

Melanocortin Receptor Agonist (Corticotrophin) in Treatment of Proteinuric Nephropathies

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Abstract: Background: Treatment of idiopathic glomerular diseases often faces several challenges, namely low initial response, relapse of the disease during/after reduction or withdrawal of the therapy and side effects or prohibitive cost of the medicines. These have led to a research for second, third or fourth line therapies to attain sustained remission, at the same time avoiding complications. ACTH was employed many years ago for the treatment of nephrotic syndrome in children and adults. It has been reappraised, due to its efficacy in reducing proteinuria and lipids in cases of glomerulonephritis resistant to conventional treatment with steroids and immunosuppressive. This effect has persisted for several patients many months after the discontinuation of treatment. ACTH has reemerged as a potential treatment option in a variety of glomerular diseases, including those which have initially shown a less than satisfactory response to the usual therapies in idiopathic nephrotic syndrome. **Aim of the Work:** is to evaluate different therapeutic modalities given to those patients and asses the response and efficacy of treatment and determine if the patient need treatment with ACTH as primary treatment or for resistant cases. **Patients and Methods:** 77 patients presented with proteinuric nephropathies with no history of diabetes mellitus, chronic kidney disease and HCV were subjected to complete history taking, thorough clinical examinations, laboratory investigations, abdominal ultrasonography and they will be classified according to the pathology present in the renal biopsy into groups (minimal change nephropathy- membranous GN- focal segmental glomerulosclerosis- membranoproliferative GN-lupus nephritis stage III-IV-V-thrombotic microangiopathy) Each group was subdivided into three subgroups one group had received ACTH only-one group had received ACTH plus conventional therapy-and one group had received conventional therapy only –all groups had received non specific measures of reduction of proteinuria as ACEI or ARBS and statins. ACTH was given as intramuscular injection according to the body weight(8,3-30microgram/kg) twice weekly with most patients receive average 1 mg in dose as primary therapy- secondary therapy –as adjuvant therapy –and after failure of other immunosuppressives for resistant cases **Results:** 27 of 77 patients (35%) achieved a complete remission and 26 of 77 patients achieved partial remission (33%) total 68%. Of the 53 patients who achieved complete or partial remission, 12 had IMN, 14 had FSGS, and 8 had minimal change nephropathy and 13 patients with lupus nephritis 6 patients with MPGN. In IMN9 of 12 patients received ACTH either as monotherapy or as adjuvant therapy with response rate of 75% -5 patients were on ACTH only show remission rate 41% - 3patients were on conventional therapy show remission rate 25%.in FSGS 10 of 14 patients received ACTH either as monotherapy or as adjuvant therapy with response rate of 71% -4 patients were on ACTH only show remission rate 28% - 4 patients were on conventional therapy show remission rate 28%. In MCN 6 of 8 patients received ACTH either as monotherapy or as adjuvant therapy with response rate of 75% -3 patients were on ACTH only show remission rate 37% - 2 patients were on conventional therapy show remission rate 25%. In MPGN2 of 6 patients received ACTH either as monotherapy or as adjuvant therapy with response rate of 33% -2 patient was on ACTH only show remission rate 17 % - 4 patients were on conventional therapy show remission rate 66%. **Conclusion:** Synthetic ACTH can be used in treatment of proteinuric nephropathies as primary therapy especially in podocytopathies and in membranous nephropathy and as adjuvant therapy in lupus nephritis and in resistant cases after failure of other immunosuppressives [El-Metwaly Lotfy El-Shahawy, Mohammed El-Sayed Salem, Sameh Bahgat Hannalla, Hassan Galal Abdelsalam and Ahmed Ezzat Mansour. **Melanocortin Receptor Agonist (Corticotrophin) in Treatment of Proteinuric Nephropathies.** *Nat Sci* 2015;13(9):41-49]. (ISSN: 1545-0740). <http://www.sciencepub.net/nature>. 8

Keywords: Melanocortin; Receptor Agonist; Corticotrophin; Proteinuric Nephropathies

1. Introduction:

Adrenocorticotrophic hormone (ACTH), or corticotropin, is a pituitary polypeptide hormone consisting of 39 amino acids. It is an important component of the hypothalamic–pituitary–adrenal (HPA) axis and has a pivotal role in sustaining

homeostasis of the neuro immune endocrine system (*Dores., 2009*).

Subsequent clinical studies demonstrated that ACTH therapy induced remission of proteinuria in patients with nephrotic syndrome who were refractory to glucocorticoid and/or immunosuppressive therapies suggesting that ACTH has prominent antiproteinuric

and renoprotective effects that are not entirely explained by its steroidogenic actions (*Berg., & Arnadottir., 2000*) (*Ponticelli., 2007*).

