Clinical Kidney Journal, 2015, vol. 8, no. 4, 430–432

doi: 10.1093/ckj/sfv046
Advance Access Publication Date: 17 June 2015
CKJ Review

Glomerular nephropathies

CKJ REVIEW

A review of the re-emergence of adrenocorticotrophic hormone therapy in glomerular disease, more than a drug of last resort?

Christopher J. Goldsmith and Salim Hammad

University Hospital Aintree NHS Foundation Trust, Liverpool L9 7AL, UK

Correspondence to: Christopher J. Goldsmith; E-mail: cjgoldsmith2000@hotmail.com

Abstract

There has been a re-emergence of interest in adrenocorticotropic hormone (ACTH) in patients with resistant nephrotic syndrome. We describe a patient with severe nephrosis and advanced chronic kidney disease with idiopathic membranous nephropathy resistant to conventional immunosuppressive therapies that achieved lasting remission with ACTH therapy. We explore the literature showing the extra renoprotective effects which might explain the response of proteinuric renal diseases to this treatment.

Key words: ACTH, adrenocorticotrophic hormone, membranous nephropathy, minimal change disease, nephrotic syndrome

A 44-year-old Caucasian male, with a history of raised BMI and hypertension presented to our hospital in 2004 with deterioration in renal function. It was noted that he had significant proteinuria, measured at 11.53 g/24 h. A renal biopsy was performed, which showed membranous glomerulonephritis. Secondary causes were excluded and he was managed initially with an ACE inhibitor and angiotensin receptor blocker. Due to reduction in renal function and severity of proteinuria, immunosuppression was immediately started (Figure 1). Over the next 5 years, he was treated with combinations of 'azathioprine', cyclophosphamide, mycophenolate mofetil 'all with various doses of steroids' with no reduction in proteinuria. He was switched to cyclosporin (calcinurin inhibitor) and low-dose steroids but was stopped due to significant deterioration in renal function with a rise in creatinine from 202 to 337 µmol/L. This largely resolved with discontinuation of cyclosporin [creatinine of 252 µmol/L with an estimated glomerular filtration rate (eGFR) of 25 mL/min].

Rituximab was not considered 'appropriate' in view of his advanced chronic kidney disease. However, due to high risk of progression of renal disease and potential adverse outcomes associated with nephrotic syndrome, a trial of depot synthetic adrenocorticotropic hormone (ACTH) was administered intramuscularly at a dose of 1 mg weekly at the expense of low-dose prednisolone for 6 months. The ACTH was tolerated well, with no significant side effects experienced. A 24-h urinary protein sample was obtained every 4 weeks. At the third month of intra-muscular ACTH injections, there was an improvement seen in renal function (eGFR of 29 mL/min), and proteinuria had more than halved to 4.99 g/24 h, with very little evidence of peripheral oedema. After the 6 months of ACTH injections, proteinuria was demonstrated at 2.35 g/24 h and ACTH injections were stopped. Currently, the patient remains in remission, with proteinuria reduced to 1.55 g/24 h, 4 years after treatment, with a slowing in the rate of deterioration of his renal function (eGFR 23 mL/min).

