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Mifepristone Re-established Glycemic Control in a Cushing's Syndrome Patient That Relapsed After a 21-Month Interruption

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ABSTRACT

Objective: Mifepristone (MIFE, Korlym®, Corcept Therapeutics), a glucocorticoid receptor antagonist, was approved for the treatment of patients with Cushing's syndrome (CS) based on SEISMIC, an open-label, multicenter study. Herein we report details on a study patient who achieved significant glycemic control while on MIFE for 31 months, relapsed when MIFE therapy was interrupted for 21 months, and improved substantially when MIFE was reinstated.

Results or Case Presentation: A 46 y/o man with CS and a failed transsphenoidal surgery for an ACTH-secreting adenoma participated in SEISMIC and a study extension for a total of 31 months. MIFE was titrated over 2.5 months to a stable dose of 600 mg/d (300-900 mg/d range). Improvements in glycemic control were observed within the first few weeks of starting MIFE. After 6 months, fasting blood glucose decreased from 148 to 79 mg/dL, HbA1c decreased from 9.3% to 6.9%, and fasting insulin decreased from 186 to 168 µUnits/mL. Patient continued participation for an additional 25 months. With interruption in MIFE therapy post-study completion, patient's hyperglycemia relapsed and worsened. Attempts to control it with a concomitant combination of antidiabetic medications (metformin 1 g, glimepiride 4 mg BID, Levemir, Novolog) were unsuccessful. Fasting blood glucose worsened to 219 mg/dL and HbA1c increased to 11.1% during this 21-month interval without MIFE. MIFE was restarted and titrated to a stable dose of 900 mg/d within 3 months. After 3 months of therapy, fasting blood glucose decreased from 219 to 108 mg/dL and HbA1c decreased from 11.1% to 7.5%. An attempt to further improve glycemic control by increasing the dose to 1200 mg/d was not tolerated. The patient maintained glycemic control on 900 mg/d for another 6 months (fasting blood glucose of 105 mg/dL, HbA1c 8.0%) until he elected to undergo a second transsphenoidal surgery to remove the residual pituitary adenoma.

Conclusion: This case highlights the contributions of MIFE in improving glucose parameters driven by hypercortisolemia and reinforces the importance of maintenance therapy. This patient initially achieved glycemic control while on MIFE but experienced significant deterioration after interruption of therapy. Conventional antidiabetic medications were ineffective in this patient with CS and comorbid diabetes mellitus. The reintroduction of MIFE 21 months later re-established glycemic control.

INTRODUCTION

- Cushing's syndrome (CS), a multisystemic endocrine disorder resulting from chronic exposure to elevated cortisol, is associated with substantial metabolic dysfunction (eg, weight gain, hypertension, insulin resistance, and diabetes mellitus) and increased mortality[1,2]
- In patients with Cushing's disease (CD)—the most common form of endogenous CS—initial pituitary surgical success rates range from 65% to 90% when performed by an experienced surgeon[3,4]
- The 5-year recurrence rate for hypercortisolism among CD patients who achieve immediate surgical remission is 26%[5]
- Therefore, additional treatments are often needed to reduce the clinical symptoms of hypercortisolism, including metabolic derangements
- The glucocorticoid receptor antagonist mifepristone is approved for patients with all forms of CS who have diabetes or glucose intolerance and have failed or are not candidates for surgery
- The SEISMIC study was a 24-week, open-label, multicenter, phase 3 study of mifepristone administered as a single daily oral dose[6]
  - In addition to improvement in glucose parameters and hypertension, significant clinical improvement was noted in 87% of patients treated with mifepristone[6]
- We describe the case of a patient who had substantial improvement in glycemic control while treated with mifepristone therapy during the SEISMIC and long-term extension studies; this patient's glycemic control deteriorated during a period after study completion when treatment was interrupted

History of present illness

- 46-year-old man with a history of ongoing CD (post-transsphenoidal surgery [TSS])
  - Elevated baseline urinary free cortisol (347.8 nmol/24 hr), serum cortisol (671 nmol/L), salivary cortisol (5.2 nmol/L), and adrenocorticotropin hormone (63 ng/L)
- Multiple comorbidities
  - Obesity
  - Diabetes mellitus
  - Hypertension
  - Hyperlipidemia
  - Asthma
  - Obstructive sleep apnea
  - Back pain, knee pain
  - Edema
- Concomitant medications are listed in **Table 1**

Table 1. Concomitant medications prior to mifepristone treatment (~2009)

Medications	Dose
Antidiabetes	
Glimepiride	4 mg twice daily
Insulin glargine (Lantus)	24 units daily
Metformin ER	1000 mg twice daily
Antihypertensives	
Amlodipine	10 mg twice daily
Atenolol	50 mg twice daily
Lisinopril	20 mg daily
Furosemide	40 mg daily
Other	
Albuterol	90 µg inhalation as needed
Rosuvastatin	5 mg daily
KCL SR	10 mEq daily
Fluticasone/salmeterol	50/500 µg inhalation as needed
Hydrocodone/acetaminophen	10/500 mg every 6 hrs as needed for back pain