ACTH is also an important physiological agonist of the melanocortin system. This system comprises multiple components, including five class of guanine nucleotide-binding protein (G protein)-coupled melanocortin receptors (MCRs) MC1R–MC5R; peptide agonists derived from POMC; and endogenous antagonists (*Cone., 2006*) (*Voisey., et al 2003*).

The five MCRs each have a distinct tissue distribution, convey signaling of different melanocortins and exert varying biological activities (*Voisey., et al 2003*).

Receptor-binding studies have revealed that all five MCRs show a strong affinity for ACTH, thereby establishing the potential for this hormone to activate these receptors (*Penhoat., et al 2001*).

MCRs are expressed in kidney cells, which indicates that the kidney is a target organ for the effects of ACTH (*Lindskog., et al 2010*) (*Lee., et al 2008*).

At present, 2 products that contain ACTH, The first one is ACTH gel, isolated from porcine pituitary extracts. It contains the intact ACTH (1_39), but in addition, also contains some POMC derived peptides having biological activity.

The second product is a synthetic ACTH analogue (tetra copeptide), which consists of the first 24 amino acids of the native hormone ACTH (1_24) (*Beloff-Chain et al., 1983*).

Histologically, glomerulosclerosis and tubulointerstitial fibrosis, renal inflammation, tubular atrophy, and tubular epithelial–mesenchymal transdifferentiation all improved (*Gong., & Dworkin., 2010*).

These effects included notable reductions in foot-process effacement and podocyte apoptosis, and amelioration of the decline in glomerular expression of podocyte markers, including vimentin, nephrin, podocin and the transcription factor WT1 (*Gong., & Dworkin., 2010*).

Several studies have demonstrated that ACTH gel and ACTH1–24 improve proteinuria in adult patients with nephrotic syndrome caused by proteinuric nephropathies, including idiopathic membranous nephropathy (IMN) (*Berg., & Arnadottir., 2000*) (*Berg., et al 2004*) (*Ponticelli., 2007*) (*Lindskog., et al.2010*) (*Bomback., et al 2011*).

ACTH-induced remission of proteinuria in patients with IMN was associated with a reduction in the levels of autoantibody against M-type phospholipase A2 receptor (PLA2R), which is a major target antigen in this disease (*Beck., et al 2009*).

Striking antiproteinuric effects of ACTH1–24 have also been found in patients with nephrotic kidney diseases other than IMN, including FSGS, proliferative glomerulonephritis and hereditary nephropathy, implying that the therapeutic effect of ACTH1–24 is not dependent on the type of glomerular injury, but is probably mediated by a general glomeruloprotective mechanism (*Berg., & Arnadottir., 2004*).

Skin pigmentation (bronze coloration) has been noted in some patients treated with synthetic ACTH1–24 and a few treated with ACTH gel a case series published in 2011 reported that very few patients with nephrotic syndrome developed hyperglycemia (2 out of 21 patients), had significant weight gain or exhibited evidence of accelerated bone loss after ACTH gel therapy (*Ponticelli., et al 2006*)

In most cases, adverse effects were tolerable and completely disappeared after the cessation of therapy.

Aim of the Study:

This study was undertaken to evaluate different therapeutic modalities given to those patients and assess the response and efficacy of treatment and determine if the patient need treatment with ACTH as primary treatment or for resistant cases.

2. Subjects and Methods:

This study was conducted on 77 patients with proteinuric nephropathies admitted to the Department of Internal Medicine, nephrology Unit at Benha University Hospital within the period between August 2012 to October 2014.

Criteria of Selection:

Inclusion Criteria

- Patients with nephrotic syndrome diagnosed by clinical manifestations, biochemical investigations and Ultrasonographic findings.

Exclusion Criteria

- Diabetes mellitus
- Chronic kidney disease
- HCV +ve patients.

Patients were classified according to the pathology present in the renal biopsy into groups (minimal change nephropathy- membranous GN- focal segmental glomerulosclerosis- membranoproliferative GN-lupus nephritis stage III-IV-V-thrombotic microangiopathy).

Each group was subdivided into three subgroups one group had received ACTH only-one group had received ACTH plus conventional therapy-and one group had received conventional therapy only –all groups had received non specific measures of reduction of proteinuria as ACEI or ARBS and statins. ACTH was given as intramuscular injection according to the body weight(8,3-30microgram/kg) twice weekly

with most patients receive average 1 mg in dose as primary therapy- secondary therapy –as adjuvant therapy –and after failure of other immunosuppressives for resistant cases

For All patients, after giving their informed consent, they were subjected to the following:

1. Detailed medical history.
2. Complete clinical examination.
3. Laboratory investigations including (Immunological markers (ANA-Anti double stranded- ANCA)
 - Viral markers (HCVAb -HBsAg)
 - Anti bilharzial antibodies.
 - Urine analysis.
 - Protein in 24 hour urine
 - C3-C4
 - Blood Urea – serum creatinine
 - Complete blood picture
 - Serum Sodium –serum potassium
 - Serum cholesterol
 - Renal biopsy.

