levels of α -melanocyte-stimulating hormone (α -MSH) in the synovial fluid of patients with RA or juvenile RA, and it also has been shown to reduce joint pathology in rats with adjuvant-induced arthritis.¹¹

Acthar Gel is a highly purified preparation of ACTH (ACTH_{1-39}). ACTH_{1-39} is a bioactive peptide derived from a large precursor protein named pro-opiomelanocortin. ACTH is biochemically cleaved in vivo into another bioactive peptide, α -MSH, that corresponds to the first 13 amino acids of ACTH_{1-39} ¹² and exhibits biologic efficacy by modulating proinflammatory cytokines and subsequent leukocyte

extravasation.¹³ Investigations into the biologic distribution and function of MC receptors show that ACTH_{1-39} has anti-inflammatory or immunomodulatory functions related to the activation of MC1R, MC3R, and MC5R and is the only known MC peptide that will activate MC2R in the adrenal cortex.¹² Mechanisms of action now being considered for Acthar Gel hypothesize effects beyond steroidogenesis. The precise role of MCs in RA is uncertain, but evidence suggesting that MCs exert anti-inflammatory properties in RA is drawn from clinical studies that showed ACTH_{1-39} decreased joint pain, swelling, and rheumatic symptoms.¹³ MC peptides modulate inflammation through MC receptors and the activation of MCs initially reduce inflammatory cytokines and chemokines, later followed by the induction of anti-inflammatory mediators that facilitate the resolution of inflammatory response.¹³ In RA, the inflamed joint is characterized by infiltrating leukocytes as well as activated bone/cartilage cells, and studies suggest that MC peptides could act locally in an autocrine/paracrine manner.¹³

Evidence for this is supported by an experimental murine model that mimics the flare of RA, in which the administration of an MC-3 agonist attenuated disease in incidence and severity in wild-type mice but not in MC-3 deficient mice, with sustained NF- κ B signaling in the osteoclasts of MC-3 deficient mice.¹⁴ This experimental model suggests that endogenous MC-3 controls the arthritic response in a model of passive serum-transfer arthritis.¹⁴

The mechanism of action of Acthar Gel comprises multiple components, including five MC receptors, each having varying biological activities.¹⁰ Receptor-binding studies have revealed that all five MC receptors show a strong affinity for ACTH, which is one of four MC peptides, thereby establishing the potential for this hormone to activate these receptors.¹⁰ ACTH has shown efficacy as primary and secondary therapy for NS. Two recent studies have prospectively examined the use of Acthar Gel in patients with FSGS.^{15,16} One was a prospective open-label trial of 15 subjects with resistant glomerular disease treated with Acthar Gel (80 U, subcutaneously, twice weekly).¹⁵ Five subjects had resistant FSGS or minimal-change disease (MCD) and preserved renal function at baseline (serum creatinine 0.6–1.2 mg/dL) and had failed a traditional course of CS.¹⁵ All subjects with FSGS/MCD failed to achieve sustained remission with CS therapy and at least one other immunosuppressive therapy.¹⁵ Among the five subjects, two subjects (one with FSGS, one with MCD) showed sustained improvement in UPCr from baseline to 24 weeks (3.16–0.78, MCD; 1.94–0.43, FSGS).¹⁵ Of the

remaining three subjects, two showed an increase in UPCR from baseline to week 24, and one showed no appreciable change.¹⁵ These results should be interpreted in the context of a population of treatment-resistant patients in whom the failure of first-line treatment increases the likelihood for the failure of second-line therapy, and so forth.¹⁵ Given the small sample size, the study provides evidence to warrant further investigation in controlled trials.

Another study was a retrospective case series that evaluated the use of Acthar Gel in 21 adult patients with idiopathic NS, including one patient with FSGS.¹⁷ Three patients received Acthar Gel as primary therapy, 18 patients had failed prior immunosuppressive therapy, nine of whom had failed at least three therapies. Acthar Gel was administered subcutaneously in varying regimens ranging between 80 IU and 160 IU per week.¹⁷ The patient with FSGS was a 63-year-old Hispanic female who had been previously treated with CS, mycophenolate mofetil, and a calcineurin inhibitor and had proteinuria of 10,275 mg/d.¹⁷ The patient was treated with Acthar Gel, 80 U biweekly, for 6 months and achieved partial remission, with a decrease in proteinuria from 10,275 mg/d before treatment to 2,970 mg/d.¹⁷

In the largest retrospective case series to date, 44 patients with NS were treated with Acthar Gel, including 15 patients with FSGS.¹⁸ Eligible cases underwent an assessment of 24-hour proteinuria level or spot UPCR prior to and following ≥ 6 months of Acthar Gel therapy. Thirteen of 15 FSGS patients had prior immunosuppressive or cytotoxic therapy. Complete remission was defined as proteinuria ≤ 500 mg/g and partial remission as proteinuria > 500 mg/g to $\leq 3,500$ mg/g and with $\geq 50\%$ reduction in proteinuria from baseline. Clinical response was defined as $\geq 25\%$ reduction in proteinuria level from baseline and the reduction in final proteinuria did not meet the definitions for complete or partial remission. Twelve of the 15 patients with FSGS showed partial remission ($n=8$) or a clinical response ($n=4$) of approximately 30% reduction in proteinuria. Fifteen of 44 patients had treatment-related side effects, mainly steroid-like such as hypertension, weight gain, and hyperglycemia. Seven patients had early termination of treatment due to increased edema, fatigue, weight gain, hypertension, and seizures. Acthar Gel causes the release of endogenous cortisol from the adrenal gland. Therefore, all the adverse effects known to occur with elevated cortisol may occur with Acthar Gel administration as well.¹⁹ According to the existing experience of clinical use of ACTH as well as ongoing clinical trials of other MC analogs, the side effects of MC-based therapy seem mild, tolerable, and reversible.²⁰ ACTH therapy through the cortisol effect

