ORIGINAL RESEARCH

Low-dose synthetic adrenocorticotropic hormone-analog therapy for nephrotic patients: results from a single-center pilot study

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Introduction: This report describes our experience using a low-dose synthetic adrenocorticotropic hormone (ACTH) analog for patients affected by nephrotic syndrome who had not responded to or had relapsed after steroid and immunosuppressive treatments.

Patients and methods: Eighteen adult nephrotic patients with an estimated glomerular filtration rate >30 mL/min were recruited. Histological pictures included ten of membranous nephropathy, three of membranous proliferative glomerulonephritis, three of minimal change, and two of focal segmental glomerular sclerosis. All patients received the synthetic ACTH analog tetracosactide 1 mg intramuscularly once a week for 12 months. Estimated glomerular filtration rate, proteinuria, serum lipids, albumin, glucose, and potassium were determined before and during the treatment.

Results: One of the 18 patients discontinued the treatment after 1 month because of severe fluid retention, and two patients were lost at follow-up. Complete remission occurred in six cases, while partial remission occurred in four cases (55.5% responder rate). With respect to baseline, after 12 months proteinuria had decreased from 7.24±0.92 to 2.03±0.65 g/day ($P<0.0001$), and serum albumin had increased from 2.89±0.14 to 3.66±0.18 g/dL ($P<0.0001$). Total and low-density lipoprotein cholesterol had decreased from 255±17 to 193±10 mg/dL ($P=0.01$), and from 168±18 to 114±7 mg/dL ($P=0.03$), respectively. No cases of severe worsening of renal function, hyperglycemia, or hypokalemia were observed, and no admissions for cardiovascular or infectious events were recorded.

Conclusion: Tetracosactide administration at the dosage of 1 mg intramuscularly per week for 12 months seems to be an acceptable alternative for nephrotic patients unresponsive or relapsing after steroid-immunosuppressive regimens. Further studies should be planned to assess the effect of this low-dose ACTH regimen also in nephrotic patients not eligible for kidney biopsy or immunosuppressive protocols.

Keywords: ACTH, glomerulonephritis, proteinuria, nephrotic syndrome, CKD, Tetracosactide

Introduction

Steroid-immunosuppressive regimens for patients with nephrotic syndrome depend on the histological patterns and on the severity of the glomerular damage. Unfortunately, in several cases nephrotic syndrome does not reverse or frequently recurs. In addition, immunosuppressant and steroid treatments have limitations with regard to duration and dosage administration, and may expose patients to mild-to-severe side effects.[1–6]

Among possible pharmacological treatments of nephrotic syndrome, adrenocorticotropic hormone (ACTH) or the synthetic ACTH analog tetracosactide (Figure 1) has raised new interest, because of its noncorticosteroid mechanism of action,[7,8] namely

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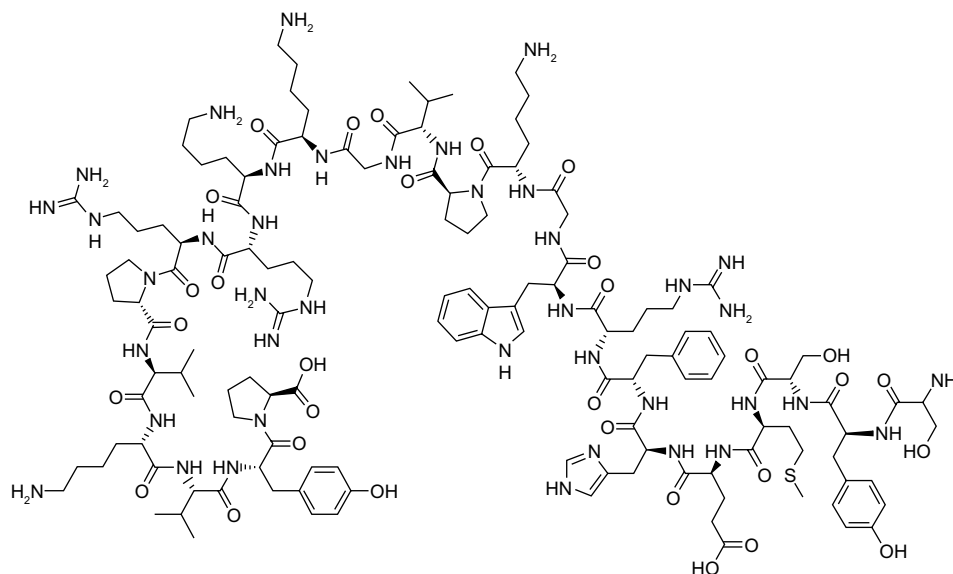Email p.lorusso@ao-pisa.toscana.it

