Research Square

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Experience With Acth In Membranous Nephropathy In Older Patients

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Abstract

Background The most common cause of nephrotic syndrome in the older population is probably memranous nephropathy (MN). Treatment of patients with nephrotic syndrome caused by MN with adrenocorticotrophic hormon (ACTH) is shown to be efficient as primary and secondary therapy. We present our experience using ACTH in older patients with MN.Methods Between 2016 and 2019 six older patients with MN were treated with ACTH gel. We have used tetracosactide, a synthetic analog of ACTH, in intramuscular doses of 1 mg twice a week for 6-9 months. Estimated glomerular filtration rate, levels of albumin, glucose and proteinuria were studied both before and monthly during the follow-up period. Response in proteinuria was assessed as percent reduction from baseline level and as percent of patients with complete or partial remission or no response. Safety and tolerability were evaluated using the reported adverse event frequency either by the patients or the treating nephrologist and using the frequency of discontinuation due to adverse events.Results Three patients achieved total and another two partial remission with ACTH therapy for 6 months. One of the patients did not meet partial remission criteria but had a decrease in proteinuria level. None of the patients experienced cardiovascular or infectious events or a decrease in renal function.Conclusions ACTH is a good therapeutic alternative in older patients with MN with preserved renal function. Further controlled studies are needed to clarify the benefits of ACTH as a first line treatment option in older patients with MN and compare its use with other currently available therapies.

Background

The most common type of nephropathy presenting with nephrotic syndrome (NS) in older patients is the membranous type. Demonstration of anti PLA2R antibody positivity in most of these patients is a recent contribution to our understanding of its autoimmune etiology [1]. The natural course of membranous nephropathy (MN) is an eventual progress to renal failure though some of the patients may have spontaneous remission. Though best mode of therapy in idiopathic MN is still controversial it seems that patients on immunosuppressive drugs benefit with higher remission rates and better survival. Unfortunately the alkylating agents used may cause serious side effects. The risk of progressive disease is higher in older patients diagnosed to have idiopathic MN. Treatment modalities with combined use of two immunosuppressive drugs are frequently withheld in the older population due to their possible side effects. Therefore the majority of such patients are followed up conservatively and the disease is left to its natural course. This warrants further research to develop new drugs with less or no toxicity.

In 1950s adrenocorticotropic hormone (ACTH) was the first line treatment in patients with NS since it induced disease remission and improved survival [2, 3]. In 1960s, ACTH which was thought to exert its effect over stimulation of corticosteroid production was replaced by oral prednisone which was easier to administer. In some more recent case series ACTH was found to be efficient to induce and sustain remission and improve GFR in patients with NS resistant to steroids and several multidrug modalities. Studies on the efficacy of ACTH on remission of proteinuria in patients with NS where glucocorticoids and/or immunosuppressive drugs [4–6] do not seem beneficial showed that ACTH may help and this suggests it has renoprotective and antiproteinuric effects which can’t be solely via its steroidogenic effect. Increase in melanocortin receptor activity on several inflammatory cells including B and T cells and antigen presenting

cells, increase in production of endogenous steroids and its direct binding to podocyte membrane via melanocortin receptors may be responsible for its effects.

Nearly all of our knowledge about ACTH use in patients with NS is derived from retrospective, observational studies in heterogeneous populations. ACTH was used either as a first line medication or following unsuccessful immunomodulatory treatments. This study reports our experience with ACTH use in older patients with MN which we believe is an effective and safe medication in these patients.

Methods

We evaluated 6 older patients with nephrotic syndrome (mean age 74.8) who were treated with ACTH therapy in Ankara University Medical Center between 2016 and 2019. All patients had biopsy proven MN and were evaluated retrospectively on the basis of chart reviews. They met one or more of the following criteria: 1) despite being treated with an ACEI or ARB urinary protein-creatinine ratio (UPCR) is persistently over 4 g/d for more than 6 months, 2) there are debilitating or life threatening symptoms caused by NS, 3) renal function is deteriorating, i.e. MN attributed 30% rise in serum creatinine from baseline. Two of the patients were treated with rituksimab previously while the remaining 4 were on conventional therapy. All patients were screened for secondary causes of MN. This screening included history, physical exams, hepatitis B and C virus screening, testing for antinuclear antibody, evaluation of drug adverse reactions, studies for overt or occult malignancy. Patients who had known or found to have malignancy, who have active hepatitis B or C, and those who have a history of exposure to a medication known to cause MN were excluded. All patients were followed up for at least 2 years.

All patients provided signed informed consent. Renal biopsy specimens were examined under light microscopy and immunofluorescence by a single experienced pathologist. The presence of interstitial fibrosis with tubular atrophy and mesangial glomerular sclerosis were recorded.

All patients were given initially a 1 mg/ml slow release suspension of tetracosactide hexaacetate (Synacten Depot, Cosyntrophin Zinc hydroxide suspension, Novartis) which is a synthetic analogue of ACTH prepared for intramuscular injection. The IM injection was planned between 07:00 and 09:00 AM. After initiating the ACTH injections with a single dose every other week, the dose was increased to 2 injections per week over a period of 6–9 months as reported by Berg et al [4]. After reaching the maximum dose of 2 injections per week it was continued for 18 weeks and then tapered slowly.

