Improvement in Muscle Strength and Psychiatric Symptoms in a Patient With Persistent Cushing Disease Treated With Mifepristone

Tamer Yacoub, MD[1]; Kiruthi Palaniswamy, PharmD[2]

[1]Prima CARE, Fall River, MA, USA; [2]Corcept Therapeutics, Menlo Park, CA, USA

INTRODUCTION

- Transsphenoidal surgery (TSS) success rates for Cushing disease (CD) can vary greatly, allowing for the possibility of persistent hypercortisolism
  - In a recent multicenter study (n=230), only 41% of patients achieved remission of hypercortisolism after initial TSS[1]
- Neuropsychiatric disorders and proximal muscle weakness are common presentations of hypercortisolism[2]
  - Major depression is one of the most frequent and severe psychiatric disorders associated with hypercortisolism[3]
- Mifepristone (Korlym®, Corcept Therapeutics) is a competitive glucocorticoid receptor antagonist approved to treat patients with endogenous hypercortisolism of all etiologies
- We describe a 51-year-old woman with persistent hypercortisolism after unsuccessful TSS
  - Progressively worsening symptoms included severe muscle weakness, depression, and type 2 diabetes mellitus (T2DM) without complications
- Treatment with mifepristone was initiated, which led to substantial improvement in her muscular and psychiatric symptoms

CASE HISTORY AND PRESENTATION

- A 51-year-old woman referred from a rehabilitation facility presented for evaluation of weight gain (2017)
- Patient had a history of persistent hypercortisolism following TSS surgery and over time developed multiple, progressive symptoms and cushingoid features during a period of active disease (off treatment) (**Figure 1**)
- Patient became extremely depressed, requiring extensive pharmacologic treatment; she also experienced easy fatigability and severe insomnia

Figure 1. History of Hypercortisolism Progression

2007	2010	2015	2016	2017
• TSS for ACTH-secreting pituitary adenoma	• Persistent hypercortisolism – Uncontrolled on cabergoline – Controlled on ketoconazole	• Suicide attempt (history of bipolar disorder)	• Hospitalized due to muscle weakness and incontinence • Patient stopped ketoconazole and developed: – 80-lb weight gain – Worsening depression – Severe muscle weakness requiring rehabilitation (nursing care) – T2DM – Hyperlipidemia – Obstructive sleep apnea	• Physical examination revealed profoundly cushingoid features[a] • Patient became extremely depressed and experienced easy fatigability and severe insomnia • Developed osteopenia and hypercoagulable state

[a]Cushingoid features included: facial plethora; dorsal hump; 1-inch thick, pigmented abdominal striations; proximal muscle wasting; and abdominal obesity
ACTH, adrenocorticotropic hormone; T2DM, type 2 diabetes mellitus; TSS, transsphenoidal surgery.

WORKUP FOR HYPERCORTISOLISM

- Biochemical cortisol assessment and clinical examination results are shown in **Table 1**

Table 1. Biochemical and Clinical Examination

Parameter	Value
UFC (µg/24 hrs) [normal: <50]	95
Random AM cortisol (µg/mL) [normal: 20-30]	20
ACTH (pg/mL) [normal: 6-50]	34
HbA1c (%)	6.9
Weight (lbs)	245
BMI (kg/m^2)	40.8

ACTH, adrenocorticotropic hormone; BMI, body mass index; HbA1c, glycated hemoglobin; UFC, urinary free cortisol.

- Persistent hypercortisolism was indicated by the patient's clinical symptoms and cortisol assessment
- Additional diagnoses included:
  - T2DM without complications
  - Mixed dyslipidemia
  - Osteopenia
  - Depression
  - Hypercoagulable state
- Mifepristone was initiated at 300 mg/day and titrated up to a final dose of 900 mg/day
- Baseline biochemical and clinical assessment at start of mifepristone are shown in **Table 2**
- Patient was not placed on pharmacologic therapy for T2DM due to anticipated improvement with mifepristone treatment

Table 2. Baseline Biochemical and Clinical Examination at Mifepristone Initiation

Parameter	Value
HbA1c (%)	6.6
K+ (mEq/L)	5.2
Weight (lbs)	250.4
BMI (kg/m^2)	41.7

BMI, body mass index; HbA1c, glycated hemoglobin; K+, potassium levels.

RESULTS WITH MIFEPRISTONE

- At Month 4, the patient experienced minimal cortisol withdrawal symptoms; her depression and fatigue were still present and mifepristone was increased to 600 mg and spironolactone 50 mg was initiated
- By Month 5, she was able to move out of the rehabilitation facility
- By Month 6, she experienced a 23-lb weight loss (9.2%) (**Figure 2**) and improvement in psychiatric symptoms, allowing for discontinuation of several psychiatric medications (lurasidone, buspirone, trazodone, and lorazepam); sertraline dose was increased to 100 mg (**Figure 3**)