Figure 1 Chemical structure of tetracosactide.

direct melanocortin receptor-mediated immunomodulation and podocyte protection.[9]

ACTH was employed many years ago for the treatment of nephrotic syndrome in children and adults.[10–12] It has been reappraised, due to its efficacy in reducing proteinuria and lipids in cases of glomerulonephritis resistant to conventional treatment with steroids and immunosuppressors. This effect has persisted for several patients many months after the discontinuation of treatment.[13–17] Since ACTH action is mediated by a protective effect activity on podocytes, it may be favorably used in different types of glomerular disease. Namely, ACTH reduces foot-process effacement and podocyte apoptosis, and ameliorates the decline in glomerular expression of podocyte markers, including vimentin, nephrin, and podocin.[8]

A natural, highly purified ACTH gel has been recently employed in the US, and has exhibited a good therapeutic effect on proteinuria in idiopathic nephrotic syndrome,[18] advanced diabetic nephropathy with nephrotic-range proteinuria,[19] and idiopathic membranous nephropathy.[20] This natural form is different from the synthetic ACTH 1–24, available outside the US, in terms of pharmacokinetics, pharmacodynamics, and physiologic actions. Melanocortin peptides, pharmacologically active molecules derived from proopiomelanocortin, exist in natural ACTH but not in the synthetic form. Similarly, the insulinotropic effect of the endogenous hormone is due to the C-terminal ACTH 1–39 which is omitted from the synthetic analog.[21]

Synthetic ACTH 1–24 is the form available in Europe, and its standard dosage is 1 mg given intramuscularly

twice a week for 1 year. This schedule was as effective as methylprednisolone plus a cytotoxic agent for 6 months in idiopathic membranous nephropathy.[22] In addition to nephrotic syndrome, other potential indications of this drug are neurologic diseases (acute exacerbations of multiple sclerosis and infantile myoclonic encephalopathy with hypsarrhythmia), rheumatologic diseases (acute rheumatic fever, rheumatoid arthritis, lupus erythematosus, periarteritis nodosa, psoriatic arthritis, scleroderma, rheumatoid spondylitis, and Still's disease), dermatologic diseases (exfoliative dermatitis, dermatomyositis, and pemphigus), gastrointestinal diseases (regional enteritis and ulcerative colitis), and as adjuvant treatment to improve tolerability to chemotherapy.

Although ACTH administration is usually well tolerated, such side effects as hypokalemia, fluid retention, and hyperglycemia have been reported. This study reports our experience of a different ACTH-administration schedule, namely 1 mg once a week for 12 months with the aim of reducing side effects and increasing tolerability.

Patients and methods

Adult patients affected by nephrotic syndrome who were unresponsive or relapsing after immunosuppressive-steroid treatment were considered for the study. Patients with persisting nephrotic syndrome or proteinuria reduction less than 50% after treatment were defined as "non-responders", whereas patients with a nephrotic syndrome recurrence following an initial partial or complete remission were considered as "relapsers". Patients with advanced chronic

kidney disease (stages IV–V), infections, diabetes, glaucoma, active cancer, severe hypertension, peptic ulcer, or pregnancy were excluded. Eighteen patients were ultimately included. The characteristics of the studied population are reported in Table 1.

Histological diagnoses were membranous nephropathy (MN) in ten cases, membranous proliferative glomerulonephritis (MPGN) in three cases, minimal-change disease (MCD) in three cases, and focal segmental glomerular sclerosis (FSGS) in two cases.

All patients had previously received different immunosuppressive treatments such as: high-dose prednisolone, cyclophosphamide, cyclosporine, and mycophenolate mofetil. These drugs were stopped at least 3 months before the first ACTH administration (Table 1). Treatment with angiotensin-converting enzyme inhibitors (ten cases), angiotensin-receptor blockers (one patient), both angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers (five patients), and statins (15 patients) remained unmodified. All patients received ACTH (synthetic form 1–24) at a dose of 1 mg intramuscularly once a week for 12 months.

The following parameters were studied before and during the 12-month treatment period: arterial blood pressure, body weight, estimated glomerular filtration rate, 24-hour urinary protein excretion, and serum levels of glucose, glycated hemoglobin, total and low-density lipoprotein (LDL) cholesterol, potassium, and albumin. Complete remission was defined as stable or improved renal function and urine protein excretion <0.3 g/day. Partial remission was defined as stable or improved renal function together with urine protein excretion reduced by >50% or lower than 3.5 g/day.[23] Patients were followed up for 24–36 months after the end of treatment. All patients gave their informed consent for the study.