Statistical analysis:

- Descriptive statistics was calculated for all variables of interest Continuous measures were summarized using mean \pm standard deviation, whereas categorical measures were summarized using counts and percentages. Paired testing was used to assess changes over time. Fisher's exact test was utilized to compare proportions. An analysis of variance was used to compare responses by dose with the Newman-Keuls test utilized for between group comparisons. Correlation was used to assess the relationship between response to treatment, i.e. proteinuria reduction.
- A *P*-value of <0.05 was deemed statistically significant. All analyses were carried out using SAS Version 9.1 (SAS Institute, Cary, NC, USA)

3. Results:

A total of 27 patients (35%) achieved a complete remission and 26 of 77 patients achieved partial remission (33%) total 68%.7 patients achieved a limited response, while 11 patients had no overall response to therapy.

One patient with minimal change –one patient with lupus nephritis class V, two patients with membranous GN and two patients with FSGS show relapse after initial response.

Of the 53 patients who achieved complete or partial remission, 12 had IMN, 14 had FSGS, and 8 had minimal change nephropathy and 13 patients with lupus nephritis 6 patients with MPGN.

Of the 14 patients with IMN 6 achieved complete Remission two patients on ACTH and 4 patients on

combined therapy and 6 achieved partial remission 3 patients on ACTH and 3 patients on conventional therapy with overall 9 of 12 patients received ACTH either as monotherapy or as adjuvant therapy with response rate of 75% -5 patients were on ACTH only show remission rate 41% - 3patients were on conventional therapy show remission rate 25%.

9 patients with FSGS achieved complete remission 3 patients on ACTH, 5 patients on combined therapy and 1 patient on conventional and 5 patients achieved partial remission 1 patient on ACTH, 1 patient on combined and 3 patients on conventional therapy –with 10 of 14 patients received ACTH either as monotherapy or as adjuvant therapy with response rate of 71% -4 patients were on ACTH only show remission rate 28% - 4 patients were on conventional therapy show remission rate 28%.

4 patients with MCN achieved complete remission 1 on ACTH, 2 on combined therapy and 1 on conventional therapy and 4 patients achieved partial remission 2 on ACTH, 1 on combined and 1 on conventional therapy- with 6 of 8 patients received ACTH either as monotherapy or as adjuvant therapy with response rate of 75% -3 patients were on ACTH only show remission rate 37% - 2 patients were on conventional therapy show remission rate 25%.

4 patients with MPGN achieved partial remission 1 on ACTH, 1 on combined and 4 on conventional therapy- with 2 of 6 patients received ACTH either as monotherapy or as adjuvant therapy with response rate of 33% -2 patient was on ACTH only show remission rate 17 % - 4 patients were on conventional therapy show remission rate 66%.

8 patients with lupus nephritis show complete remission on combined therapy and 5 patients had partial remission 4 on conventional and 1 on combined therapy - 9 of 13 patients on combined therapy with remission rate of 69% and 4 on conventional therapy with remission rate of 31%.

4. Discussion

Treatment of idiopathic glomerular diseases often faces several challenges, namely low initial response, relapse of the disease during/after reduction or withdrawal of the therapy and side effects or prohibitive cost of the medicines (**Berg & Arnadottir 2000**).

These have led to a research for second, third or fourth line therapies to attain sustained remission, at the same time avoiding complications (**Berg & Arnadottir 2000**).

ACTH was employed many years ago for the treatment of nephrotic syndrome in children and adults. It has been reappraised, due to its efficacy in reducing proteinuria and lipids in cases of glomerulonephritis resistant to conventional treatment

with steroids and immunosuppressives. This effect has persisted for several patients many months after the discontinuation of treatment (Coppo 2008; Rauen et al., 2009).

ACTH has reemerged as a potential treatment option in a variety of glomerular diseases, including those which have initially shown a less than satisfactory response to the usual therapies in idiopathic nephrotic syndrome (Cone, 2006).