Figure 2. Patient Weight During Treatment

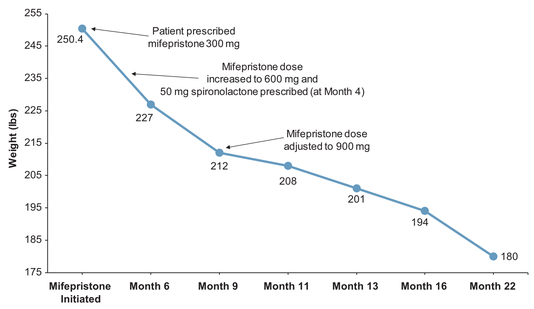


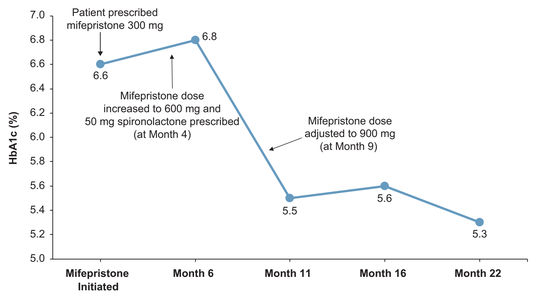
Figure 3. Psychiatric Medications During Treatment

Mifepristone Initiation	Month 6	Month 11
• Sertraline 50 mg daily • Oxcarbazepine 150 mg daily • Lurasidone 40 mg daily • Lithium carbonate 300 mg BID • Buspirone 5 mg TID • Lorazepam 0.5 mg BID as needed • Trazodone 100 mg daily	• Sertraline 100 mg daily • Oxcarbazepine 150 mg BID	• Sertraline 100 mg daily

BID, twice daily; TID, three times daily.

- By Month 13, her socialization increased and she was independent with daily activities
  - A 49-lb weight loss (19.6%) resulted in resolution of obstructive sleep apnea
- At Month 16, due to patient's weight loss, a physical examination allowed for detection of a thyroid nodule; patient underwent left hemithyroidectomy for Hurthle cell tumor and developed post-operative hypothyroidism (thyroid stimulating-hormone [TSH] 9.7 mIU/L)
- By Month 22, she had lost a total of 70.4 lbs (BMI 29.95 kg/m^2), and her psychiatric symptoms remained improved
- Her HbA1c levels decreased from 6.6% at initiation of mifepristone to 5.3% (**Figure 4**)

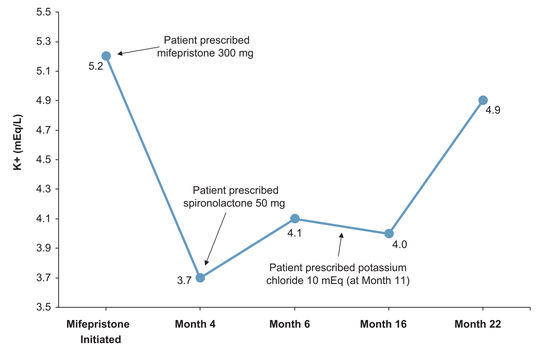
Figure 4. HbA1c Levels During Treatment



HbA1c, glycated hemoglobin.

- During mifepristone treatment, her potassium levels remained normal; however, spironolactone 50 mg and potassium chloride supplement 10 mEq were initiated as levels decreased (**Figure 5**)

Figure 5. Potassium Levels During Treatment



CONCLUSIONS

- This report details a patient with persistent CD who demonstrated marked clinical improvement in symptoms of hypercortisolism with mifepristone, including:
  - Psychiatric symptom improvement, with discontinuation of 6 out of 7 medications
  - Resolution of musculoskeletal weakness, such that stay in rehabilitation facility no longer required
  - Improvement in HbA1c levels from 6.6% to 5.3% during treatment
  - Weight loss of 70.4 lbs (28.1%) from baseline and reduction in BMI from 41.7 to 29.95 kg/m^2 (28.18%); patient went from Class III obesity at mifepristone initiation to overweight according to her current BMI categorization
  - Complete resolution of obstructive sleep apnea (no longer required CPAP machine use)
- Mifepristone treatment was well tolerated with the exception of initial generalized fatigue
  - The patient's potassium levels remained within normal range; however, spironolactone and potassium chloride supplements were provided as her potassium levels trended downward
- These results suggest that mifepristone can be useful in treating patients with persistent hypercortisolism following unsuccessful surgical treatment

REFERENCES

1. Geer EB, et al. *Endocr Pract.* 2017;23(8):962-70.
2. Nieman LK, et al. *J Clin Endocrinol Metab.* 2008;93(5):1526-40.
3. Pivonello R, et al. *Front Neurosci.* 2015;9:129

ACKNOWLEDGMENTS

Funding for editorial, design, and production support for this poster was provided by Corcept Therapeutics to MedVal Scientific Information Services, LLC, Princeton, NJ. The authors developed and revised the poster content and provided approval of the final version.

DISCLOSURES

TY: Consultant, Aventis, Novo Nordisk; Speaker, Aegerion, Aventis, Boehringer Ingelheim, Corcept Therapeutics, Eli Lilly, Novo Nordisk, Merck, Shire; Research support, Eli Lilly.

KP: Employee, Corcept Therapeutics

Presented at the American Association of Clinical Endocrinologists Annual Congress, April 24-28, 2019, Los Angeles, CA