Glomerular nephropathies

CKJ REVIEW

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

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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, adrenocorticotropic 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 (calcineurin 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).
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 ACTH1–39. 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-MCSR5) 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 MC2R receptors, located on macrophages, which suppress inflammatory response [14]. Dyslipidaemia has long been shown to have an important role in the progress 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.

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