might also induce mild hypertension. As an endogenous glucocorticoid, cortisol may directly elevate blood pressure by enhancing vascular tone or, because it has a fair amount of activity on the mineralocorticoid receptor, may cause sodium and water retention and volume expansion.²⁰ For nonsteroidogenic MCs or analogs, mildly elevated blood pressure has been reported during phase II or III clinical trials, possibly attributable to central stimulation of sympathetic outflow mediated by the interaction of α -MSH with MC4R.^{20–22}

Another recent study examined 24 subjects and the data for analysis were available for 23 patients.¹⁶ Six subjects had steroid-dependent FSGS, 15 had steroid-resistant FSGS, and two additional subjects were treated with Acthar Gel as first-line therapy between January 2009 and April 2012.¹⁶ The trial included 16 subjects in a prospective investigator-initiated pilot study (NCT01155141); four had been described previously with shorter-term results and the remaining four were evaluated retrospectively in chart review.¹⁶ The classification of steroid-dependent or steroid-resistant FSGS was based on KDIGO guidelines.¹ Treatment regimens were not entirely uniform: 12 subjects received 40 U of Acthar Gel subcutaneously, weekly for 2 weeks, 80 U, subcutaneously, weekly for 2 weeks, followed by 80 U, subcutaneously, twice weekly for 16 weeks of treatment. Seven subjects received 40 U of Acthar Gel, subcutaneously, twice weekly for 2 weeks, followed by 80 U, subcutaneously, twice weekly for 6 months of treatment. The remaining five subjects received Acthar Gel with heterogeneous dosing as determined by the treating physician. The duration of therapy ranged from 12 to 56 weeks, with a mean follow-up time of 48 weeks.¹⁶ At the end of therapy, seven of 24 (29%) patients had experienced remission (two complete and five partial).¹⁶ In subjects achieving remission of proteinuria, median time to reduced proteinuria was 5 weeks and median time to remission of proteinuria was 16 weeks.¹⁶ Although only 29% of the subjects experienced remission in this series, improved outcomes may encourage physicians to consider Acthar Gel in idiopathic FSGS cases that are refractory to previous CS therapy. This study helps to guide therapy with ACTH. On the basis of these data, we recommend that ACTH be discontinued for patients with FSGS who have not demonstrated any significant decline in proteinuria by 12–16 weeks.

The pathological basis of FSGS and MCD appears to essentially be podocyte-related, as evidenced by podocyte foot processes effacement, microvillus transformation, and podocytopenia.²³ Knockout and transgenic models have provided proof of concept that mutations in specific podocyte proteins mediate genetic forms of FSGS.²⁴ A study was

conducted in rats with subtotal nephrectomy to examine the capability of Acthar Gel for providing podocyte protection.²⁵ Compared with the control group, Acthar Gel preserved kidney function as measured by increased renal plasma flow and glomerular filtration rate and lower serum creatinine levels. These data suggest that Acthar Gel reduces proteinuria and renal injury in a preclinical model of progressive glomerulosclerosis.

Lindskog investigated the expression of MC in human kidneys to test the hypothesis that synthetic ACTH directly exerts its antiproteinuric effects via MC receptors.²⁶ Gene expression of the MC receptor MC1R (but no other MC receptor) was identified in podocytes, glomerular endothelial cells, mesangial cells, and tubular epithelial cells, and analysis showed that podocytes expressed most of the MC1R protein.²⁶ A specific MC1R agonist (MS05) demonstrated that MC1R agonism reduced proteinuria, improved podocyte morphology, and reduced oxidative stress in rats with passive Heymann nephritis (PHN).²⁶ The nonspecific MC receptor agonist α -MSH (n=8) also significantly reduced proteinuria by 52% compared with untreated PHN (n=8; $P<0.05$). Within the α -MSH group, this corresponds to a 55% decrease in proteinuria after 4 weeks of treatment compared with proteinuria at the start of treatment.

Conclusion

Acthar Gel (ACTH) has antiproteinuric and immunomodulatory effects that are not entirely explained by its steroidogenic activity. ACTH is the parent molecule of α -MSH, and exhibits biologic efficacy by modulating proinflammatory cytokines and subsequent leukocyte extravasation, and evidence suggests that MCs also may have autocrine/paracrine effects in joints. Acthar Gel was primarily administered in this case to induce the remission of proteinuria in a patient with a history of intermittent proteinuria and a confirmed diagnosis of FSGS treated with ACE inhibitor therapy, but who experienced worsening edema and serum creatinine with 4+ proteinuria. The patient also had concomitant RA usually treated with glucocorticoid and/or immunosuppressive therapies. This case is interesting not only because of its effect in improving proteinuria, but also because it showed clinically beneficial ancillary effects on the patient's inflammatory disease states. The role of ACTH in the treatment of RA or ON has not been adequately studied, but improvement in this patient's flares and pain in RA as well as orbital inflammation and reduction in the swelling of the optic nerve and thickness is noteworthy and may be related to its agonist effects on multiple MC receptors.

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