Received: November 13, 2014. **Accepted:** May 26, 2015

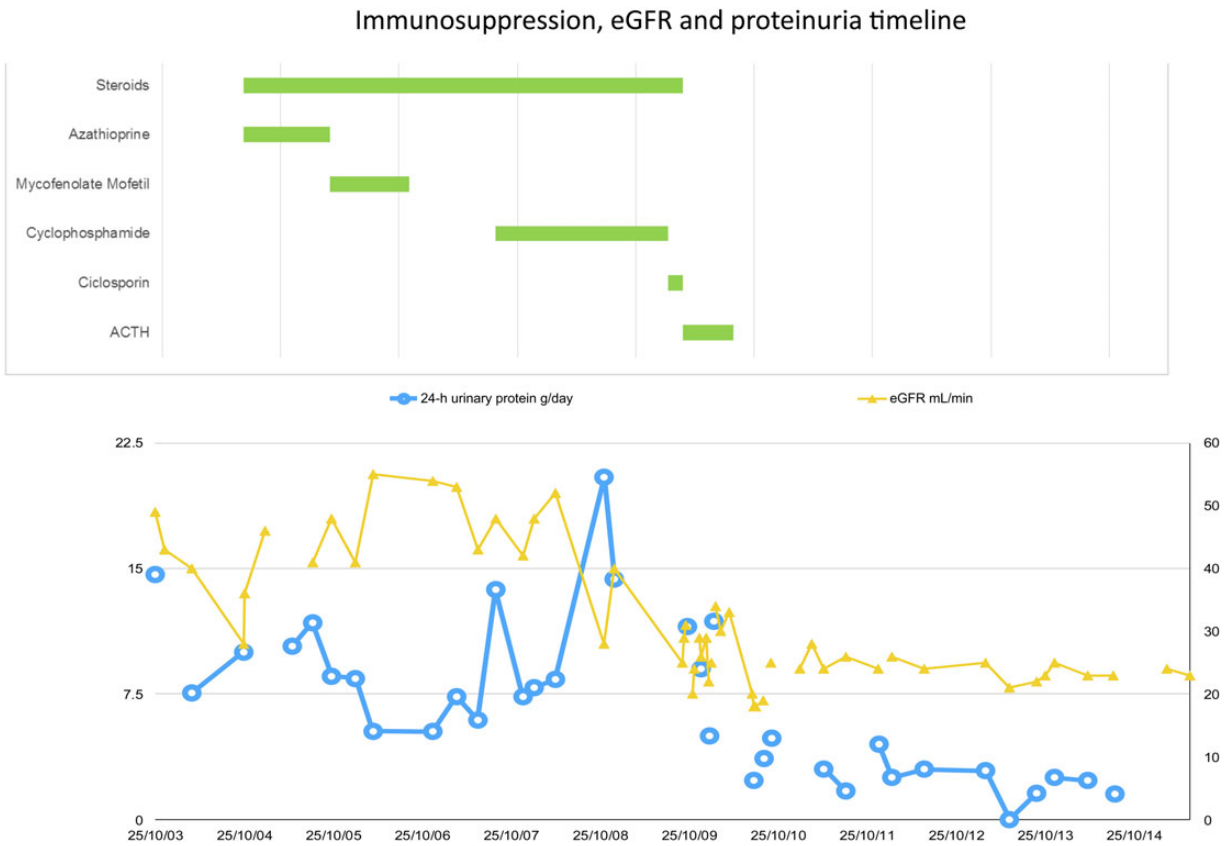

Fig. 1. ACTH therapy sustained a persistent remission after failure of all other treatment.

The emergence of ACTH

The use of adrenocorticotrophic hormone (ACTH) has been established since the 1950s and 1960s and was widely used in the treatment of childhood nephrosis [1]. ACTH was attractive in this group due to reduced growth stunting due to less adrenal suppression than traditional exogenous steroids. The use of synthetic ACTH has declined in recent decades, due to the injectable route of administration and the emergence of oral steroids preparations such as prednisolone which are cheap, and widely available.

Interestingly, ACTH became once again a 'novel' therapy due to an incidental finding by Swedish researchers, Berg *et al.* in their research into the lipid-lowering effects of ACTH in 14 patients with idiopathic membranous nephropathy (MN) [2]. This finding was surprising as steroid monotherapy was shown to have no role in the treatment of idiopathic MN [3, 4]. A treatment regime of slow-release ACTH was given in the form of Synacthen Depot at a maximal dose of 1 mg twice weekly for 2–11 months [5]. They proceeded to administer this to an uncontrolled case series of 23 patients with nephrosis due to a variety of diagnoses. All patients had a significant response to therapy.

A randomized pilot trial carried out by Ponticelli *et al.* directly compared the use of methylprednisolone plus a cytotoxic agent versus synthetic ACTH in idiopathic MN [6]. They used primary outcome measure as cumulative number of remissions as a first event and concluded that most patients with idiopathic MN responded to either treatment, and that there was a significant decrease in proteinuria with both treatments, without either being more effective.