Statistics

Descriptive statistics are given as means ± standard error or prevalence as required. Statistical analysis was performed using analysis of variance for repeated measurements. Differences were considered statistically significant at $P < 0.05$.

Results

One of the 18 recruited patients (5.5%) dropped out at month 2 because of furosemide-unresponsive fluid retention, while two patients were lost at follow-up after 2 months. Six cases of complete remission and four cases of partial remission occurred (55.5% of responders, namely 33.3% complete remission and 22.2% partial remission). Complete remissions occurred at months at months 2 (one case), 4 (two cases),

Table 1 Histological diagnosis and basal and 12-month proteinuria, serum albumin, and total cholesterol

Case	Histological diagnosis	Previous treatment	Proteinuria, baseline, g/24 hours	Proteinuria, 12 months, g/24 hours	Serum albumin, baseline, g/dL	Serum albumin, 12 months, g/dL	Total cholesterol, baseline mg/dL	Total cholesterol, 12 months, mg/dL	Proteinuria, g/24 hours at follow-up (month)
1 F	MPGN	Steroids (NR)	10	0.8	2.6	4.4	333	189	0.2 g/day (36)
2 M	MN	Steroids + CyA (Rp)	3	0.08	3.7	4.5	208	188	1.1 g/day (36)
3 M	MPGN	Steroids + CyA (NR)	16	10.8	2.7	2.8	236	227	15.6 g/day (36)
4 M	MN	Steroids + MM (NR)	5.1	3.5	3.2	4.3	201	167	Lost at follow-up
5 M	MCD	Steroids + CyA (Rp)	3.9	0.09	3.4	4.2	196	143	6.3 g/day (3)
6 M	MN	Steroids + CyA + MM (NR)	4	2.2	4.1	4.3	234	254	3.7 g/day (36)
7 M	FSGS	Steroids (NR)	13	0	3.3	4.2	195	171	12.3 g/day (9)
8 M	MN	Steroids + CyA+ MM (NR)	4	3	3.8	3.4	191	187	0.6 g/day (36)
9 F	MCD	Steroids + CyA + azathioprine (NR)	3	3.2	2.4	2.5	316	219	0.5 g/day (24)
10 M	MN	Steroids + CTX (NR)	3.2	2.5	2.6	3.3	246	178	3.3 g/day (10)
11 M	FSGS	Steroids + CyA + MM (NR)	11.5	1.86	1.7	1.8	270	220	Lost at follow-up
12 F	MN	Steroids + CyA (Rp)	10	0.09	2.2	3.4	403	157	6.7 g/day (5)
13 M	MN	Steroids + CTX (NR)	7.4	0.3	2.6	3.2	206	–	0.16 g/day (36)
14 M	MN	Steroids (NR)	3	2.06	3.8	4.3	246	253	Lost at follow-up
15 F	MN	Steroids (Rp)	8.6	0	2.9	3.8	145	128	0.2 g/day (36)

Abbreviations: F, female; M, male; MPGN, membranous proliferative glomerulonephritis; MN, membranous nephropathy; MCD, minimal-change disease; FSGS, focal segmental glomerular sclerosis; NR, nonresponder; CyA, cyclosporine A; Rp, relapsing; MM, mycophenolate mofetil; CTX, cyclophosphamide.

and 12 (three cases) of treatment, with a median value of 8 months.

The outcome after the end of the 12-month tetracosactide treatment was available in 12 patients, since three patients were lost at follow-up. Total remission was maintained in two (at 36 months of follow-up) of the six patients with complete remissions; in three of them, nephrotic syndrome relapsed (patients affected by MN, FSGS, and minimal-change disease), and in one nonnephrotic proteinuria occurred (MN) (Table 1). One patient (MN) who showed partial remission at the end of tetracosactide treatment presented with nephrotic proteinuria at 36 months (Table 1). One patient (MPGN) who did not respond to tetracosactide treatment, and one who showed partial remission, were on complete remission at the 24-month follow-up (Table 1).

The results of the 15 patients who completed the 12-month study period are shown in Table 2. The reduction in proteinuria was significant from month 6 of treatment to month 12 (Figure 2 and Table 2). Serum total cholesterol decreased significantly (Figure 2), together with changes in urine protein excretion at month 6 of treatment and even more at month 12 (Table 2 and Figure 3). Similarly, serum LDL cholesterol decreased significantly from month 6 to month 12 (Figure 3 and Table 2). Serum albumin increased significantly at month 12 (Table 2).

