Use of Mifepristone in a Hypercortisolemic Patient With End-Stage Renal Disease on Hemodialysis

Albert W. Coo, MD, FACE[1]; Rebecca Ray, FNP-C[2]

[1]Diabetes and Endocrine Associates, Privia Medical Group, Alexandria, VA; [2]Corcept Therapeutics, Menlo Park, CA

INTRODUCTION

- Establishing a diagnosis of hypercortisolism in a patient with chronic kidney disease (CKD) and end-stage renal disease (ESRD) can be challenging. Increased hypothalamic-pituitary-adrenal (HPA) axis activity may occur in these patients due to the inflammatory state of their CKD and stress from chronic dialysis.[1]
- Traditional laboratory tests (overnight 1-mg dexamethasone suppression test [ODST], late-night salivary cortisol [LNSC], serum cortisol, urinary free cortisol [UFC], and adrenocorticotropic hormone [ACTH]) used in assessing patients for hypercortisolism can render abnormal results in patients with renal failure, making diagnosis challenging
- UFC is not helpful in patients with a glomerular filtration rate (GFR) <60 mL/min because renal failure may produce falsely low results[2]
  - Furthermore, many patients with ESRD produce very little urine or are anuric, reducing the utility of the UFC test
- There are limited data available on treating patients with hypercortisolism on hemodialysis following the diagnosis of hypercortisolism
- To date, there are no published studies reporting the use of mifepristone (Korlym®, Corcept Therapeutics), a competitive glucocorticoid receptor antagonist, in patients with ESRD on hemodialysis and diagnosed with hypercortisolism
- Here we present a case of a patient with ESRD demonstrating the safe and efficacious long-term use (>4 years) of mifepristone

CASE HISTORY AND PRESENTATION

- A 67-year-old woman presented with a history of ESRD on hemodialysis since 2008 due to HIV-associated nephropathy and multiple comorbidities (type 2 diabetes mellitus [T2DM], hypertension, hyperlipidemia, obesity, hypothyroidism, tertiary hyperparathyroidism, herpes simplex virus, anemia, and depression) (**Table 1**)

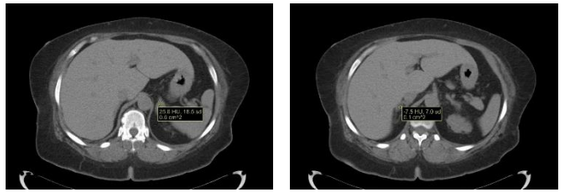
Table 1. Baseline Characteristics (2015)

Parameter	Value
Age (yrs)	67
Sex	Female
Weight (lbs)	198
BMI (kg/m^2)	36.2
Blood pressure (mmHg)	94/48 (on multiple medications)
HbA1c (%)	7.2
Daily insulin requirements	26 units Novolin 70/30
Renal parameters[a]	
GFR (>59 mL/min/1.73)	6.4
Creatinine (0.8-1.3 mg/dL)	7.6
Potassium (3.5-5 mmol/L)	4.8

[a]Normal ranges are given in parentheses.
BMI, body mass index; GFR, glomerular filtration rate; HbA1c, glycated hemoglobin.

- The patient was hospitalized in 2008 for the placement of a peritoneal dialysis catheter. Her abdominal CT showed incidentally found bilateral enlarged adrenal glands.
- After multiple testing over several years, ACTH-independent hypercortisolism was confirmed with ODST, LNSC, and adrenal imaging (CT images are presented in **Figure 1**). Because her ACTH levels were >20 pg/mL, a pituitary MRI with contrast was performed to rule out ACTH-dependent hypercortisolism. Due to anuria, 24-hour UFC was not conducted (**Table 2**).