All patients had been on treatment with an ACEI or an ARB at its maximal tolerated dose for at least 3 months. Salt restriction was advised to help blood pressure control. A blood pressure of < 130/80 mmHg was targeted; and in patients who did not reach the BP target with ACEI/ARB other antihypertensive medications were added.

The median follow up period was 28 months from the start of therapy. In 2 patients the follow up was successfully continued for 48 months. Each patient was examined at the start of therapy and monthly thereafter to evaluate the course of symptoms, measurement of blood pressure and body weight and for presence of possible side effects. Blood and urine samples were collected weekly in the first month and then

monthly. Complete blood count, panels for hepatic function and basic metabolic status, lipid profile and spot protein/creatinine ratio were studied. Anti-PLA2R antibody measurements were made in only 3 patients. In these patients anti-PLA2R antibody titers were followed up throughout the treatment period. GFR was estimated by using the CKDepi.

Primary outcomes:

Remission status at the completion of ACTH therapy was the primary outcome. Stable or improved renal function with final UPCR < 0.5 g/g and 0.5–3.5 g/g were defined as complete and partial remission, respectively.

Serious adverse events:

All 6 patients were surveyed at each visit for infections, hospitalizations, or other possible complications. Reported adverse events were recorded appropriately.

Statistical Analysis

Wherever applicable characteristics of the patients and outcomes were summarized by using counts, percentages, medians, and means and SDs.

Results

The baseline characteristics of the patients are presented in Tables 1 and 2. The mean age was 74.8 (70–81 years) at initiation of treatment. Three of 6 patients were female. Two of 6 patients were treated with low dose rituksimab previously: one 12 and the other 18 months ago. Most of the patients were diagnosed to have histological stage II on renal biopsy. None of the patients were treated with cyclophosphamide, corticosteroid or MMF previously.

Table 1

Baseline characteristics of the patients

	n = 6
Age	74.8
Distribution of ages by tertiles (60–70/>70)	- / 6
Gender (Male/Female)	3/3
Scr (mg/dl)	1.08 ± 0.4
Proteinuria (g/24hr)	6.91 ± 1.1
Serum albumin	2.53 ± 0.6
Systolic Blood Pressure	131.6 ± 19.3
Diastolic Blood Pressure	73.8 ± 6.8
Previous Treatment (steroid / steroid + cytotoxic / Rituximab)	-/-/2
ACEI/ARB	3/3
Statins	5/1

Table 2

Baseline GFR and UPCR data of the patients

	Age	Gender	Months from diagnosis	Previous immunosuppressive therapy	Pre ACTH $S_{creatinine}$ mg/dl	Pre ACTH eGFR ml/min/1.73 m^2	UPCR g/g
Patient1	77	male	16	Rituksimab (8 months ago)	1.4	63	8.2
Patient2	74	female	4	none	0.8	85	6.4
Patient3	81	male	12	none	0.8	84	4.5
Patient4	70	female	14	Rituksimab (10 months ago)	0.9	89	7.2
Patient5	72	male	6	none	1.2	71	5.8
Patient6	75	female	7	none	1.4	70	9.4

With a 6 months' course of ACTH therapy 3 of 6 patients achieved total and other 2 partial remission. One of the patients was not within range of partial remission criteria despite a documented decrease in proteinuria. Proteinuria increased in 20th month of follow up in one of the patients who had achieved

complete remission and is now on conventional therapy. Follow up parameters during and following the treatment period are given in Table 3.

Table 3
Detailed test results of 6 patients with membranous nephropathy.

	Baseline	Month 1	Month 2	Month 3	Month 6	Year 1	Year 2
Patient 1							
Scr, mg/dL	1.4	1.3	1.3	1.4	1.1	1.2	1.3
Salb, g/dL	2.7	2.6	2.8	3.1	4.0	4.1	3.9
UPCR, g/g	8.2	7.5	5.0	4.0	1.2	0.4	2.3
Patient 2							
Scr, mg/dL	0.8	0.9	1.0	1.0	0.9	1.1	1.1
Salb, g/dL	3.1	3.4	3.5	3.9	3.9	4.0	4.1
UPCR, g/g	6.4	5.1	4.0	0.8	0.3	0.3	0.2
Patient 3							
Scr, mg/dL	0.8	0.8	0.7	0.8	0.9	0.8	0.9
Salb, g/dL	2.5	3.1	3.2	3.1	3.3	3.9	3.9
UPCR, g/g	4.5	4.2	4.1	1.8	1.1	1.4	1.3
Patient 4							
Scr, mg/dL	0.9	1.0	1.1	1.0	0.9	1.1	1.0
Salb, g/dL	2.2	2.2	2.3	2.7	2.9	3.0	3.3
UPCR, g/g	7.2	8.1	6.0	5.2	3.2	3.9	3.4
Patient 5							
Scr, mg/dL	1.2	1.3	1.1	1.1	1.0	1.1	1.2
Salb, g/dL	2.9	3.2	3.6	3.8	4.0	3.9	4.0
UPCR, g/g	5.8	3.2	2.1	1.1	0.8	1.6	1.5
Patient 6							
Scr, mg/dL	1.4	1.2	1.2	1.1	1.2	1.1	1.1
Salb, g/dL	1.8	1.9	2.2	3.5	4.2	4.0	4.3
UPCR, g/g	9.4	7.3	4.5	2.5	0.6	0.4	0.2