Figure 2 Urine protein excretion (g/day) at baseline and during the treatment period (means ± standard error).
Note: *$P<0.05$ versus baseline.

Figure 3 Total cholesterol (upper line) and low-density lipoprotein cholesterol (lower line) serum levels at baseline and during the treatment period (mean ± standard error).
Note: *$P<0.05$ versus baseline.

Table 2 Proteinuria, serum albumin, eGFR (MDRD), urea, serum total cholesterol, LDL cholesterol, glycemia, HbA$_{1c}$, potassium, blood pressure, and body weight pretreatment and at end of treatment period (mean ± standard error) in the 15 patients who completed the study

	Pretreatment	End of treatment	P
Proteinuria (g/d)	7.24±0.92	2.03±0.65	<0.0001
Serum albumin (g/dL)	2.89±0.14	3.66±0.18	<0.0001
eGFR (mL/min*1.73 m2 bs)	86.9±11.7	85.9±14.3	NS
Urea (mg/dL)	50.3±6.62	48.0±9.62	NS
Serum total cholesterol (mg/dL)	255±16.7	193±9.65	0.01
Serum LDL cholesterol (mg/dL)	168±17.7	114±6.59	0.03
Glycemia (mg/dL)	81.8±2.32	85.4±3.79	NS
HbA$_{1c}$ (%)	5.53±0.11	5.80±0.20	NS
Potassium (mEq/L)	4.19±0.09	4.32±0.15	NS
Body weight (kg)	71.7±3.37	74.5±5.17	NS
Systolic BP (mmHg)	127±4.00	126±4.81	NS
Diastolic BP (mmHg)	77.4±2.58	76.0±2.88	NS
Mean BP (mmHg)	93.9±2.64	92.8±3.28	NS

Abbreviations: eGFR, estimated glomerular filtration rate; MDRD, modification of diet in renal disease; LDL low-density lipoprotein; HbA$_{1c}$, glycated hemoglobin; NS, not significant; BP, blood pressure.
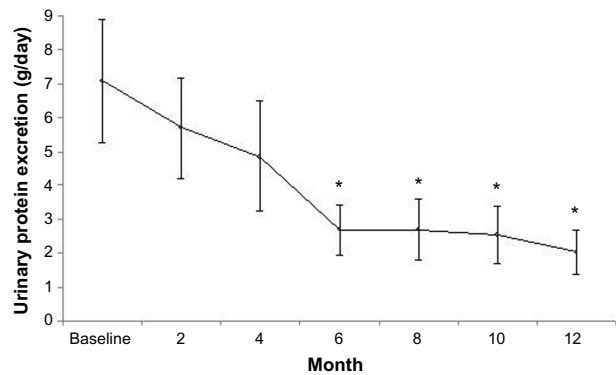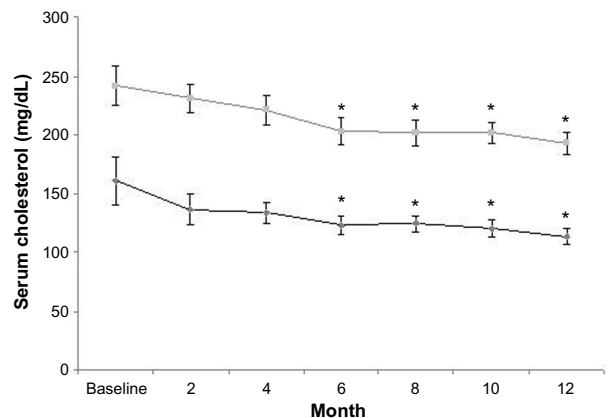
Renal function, serum glucose, glycated hemoglobin, serum potassium, urea, blood pressure, and body weight remained stable during treatment (Tables 1 and 2). No cases of hypokalemia or hyperglycemia occurred. No severe fluid retention unresponsive to furosemide was reported in the 15 patients who completed the study. No admission due to infectious or cardiovascular events was recorded throughout the study period.

Discussion

Our findings show that Tetracosactide administered at a dose of 1 mg intramuscularly once a week for 1 year was effective in reducing proteinuria in patients resistant or relapsing to conventional treatment, with a 55.5% response rate (33.3% complete remission and 22.2% partial remission).

The only two recent papers that described the effect of synthetic ACTH in adult nephrotic patients are those of Berg and Arnadottir[15] and Ponticelli et al.[22] When compared to their data, the remission rate we observed is lower.