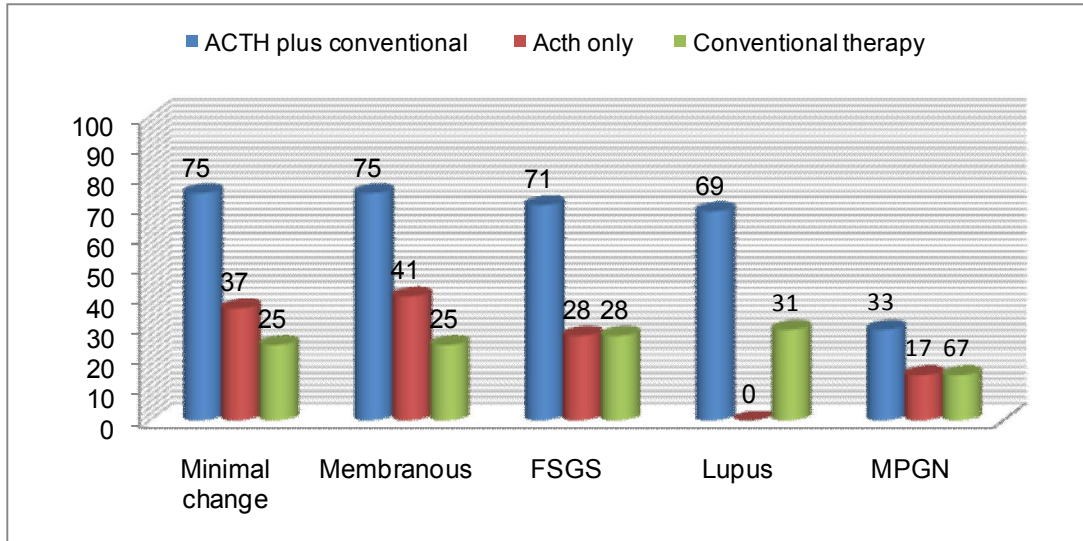


Figure (1) show the percentage of remission in different types of GN in patients received acth only as one group or combined with conventional therapy as another group and patients who received conventional therapy only as one group.

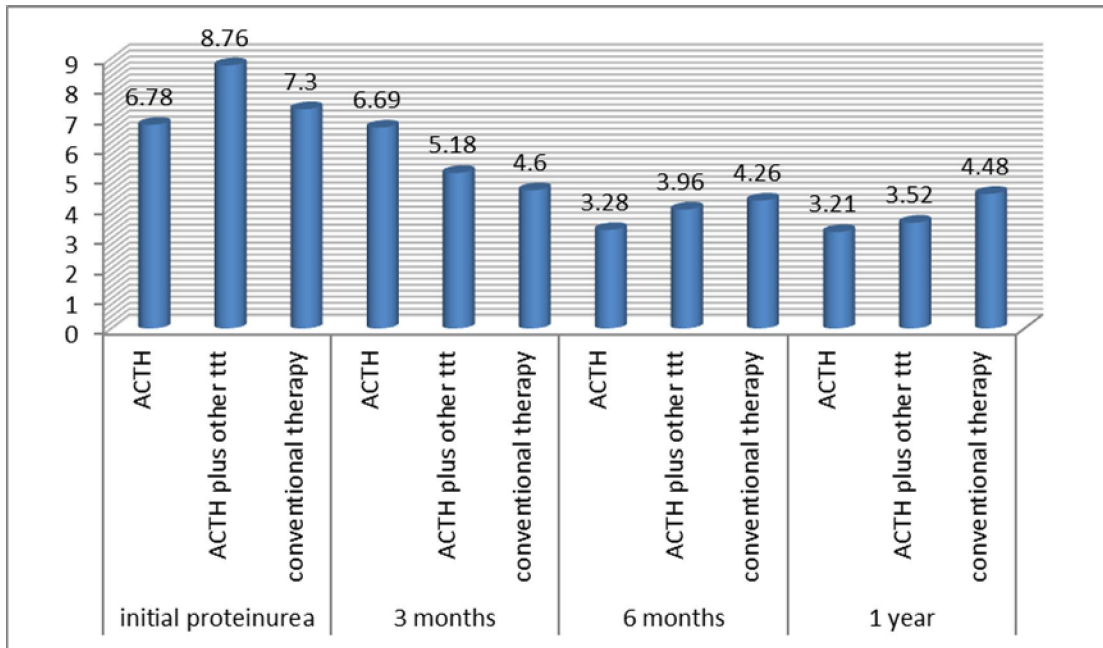


Figure (2) show that there is a significant reduction of proteinuria in ACTH and ACTH plus conventional therapy groups in minimal change nephropathy in 6months and one year more than conventional therapy and this was statistically significant.