Due to worsening of glycemic control which needed initiation of an oral hypoglycemic medication one patient discontinued ACTH therapy at the 5th month. Patient 2 had to continue oral hypoglycemic medication after her last dose of ACTH. Patients 1 and 4 gained weight and complained of skin pigmentation. Significant infection was not observed during the treatment period. Before the start of observation all patients were on stable ACEI or ARB therapy at a maximum dose tolerated by serum potassium and blood pressure levels for at least 6 months.

Discussion

In carefully selected older patients with MN intramuscular injections of synthetic ACTH with 2 injections weekly in an outpatient setting is an effective and feasible alternative as first line therapy. It seems to be a safe and effective method for older patients in whom follow up has usually been conservative. Our high remission rate may be attributed to the fact the patients we studied were neither relapsed nor refractory cases.

ACTH gel and $ACTH_{1-24}$ have been reported to improve proteinuria in NS and proteinuric nephropathy including MN in adults [4–8]. There are very few reports on the effect of synthetic ACTH in nephrotic adults. We found only two recent papers; one by Berg and Arnadottir [5] and the other by Ponticelli et al [9]. Ponticelli et al reported their findings using ACTH as a first line medication while Berg and Arnadottir studied in a group of relapsed and refractory patients. The ACTH dose used in these studies was similar to ours with few side effects necessitating cessation of therapy. Lorusso [10] et al could not attain a similar remission in refractory patients in a study with weekly injections of low dose ACTH (tetracosactid) continued for one year. The mean age of the 6 patients we evaluated is quite higher than of other series. We observed a remission rate similar to the rate achieved with first line therapy using two immunosuppressive drugs at optimal doses. There was no side effect necessitating discontinuation of the therapy.

There are 2 commercially available ACTH products. In previous studies 2 forms of ACTH were studied. A proprietary mixture isolated from porcine pituitary extracts, ACTH gel, is the first. The active and major component of this gel is $ACTH_{1-39}$ but it seems to contain some other potentially bioactive peptides derived from POMC (pro-opiomelanocortin). This preparation is not on the market in Turkey. The other commercially available product is a synthetic truncated analog of ACTH known as tetracosactide or tetracopeptid ($ACTH_{1-24}$) which is the part of the native ACTH with the first 24 aminoacids. It is on the market as a long acting formulation (Synacten) and presumed to have similar therapeutic effect as ACTH gel. However pharmacokinetic, pharmacodynamic and physiologic evidence gathered from recent studies suggests that it differs from the natural $ACTH_{1-39}$ [11]. The C terminus of the natural hormone $ACTH_{1-39}$ bears the β-cell tropic and insulinotropic effect. Though this activity is preserved in the ACTH gel it is missing in the synthetic analogue. The ACTH gel which is a naturally derived preparation may contain other POMC derived pharmacologically active molecules including other melanocortin peptides [12]. Further studies are still needed in this area.

This evaluation showed us that tetracosactide use as a first line therapy in older patients with MN who were not previously treated with two immunosuppressive drugs is effective and feasible. The 6 months' treatment

period was completed successfully in all patients despite the observation of one severe and multiple mild side effects.

Though the limited number of patients, lack of a control group and relatively short follow up period limit the value of the data presented here, this paper focuses at the response and safety profile of ACTH therapy in older patients with MN.

Conclusions

In summary our experience showed ACTH reduced proteinuria significantly in older nephrotic patients who are not eligible for immunosuppressive protocols. These preliminary results need confirmation by randomized controlled studies.

List Of Abbreviations

MN: membranous nephropathy

ACTH: adrenocorticotropic hormone

NS: nephrotic syndrome

POMC: pro-opiomelanocortin

ACEI: Angiotensin converting enzyme inhibitor

ARB: Angiotensin receptor blocker

UPCR: urinary protein creatinine ratio

Declarations

Ethics approval and consent to participate

The study complies with the Declaration of Helsinki, was approved by the ethics committee of Ankara University Faculty of Medicine (approval no 19-1199-17). All subjects have been informed about the effects/adverse effects of the planned therapy and given their written consent to receive the medication.

Consent for publication

Written informed consent to publish this information was obtained from study participants.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no conflict of interest.

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Authors' contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by all authors. The first draft of the manuscript was written by SK and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

The corresponding author SK affirms that she has listed everyone who contributed significantly to the work and there is no other contributor who is not an author.

Authors SKu, SS, SE, GKS and KK are clinicians responsible for the treatment and follow up of the patients and formal analysis, investigation, methodology and writing of the manuscript while SKi is responsible for the investigation and pathological examinations.

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