Figure 1. Adrenal CT Scan 2010: Bilateral Adrenal Adenomas



Left Right

Table 2. Biochemical Diagnostic Testing and Imaging

Date	AM Cortisol[a] (<20 mg/dL)	ODST[a] (<1.8 mg/dL)	LNSC[a] (0.01-0.09 µg/dL)	ACTH[a] (10-50 pg/mL)	Imaging
2008 inpatient	37.7	18	N/A	22	Abdominal CT: bilateral adrenal gland enlargement
2010		4.3			Pituitary MRI with contrast: normal Adrenal CT: bilateral adrenal adenomas • Right: 1.8 cm low-density nodule consistent with myelolipoma; 7.5 HU • Left: 2.0 cm lipid-poor nodule; 25 HU
2013			0.221		
2014		5.8 with dexamethasone level 442 ng/dL			

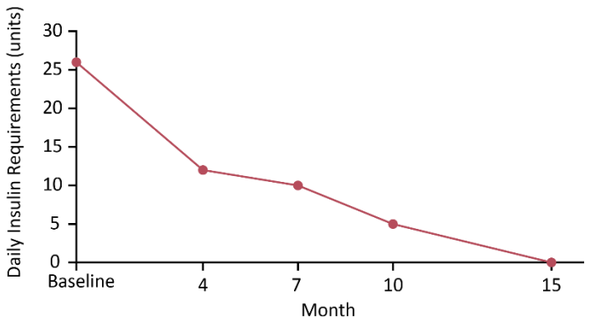
[a]Normal ranges are given in parentheses.
ACTH, adrenocorticotropic hormone; CT, computed tomography; LNSC, late-night salivary cortisol; MRI, magnetic resonance imaging; ODST, overnight 1-mg dexamethasone suppression test.

- Due to the patient's poor surgical candidacy and the lack of FDA-approved medical therapy to treat hypercortisolism in 2010, she was managed conservatively for 5 years with treatment of her underlying comorbidities
- In 2015, she was reevaluated (**Table 1**) and started on mifepristone 300 mg QD and titrated to the maximum dose for patients with renal impairment,[3] 600 mg QD, at Month 2
- Mifepristone dose and frequency were not adjusted to account for hemodialysis (scheduled 3 days/week) and medication was taken every day in the evening. Due to mifepristone being highly protein-bound, hemodialysis did not alter its efficacy.[3]

RESULTS WITH MIFEPRISTONE

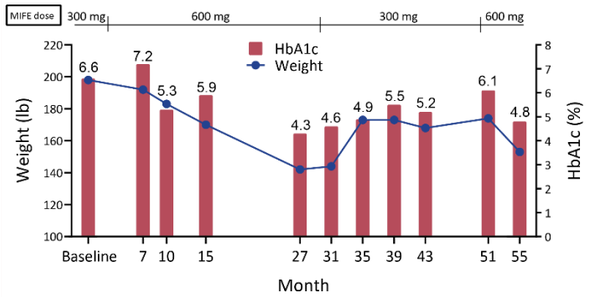
- Over 55 months of treatment with mifepristone, glycemic control improved, with all insulin discontinued at Month 15 (**Figure 2**)

Figure 2. Time to Discontinuation of Insulin



- Weight decreased from 198 to 153 lbs, HbA1c decreased from 6.6% to 4.8% (**Figure 3**), and BMI improved from 36.2 to 28.0 kg/m^2
  - Although HbA1c is not the best measure of glycemia in patients with ESRD due to the A1c test's underestimation of blood glucose levels, this was still monitored and improvements were seen
- One episode of hypokalemia (3.2 mmol/L) at Month 51 was treated with 10 meq daily KCl supplementation. Repeat potassium was 3.5 mmol/L and patient continued KCl 10 meq daily.
- HIV remained undetectable
- Blood pressure remained controlled throughout therapy with discontinuation of antihypertensive medication

Figure 3. Improvements in Weight and Glycemia



HbA1c, glycated hemoglobin, MIFE, mifepristone.

CONCLUSIONS

- Patients with ESRD present many diagnostic and treatment challenges:
  - Increased HPA axis activity from the inflammatory state of CKD and stress from chronic dialysis can produce false-positive results during the work-up for hypercortisolism
  - Anuria can prevent the utilization of traditional 24-hr UFC collections
- Data are limited on treatment approaches for patients with hypercortisolism with ESRD on hemodialysis
- This is the first presented case of a patient with ESRD on hemodialysis using mifepristone to control hypercortisolism
  - Efficacy was demonstrated through the resolution of hyperglycemia and hypertension, along with significant weight loss
  - Long-term safety of mifepristone was demonstrated by the lack of any serious adverse events over the 4+ years of treatment

REFERENCES

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DISCLOSURES

AWC: Consultant, Corcept Therapeutics.
RR: Employee, Corcept Therapeutics.

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