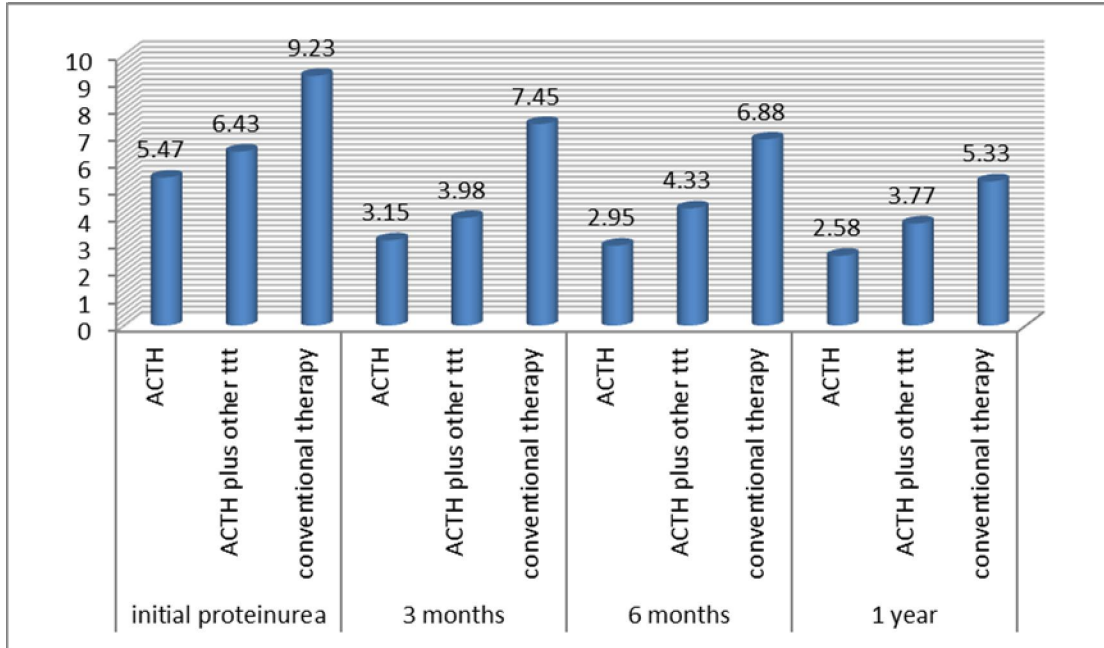


Figure (3) show that there is a significant reduction of proteinuria in ACTH group in membranous nephropathy in 3months, 6months and one year (p -value <0.05) and significant reduction in ACTH plus conventional in 3months and one year more than conventional therapy and this was statistically significant.

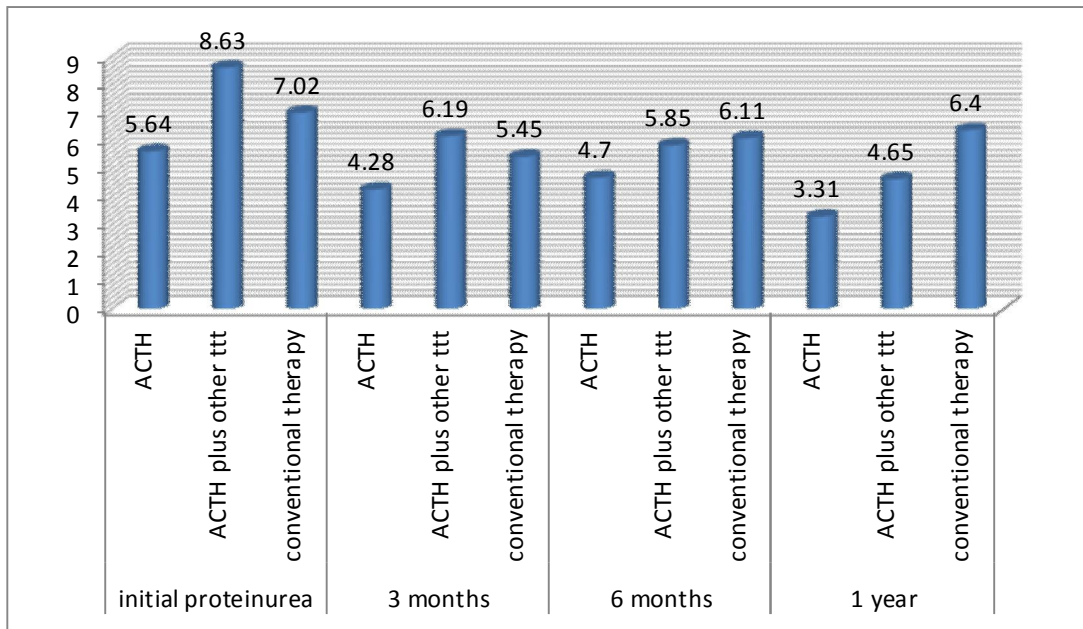


Figure (4) show that there is a significant reduction of proteinuria in ACTH and ACTH plus conventional therapy groups in FSGS in 6months and one year more than conventional therapy and this was statistically significant

The aim of this work was to evaluate different therapeutic modalities given to patients presenting with nephrotic syndrome and asses the response and efficacy of treatment and determine if the patients need treatment with ACTH as primary treatment or for resistant cases and which type of GN will benefit better with treatment with synthetic ACTH.