A further retrospective study in the United States evaluated the initial use of ACTH gel in 21 patients with nephrotic syndrome of different histopathologies [7]. They found that 11 of 21 patients achieved either complete or partial remission with at least 6 months of follow-up. While these data are encouraging, caution must be taken in interpretation of the data due to the limitations of observational studies.

ACTH formulations, dosing and indications

There are two different products currently available. HP Acthar gel is a proprietary mixture isolated from porcine pituitary extracts, the main component of which is $ACTH_{1–39}$. It is available in North America and administered subcutaneously. In Europe, a shortened, synthetic ACTH analogue, known as tetrocosactide, consisting of the first 24 amino acids of the original hormone is available in depo form and licensed for intramuscular use in testing for adrenocortical insufficiency. We use the unlicensed subcutaneous route to allow self-administration which has shown to be well tolerated [8].

The longer chained Acthar gel is the only ACTH analogue licenced in the USA for use in nephrotic syndrome. However, the treatment is expensive and optimum dose unclear [9]. In Europe, the Depo preparation is inexpensive and compares favourably to other immunosuppressant therapies. It had been presumed that both forms were equally effective in treatment of nephrotic syndrome. There is currently no head-to-head evidence to compare the two formulations.

The side effects are similar to exogenous steroids but on the whole the treatment is well tolerated with most adverse effects

settling off therapy. Serious allergic reactions are rare and reported in the literature when ACTH is used in allergic conditions [10]. Hypokalaemia has been reported requiring supplementation and hypertension. There are reports of skin discolouration with both preparations. The commonest reason for drug discontinuation in our experience is exacerbation of fluid overload and non-adherence to self-injection.

ACTH proposed modes of action

ACTH is a peptide hormone of the melanocortins group, which has an affinity to five melanocortin receptors (MC1R-MC5R) found throughout the body. ACTH is cleaved to α-MSH, but these two proteins have different properties, with ACTH being the only peptide that binds to the MC2R melanocortin receptor in the adrenal cortex, responsible for the instigation of steroidogenesis. As steroid therapy alone has not been proven to be an effective therapy to induce remission or delay end-stage renal disease for idiopathic MN [2, 3], it is proposed that there may be other mechanisms of action.

ACTH and α-MSH have both been proposed to have a potent anti-inflammatory and immune modulating response. Kidney-specific effects of α-MSH have protected against acute kidney injury in rodents with ischaemia reperfusion by reducing inflammatory cell recruitments and infiltration into injury sites [11]. ACTH may work directly on the podocyte to reduce proteinuria, reduce oxidative stress and improve glomerular morphology [12]. Furthermore, ACTH may have a direct architectural effect on podocytes by decreasing NF-κB activity [13]. ACTH has been shown to have a stronger affinity than α-MSH for MC3R receptors, located on macrophages, which suppress inflammatory response [14].

Dyslipidaemia has long been shown to have an important role in the progression of nephrotic syndrome, with lipid-lowering agents proven to improve proteinuria in randomized, controlled trials of patients with idiopathic MN [15]. Furthermore, reduced levels of apolipoprotein J is a cause of proteinuric glomerulonephropathy, including MN and focal segmental glomerulosclerosis (FSGS) [16]. ACTH directly regulates hepatic lipoprotein metabolism, modifying apolipoprotein metabolism, restoring levels of certain lipoproteins, such as lipoprotein J and E [17]. These increased circulating lipoproteins may neutralize the activity of circulating permeability factors, such as in FSGS, thereby inducing remission of proteinuria. Further studies have shown that apolipoprotein J may actually competitively bind to the megalin receptor in the podocyte, preventing components of complement binding, reducing glomerular injury [16, 18].

The full picture is that a combination of all the above factors is responsible for the effectiveness of ACTH therapy in nephrotic syndrome particularly when other therapies have failed [19]. What is understood is there is increasing evidence to show that ACTH can be as effective as more established therapies for nephrotic syndrome, and further study and research is warranted into the field.

Conflict of interest statement

None declared.