TREATMENT COURSE

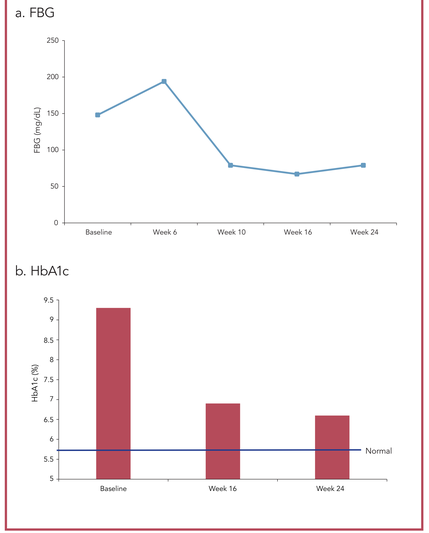
Mifepristone

- Patient completed SEISMIC trial and long-term extension (LTE) trial (**Figure 1**) for a total duration of ~31 months

Figure 1. SEISMIC and long-term extension study design

- Mifepristone was initiated at 300 mg/day and titrated over 2.5 months to a stable dose of 600 mg/day (range 300-900 mg/day)
- After 6 months of treatment in SEISMIC, improvements in fasting blood glucose (FBG) (148 to 79 mg/dL) and HbA1c were observed (9.3% to 6.6%) (**Figure 2**)
  - Fasting insulin decreased from 186 to 168 µUnits/mL at the end of SEISMIC

Figure 2. Glycemic parameters over the course of mifepristone treatment during SEISMIC

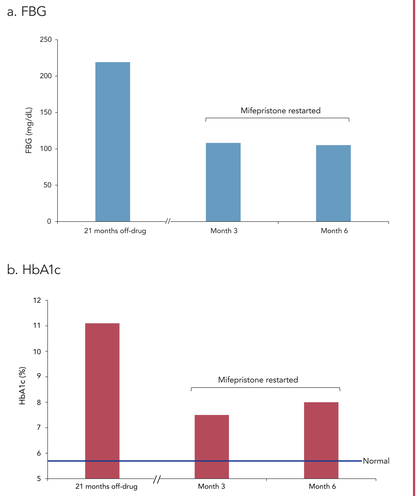


- BP was well controlled during the 6-month study and LTE (baseline, 116/70 mm/Hg; Week 24, 116/79 mm/Hg; Month 24, 130/80 mm/Hg)
- Dose adjustments to concomitant medications during the 6-month SEISMIC study included increasing furosemide (80 mg twice daily) and KCL (20 mEq twice daily) and decreasing amlodipine (5 mg twice daily)
- During the LTE, furosemide (80 mg) was used as needed, rosuvastatin was increased (10 mg daily), and insulin therapy changes were made including discontinuing Lantus (insulin glargine) and subsequently starting Novolog (insulin aspart) and Levemir (insulin detemir)
- Mifepristone was well tolerated overall by the patient during SEISMIC and LTE; most adverse events were mild or moderate in nature with the exception of 4+ peripheral edema

Interruption of mifepristone

- Post-study completion, the patient's hyperglycemia worsened when treatment with mifepristone was interrupted for 21 months (**Figure 3**)
  - Hyperglycemia was resistant to multiple antidiabetic medications including metformin, glimepiride, Levemir (insulin detemir), and Novolog (insulin aspart)

Figure 3. Glycemic parameters post-SEISMIC and long-term extension study completion



Mifepristone restarted

- Mifepristone was restarted and titrated to 900 mg/day over 3 months
- After 3 months of mifepristone treatment, FBG and HbA1c decreased, and improvement was maintained during 6 additional months of treatment (**Figure 3**)

Surgical intervention

- Patient underwent second TSS surgery (July 31, 2014); mifepristone was discontinued 1 month prior to surgery for pre-operative evaluation
- 8 months after surgery, insulin was discontinued and glimepiride dose was reduced by half
  - Patient's weight decreased by 31 kg
  - FBG decreased from 105 to 84 mg/dL and HbA1c decreased from 8.0% to 6.6%

SUMMARY AND CONCLUSIONS

- CS is associated with substantial metabolic dysfunction contributing to increased cardiovascular risk and elevated mortality
- This report details a patient with CD who was treated with mifepristone for 31 months in the SEISMIC and LTE clinical studies, during which substantial improvement in glycemic control was observed
- The patient's glycemic control deteriorated following a 21-month interruption of mifepristone treatment despite taking several antidiabetic medications, including insulin
- Reintroduction of mifepristone re-established glycemic control and improved the patient's candidacy for additional surgery, thus highlighting the importance of maintenance treatment for the ongoing symptoms of CS
- Mifepristone is a useful treatment option for long-term control of the clinical symptoms of hypercortisolism

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DISCLOSURES

TWF has no potential conflicts of interest to disclose.

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