The results of this work were tabulated and statistically analysed using suitable statistical tests.

We present here a prospective study evaluating the initial experience of 77 patients in Banha University Hospital treated with synthetic ACTH for nephrotic syndrome.

Treatment with angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers and statins (48 patients) remained unmodified. All patients received ACTH synthetic form (1–24) at a dose of 1 mg intramuscularly twice per week for 6 to 12 months.

Some of these patients received ACTH as second-, third-, line therapy for resistant nephrotic syndrome but without stoppage of the initial immunosuppressives in most patients as some of them was on reduced doses trying to withdraw the drugs as there were no response and some patients were still on their initial doses.

ACTH was used as initial therapy in patient with minimal change nephropathy, membranous glomerulonephritis and focal segmental glomerulosclerosis.

These 77 patients were (14) patients with minimal change nephropathy-(20) patient presented with focal segmental glomerulosclerosis-(14) patient with membranous GN-(6) patients with lupus nephritis class III-(6) patients with lupus nephritis class IV – (4) patients with lupus nephritis class V-(13) patients with membranous proliferative GN.

In our study we found that:

Membranous glomerulonephritis showed the greatest benefit of therapy, Of the 14 patients with IMN 6 achieved complete remission two patients on ACTH and 4 patients on combined therapy and 6 achieved partial remission 3 patients on ACTH and 3 patients on conventional therapy with overall 9 of 12 patients received ACTH either as monotherapy or as adjuvant therapy with response rate of 75% - 5 patients were on ACTH only show remission rate 41% - 3 patients were on conventional therapy show remission rate 25%. 3 patients show relapse after trial of stoppage of ACTH after 6 months but they show remission after receiving ACTH again.

Adverse events associated with therapy were relatively minor and included pigmentation in hands and legs, hyperglycemia and hypokalemia.

Our observations are concordant with previously published reports from Europe using a synthetic ACTH analog for nephrotic syndrome due to IMN.

Berg and Arnadottir, in a seminal paper from 2004⁽⁴⁾, reported the results of ACTH treatment in 23 cases of nephrotic syndrome of various etiologies, including 10 cases of IMN.

Half of these IMN patients had previously been treated with at least 1 prior immunosuppressive therapy, and all 10 achieved sustained remission of proteinuria.

A more recent series from Germany reported the results of 8 months of synthetic ACTH therapy for 4 patients with IMN refractory to prior therapies of steroids, cyclosporine, cyclophosphamide,

mycophenolate mofetil, or azathioprine. **(Rauen et al., 2009).**

Within the first year, 2 had achieved complete remission, and 2 had achieved partial remission.

The most convincing data, however, come from the randomized trial by Ponticelli et al, in which 16 patients with IMN received steroids alternating with a cytotoxic drug for 6 months versus 16 patients with IMN treated with synthetic ACTH for 1 year **(Ponticelli et al., 2006).**

Most of these patients were on renin angiotensin system blocking drugs, but none had previously received immunosuppression. After a median follow-up of 24 months, there were 4 complete and 8 partial remissions in the steroid/cytotoxic therapy group versus 8 complete and 6 partial remissions in the ACTH group.

ACTH therapy resulted in a similar remission rate (83%) as compared with the Ponticelli immunosuppressive regimen (75%) **(Ponticelli et al., 2006).**

Furthermore, there were no significant difference in the relapse rate between the two therapeutic regimens after a median follow-up of 24 months. This study, at least, demonstrated that the therapeutic efficacy of ACTH monotherapy is not inferior to that of the standard Ponticelli immunosuppressive regimen for IMN.

Our observations are also concordant with previously published reports from **(Bomback et al., 2011)** recruited 21 patients with refractory nephrotic syndrome due to a variety of glomerular diseases. Among the 21 patients, 11 were diagnosed as IMN and most of them were previously treated and failed to respond to a mean of 2 immunosuppressive regimens. After ACTH gel treatment at a most commonly used dose of 80IU twice a week for 5 to 12 months, 9 of the 11 patients (82%) with IMN achieved either partial (55%) or complete (27%) remission of proteinuria.