References

1. Arneil GC, Wilson HE. ACTH in nephrosis. *Arch Dis Child* 1953; 28: 372–380
2. Berg AL, Nilsson-Ehle P. ACTH lowers serum lipids in steroid-treated hyperlipemic patients with kidney disease. *Kidney Int* 1996; 50: 538–542
3. Hogan SL, Muller KE, Jennette JC *et al*. A review of therapeutic studies of idiopathic membranous glomerulopathy. *Am J Kidney Dis* 1995; 25: 862–875
4. Perna A, Schieppati A, Zamora J *et al*. Immunosuppressive treatment for idiopathic membranous nephropathy: a systematic review. *Am J Kidney Dis* 2004; 44: 385–401
5. Berg AL, Arnadottir M. ACTH-induced improvement in the nephrotic syndrome in patients with a variety of diagnoses. *Nephrol Dial Transplant* 2004; 19: 1305–1307
6. Ponticelli C, Passerini P, Salvadori M *et al*. A randomized pilot trial comparing methylprednisolone plus a cytotoxic agent versus synthetic adrenocorticotropic hormone in idiopathic membranous nephropathy. *Am J Kidney Dis* 2006; 47: 233–240
7. Bomback AS, Tumlin JA, Baranski J *et al*. Treatment of nephrotic syndrome with adrenocorticotropic hormone (ACTH) gel. *Drug Des Devel Ther* 2011; 5: 147–153
8. Gan EH, MacArthur K, Mitchell AL. Residual adrenal function in autoimmune Addison's disease: improvement following tetracosactide (ACTH1–24) treatment. *J Clin Endocrinol Metab* 2014; 99: 111–118
9. Hladunewich MA, Cattran D, Beck LH *et al*. A pilot study to determine the dose and effectiveness of adrenocorticotropic hormone (H.P.: Acthar Gel) in nephrotic syndrome due to idiopathic membranous nephropathy. *Nephrol Dial Transplant* 2014; 29: 1570–1577
10. Rosenblum AH, Rosenblum P. Anaphylactic reactions to adrenocorticotrophic hormone in children. *J Pediatr* 1964; 64: 387–395
11. Anderson GN, Hägglund M, Nagaeva O *et al*. Quantitative measurement of the levels of melanocortin receptor subtype 1, 2, 3 and 5 and pre-opio-melanocortin peptide gene expression in subsets of human peripheral blood leucocytes. *Scan J Immunol* 2005; 61; 279–284
12. Chiao H, Kohda Y, McLeroy P *et al*. Alpha-melanocyte-stimulating hormone protects against renal injury after ischemia in mice and rats. *J Clin Invest* 1997; 99: 1165–1172
13. Lindskog A, Ebefors K, Johansson M *et al*. Melanocortin 1 receptor agonists reduce proteinuria. *J Am Soc Nephrol* 2010; 21: 1290–1298
14. Catania A, Gatti S, Colombo G *et al*. Targeting melanocortin receptors as a novel strategy to control inflammation. *Pharmacol Rev* 2004; 56: 1–29
15. Rayner BL, Byrne MJ, van Zyl Smit R. A prospective clinical trial comparing the treatment of idiopathic membranous nephropathy and nephrotic syndrome with simvastatin and diet, versus diet alone. *Clin Nephrol* 1996; 46: 219–224
16. Ghiggeri GM, Bruschi M, Candiano G *et al*. Depletion of clusterin in renal diseases causing nephrotic syndrome. *Kidney Int* 2002; 62: 2184–2194
17. Berg A, Nilsson-Ehle P. Direct effects of corticotropin on plasma lipoprotein metabolism in man-studies in vivo and in vitro. *Metabolism* 1994; 43: 90–97
18. Rastaldi MP, Candiano G, Musante L *et al*. Glomerular clusterin is associated with PKC-alpha/beta regulation and good outcome of membranous glomerulonephritis in humans. *Kidney Int* 2006; 70: 477–485
19. Gong R. The renaissance of corticotropin therapy in proteinuric nephropathies. *Nat Rev Nephrol* 2012; 8: 122–128