However, it is noteworthy that Ponticelli et al treated only MN patients at their first-line treatment, and hence had a higher chance of favorable results with respect to resistant or relapsing nephrotic patients. Two patients stopped the ACTH therapy because of severe dizziness or fluid retention. An additional two patients developed glucose intolerance, one onychodystrophy, one patient folliculitis, and six developed a bronze color of the skin. These side effects did not cause a cessation of treatment, and they completely disappeared after the end of therapy.

Berg and Arnadottir[15] studied a population similar to our series, but the prevalence of unwanted side effects was not reported. From their data, it emerges that one patient had a rapid progression to end-stage renal disease within 9 months of the end of the study, one patient showed a psychiatric syndrome, and one patient was deceased 3 months after the end of ACTH therapy.

The response rate we observed was similar to Bomback et al.[24] Most of the remissions occurred within 6 months of therapy, and this is in keeping with Hladunewich et al.[20] These studies employed ACTH gel, as well as the recent investigation on FSGS patients.[25] In this study, side effects were reported in 21 of the 24 studied patients treated with ACTH gel. These consisted of fluid retention (five patients), mood alteration (four patients), elevated blood pressure (three patients), dyspepsia (two patients), hyperglycemia (one patient), upper respiratory tract symptoms (four patients), muscle cramps (four patients), polyuria (one patient), rash (two patients), nausea, headache, and palpitations (one patient), and worsening of renal function (one patient). However, most adverse events were mild and transient.[25]

In our series, the treatment schedule was well tolerated: we had only one case of dropout due to fluid retention. In fact, sodium and water retention, potassium wasting, and expansion of effective circulating volume may be related to mineralocorticoid-receptor activation due to the ACTH-induced cortisol production.[26]

The weekly dose of synthetic ACTH analog we administered was lower than that used by other authors.[14–17,22] This lower dosage can explain the negligible occurrence of side effects or complications related to Tetracosactide administration. It is important to keep in mind that the insulin-like effect of ACTH is related to the C-terminal sequence, and thus it should not occur with tetracosactide (synthetic ACTH 1–24).[27]

In accordance with other studies,[14,16] we observed a decrease in total and LDL cholesterol from month 6 to 12. The reduction in serum lipids occurred not only in remitting patients: this may be in agreement with some evidence suggesting that ACTH may affect serum lipids independently of changes in proteinuria.[16]

Berg et al showed that ACTH has a pronounced lipid-lowering effect,[14,16] mediated by modification of apolipoprotein metabolism. This change can restore glomerular expression of apolipoprotein J (clusterin), which was found to be reduced in MN.[28] The clusterin competes in the terminal component of complement C5b-9 for the same receptor in podocytes with megalin, identified as the target of the C5b-9 injury.[28]

The melanocortins (ACTH and α-, β-, and γ-melanocyte-stimulating hormone) derive from the same precursor – proopiomelanocortin. The melanocortins exhibit anti-inflammatory and protective effects in vitro and in vivo in many conditions of local or systemic inflammation.[9,29] A recent report identified gene expression of the melanocortin receptor MC1R in podocytes, glomerular endothelial cells, mesangial cells, and tubular epithelial cells. The administration of MS05, a specific MC1R agonist, in rats with passive Heymann nephritis significantly reduced proteinuria and oxidative stress, and improved podocyte morphology.[7]

The antiproteinuric effect of tetracosactide that we observed in patients unresponsive to previous steroid therapy seems to support the potential nonsteroidogenic mechanism accounting for the ACTH 1–24 therapy.[30]

Because of the nonsteroid-related action of ACTH, namely its favorable effects on podocyte structure and functions, it may be used in those patients for whom immunosuppressive or steroid treatment may not be free from risks, eg, in cases when renal biopsy cannot be safely performed or where the patient is at high risk of complications due to classical immunosuppressive regimens. Furthermore, there are situations where patients do not give their informed consent to procedures and/or treatments. These conditions may represent a possible indication for first-line therapy with ACTH in nephrotic patients. Future studies should address this point.

In summary, our investigation showed that a low dosage of ACTH was able to significantly reduce proteinuria and cholesterol in a cohort of nephrotic patients resistant or relapsing to immunosuppressive regimens. Although our regimen resulted in a lower rate of remissions with respect to the standard dosage, the treatment was safe and well tolerated. The preliminary results of our pilot investigation need to be confirmed by randomized controlled studies. In addition, because ACTH mechanism of action and tolerability, the antiproteinuric effect at this low dose should be investigated in elderly or frail nephrotic patients who are not eligible for kidney biopsy or immunosuppressive protocols.

Disclosure

The authors report no conflicts of interest in this work.

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