In our case series the result of ACTH in other diagnoses other than IMN were 9 patients with FSGS achieved complete remission 3 patients on ACTH, 5 patients on combined therapy and 1 patient on conventional and 5 patients achieved partial remission 1 patient on ACTH, 1 patient on combined and 3 patients on conventional therapy –with overall 10 of 14 patients received ACTH either as monotherapy or as adjuvant therapy with response rate of 71% - 4 patients were on ACTH only show remission rate 28% - 4 patients were on conventional therapy show remission rate 28%. 2 patients show relapse after trial of stoppage of ACTH after 6 months but they show remission after receiving ACTH again 4 patients with MCN achieved complete remission 1 on ACTH, 2 on combined therapy and 1 on conventional therapy and 4 patients achieved partial remission 2 on

ACTH, 1 on combined and 1 on conventional therapy- with 6 of 8 patients received ACTH either as monotherapy or as adjuvant therapy with response rate of 75% -3 patients were on ACTH only show remission rate 37% - 2 patients were on conventional therapy show remission rate 25%.

Our observations are also concordant with previously published reports from an observational study by **(Berg et al., 2004)**, 2 patients with MCD and 1 patient with FSGS had nephrotic range proteinuria and demonstrated no response to previous steroid and cytotoxic treatments. After the patients were converted to synthetic ACTH monotherapy for 2 to 7 months, the 2 MCD patients achieved complete remission and the FSGS patient attained partial remission. The patients all remained in remission after they were followed up for 4 to 28 months following cessation of ACTH therapy.

In another retrospective case series abstract report **(Hogan et al., 2010)**, 12 patients with primary FSGS and nephrotic syndrome resistant to prior immunosuppressive therapies (median 3 therapies) were administered ACTH gel (median dose 80 IU subcutaneous injection twice weekly) for a median of 26 (range 12–56) weeks.

Five of 12 patients (42%) experienced partial remission at last follow-up (median follow-up time 58 weeks after stopping ACTH). The median time-to-remission was 6 (range 6–24) weeks.

This ACTH induced remission rate in patients with refractory FSGS is consistent with the finding by another prospective trial **(Bombeck et al., 2011)**, in which 5 patients with either MCD or FSGS failed 2 to 4 previous immunosuppressive treatments and were converted to ACTH gel monotherapy. After 6-month treatment, 2 of 5 patients (40%), 1 MCD and 1 FSGS, achieved partial remission in a recent study reported as a conference abstract, **(Berg et al., 2012)** recruited 10 patients with severe FSGS that failed to respond to prior treatments with prednisolone in combination with other immunosuppressants, including cyclosporine, tacrolimus, mycophenolate mofetil and/or cyclophosphamide. After prednisolone was replaced with synthetic ACTH for a median 18 months while continuing therapy with a second immunosuppressive agent, 8 of 10 patients reached either complete (3 patients) or partial remission (5 patients), again suggesting a steroidogenic independent mechanism mediating such a robust therapeutic efficacy 4 patients with MPGN achieved partial remission 1 on ACTH, 1 on combined and 4 on conventional therapy- with 2 of 6 patients received ACTH either as monotherapy or as adjuvant therapy with response rate of 33% -2 patient was on ACTH only show remission rate 17 % - 4 patients were on conventional therapy show remission rate 66%. Our

observations are not concordant with previously published reports of Both **(Berg et al., 2004)** and **(Bombeck et al., 2011)** reported in their case series studies that patients with steroid resistant MsPGN, IgAN or MPGN responded very well to ACTH therapy in terms of remission of proteinuria, inferring steroidogenic-independent melanocortin mechanisms mediating a renoprotective benefit. 8 patients with lupus nephritis show complete remission on combined therapy and 5 patients had partial remission 4 on conventional and 1 on combined therapy - 9 of 13 patients on combined therapy with remission rate of 69% and 4 on conventional therapy with remission rate of 31%. Our observations are concordant with previously published reports of In a recent study by **(Berg & Back 2013)** that was presented as a conference abstract, 5 patients with lupus nephropathy received synthetic ACTH treatment for average 6 months. Urinary albumin excretion decreased from average 4278 µg/ml to 285µg/ml, associated with significant improvement in hypoalbuminemia and stabilization of kidney function. Three of the 5 patients previously failed multiple immunosuppressive regimens including glucocorticoids, again suggesting a steroidogenic independent melanocortin mechanism mediating the renoprotective effect in lupus nephritis 11 patients had no response, 7 patients had limited response and 6 patients relapsed In part, this may be due to these patients having worse baseline renal function. Notably, 7 of the 22 patients reported previously who show no or limited response had advanced renal insufficiency (GFR range from 20%-40%) when prescribed ACTH.

In our case series, patients treated with synthetic ACTH for diagnoses other than IMN for example, only 5 of 14 MCD patients 2 patients demonstrated no response and 3 patients demonstrate limited response. 3 patients diagnosed with membranous GN of 14 patients 2 patients show relapse one of them show remission and one patient show limited response 6 patients of 20 patients presented with FSGS 4 patients show no response and 2 patients show relapse. 6 patients of 13 presented with MPGN 3 patients show no response and 3 patients show limited response 2 patients with lupus nephritis 1 with stage III show no response and 1 with stage IV show no response and changed to MMF.

Our series include 77 patients 63 of these patients were diagnosed with diseases other than MN, from which 22 patients their response rate to ACTH was generally poor. The lack of response exhibited by these patients may reflect the degree of renal failure more than the specific diagnosis itself.

Our observations are concordant with The results, of the successful experiences of Berg and Arnadottir in treating nephrotic syndromes other than IMN.

Thirteen of the 23 cases presented in their series were nephrotic syndrome diagnoses other than iMN. Only 1 patient with MPGN did not respond to synthetic ACTH.

The remaining 12 patients – with diagnoses of MPGN, MCD, FSGS, diabetic nephropathy, and hereditary nephritis – all experienced at least a 50% reduction in proteinuria during synthetic ACTH therapy, and 8 patients achieved sustained complete remission (proteinuria, 500 mg/day).

Theoretically, the difference in response could also be explained by inherent differences between the synthetic and natural formulations of ACTH.

Although encouraging, the initial results of synthetic ACTH therapy must be interpreted cautiously in light of the limitations of an observational series such as this.

Our study is different in that our patients were randomized to therapy, and there is a comparison or control group against which to interpret these results.

In some respects, however, the patients may serve as their own controls, having failed on average between 2 and 3 prior immunosuppressive regimens and those patients receive ACTH as adjuvant therapy. We did not have accurate detailed data on duration of time between prior immunosuppressive therapies and initiation of ACTH as some patients were already on their treatment and some patients were on a reduced doses and some patients have stopped their treatment if this duration was short, some of the response could be attributed to a delay in response to prior agents. In addition, the data presented here reflect only short-term follow-up, most patients having 1 year of follow-up at the time of this report.

Given that 6 of the patients presented here has relapsed off therapy, the follow-up period is likely too short to label the remissions as sustained.

In previous reports of synthetic ACTH therapy Berg and Arnadottir, some patients have relapsed but responded to second courses of ACTH with good results.

The short duration of follow-up may also understate adverse events in this study, which thus far have been mild and mostly steroid like in presentation. Finally, our report does not address cost analysis of the various agents available to treat the nephrotic syndrome (**Rauen et al., 2009**).

These data also do not provide any further understanding of the mechanism of action by which ACTH ameliorates proteinuria in the nephrotic syndrome. Speculatively, its better performance in IMN than other causes of nephrotic syndrome might point to a target of action; eg, antibodies against the phospholipase A2 receptor. (**Ponticelli et al., 2006**).

However, a recent study using rats with passive Heymann nephritis, an animal model of membranous

nephropathy, proposes that ACTH may work at the melanocortin receptor MC1R in podocytes to reduce proteinuria, improve glomerular morphology, and reduce oxidative stress (**Beck et al., 2009**).

This finding suggests that ACTH should be equally, if not more, effective in podocytopathies such as MCD and FSGS than in IMN (**Lindskog et al., 2010**).

And this was evident in our study as the best results were in IMN show 41% having partial or complete remission then FSGS 28% show complete or partial remission then MCN 37% show partial or complete remission we use ACTH as adjuvant therapy in all cases of lupus nephritis stage III, IV and v as most patients were presented with rapidly progressive GN and we find that the usage of ACTH as adjuvant therapy show more response 69% than conventional therapy show 31%. the least effective results were in MPGN as only 17% show partial remission.

In our study we will compare between the use of ACTH as primary therapy and when used as adjuvant as add on therapy and other conventional therapies used in treatment of different glomerulonephritis.

Another item need to be addressed is the possibility of using increasing doses of ACTH in patients showing partial remission or limited or no response but this was not applicable in our study.

We also do not have a precise method of stopping ACTH either sudden stoppage or gradual withdrawal but most patients show sustained response without relapse if the period of therapy extend to one year.

The rate of complication is mild and tolerable and it is mainly the pigmentation with 36.8% in ACTH group and the incidence increase in combined therapy as regard hyperglycemia and hypokalemia.

Conclusion:

Synthetic ACTH can be used in treatment of proteinuric nephropathies as primary therapy specially in podocytopathies and in membranous nephropathy and as adjuvant therapy in lupus nephritis and in resistant cases after failure of other immunosuppressives.

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8/16/2015