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Improved Response to Octreotide LAR for Ectopic Cushing's Syndrome During Mifepristone Therapy: a Case Study

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ABSTRACT

Objectives: Ectopic ACTH syndrome (EAS) is often caused by a malignant neuroendocrine tumor expressing functional somatostatin receptors (sst). Medical therapies targeting these receptors are used to reduce ACTH secretion and control the hypercortisolism when the tumor is unresectable. However, glucocorticoid-induced down-regulation of sst can lead to lack of efficacy or loss of response.

We describe a patient with EAS poorly responsive to octreotide LAR (OCT) therapy, a potent sst agonist, prior to the addition of mifepristone (MIFE, Korlym®, Corcept Therapeutics), a glucocorticoid receptor (GR) antagonist.

Case Presentation: A 30 YO man with EAS due to a metastatic pancreatic neuroendocrine tumor presented for enrollment in the 24-wk Phase III MIFE study (SEISMIC).

3mo prior to SEISMIC, OCT 30mg/mo was initiated with modest effect on ACTH (517 to 345 pg/mL). At baseline, cortisol remained high (serum cortisol (SC) 46 µg/dL, UFC 2250 µg/d, late-night salivary 1.71 µg/dL). His cushingoid features (fat pads, moon facies, purple striae, muscle weakness) did not improve.

In SEISMIC, MIFE 300mg was initiated with OCT 30mg/mo and eventually titrated to 1200mg.

As MIFE is a competitive GR antagonist, circulating cortisol and ACTH levels might rise during therapy in the EAS. However, it was observed that UFC and ACTH fell below baseline levels in this patient. UFC appeared to decline progressively as the dose was increased. ACTH fluctuated but remained below baseline levels. Upon MIFE interruption, both values rebounded beyond the baseline. Long term effects could not be analyzed as OCT was halted 2mo after MIFE reinstatement in the extension phase.

The patient's cushingoid features resolved and comorbidities improved during SEISMIC independent of ACTH and cortisol fluctuations. MIFE was well tolerated; one event of reported fatigue led to a reduction in MIFE dose.

Discussion: Prior studies have found down-regulation of sst in tumors causing EAS and up-regulation during MIFE treatment, which enabled tumor localization with [^{111}In]-pentotreotide scintigraphy. The marked reduction of ACTH and cortisol when MIFE was added to OCT suggests that MIFE increased the efficacy of OCT by upregulating tumor sst receptors. We cannot exclude a delayed response to OCT alone; however, the abrupt rise in ACTH and cortisol 2 weeks after stopping MIFE is compelling evidence of a direct but non-sustained MIFE effect.

Conclusion: We suggest a potential synergistic effect of MIFE in combination with OCT in EAS through up-regulation of tumor sst. The ability of MIFE to augment OCT efficacy in EAS deserves further study.

INTRODUCTION

- Ectopic adrenocorticotropin hormone syndrome (EAS) (non-pituitary) accounts for approximately 10% to 20% of all adrenocorticotropin hormone (ACTH)-dependent Cushing's syndrome (CS)[1,2]
- Although localized primarily in the lungs, consisting of mainly bronchial carcinoids and small cell lung carcinoma, EAS is also associated with a variety of other tumor types, including medullary thyroid carcinomas, gastrointestinal neuroendocrine tumors (NETs), and thymic carcinoids[2-4]
- Medical therapy for EAS may be needed when the tumor is unresectable or in the event that the tumor source cannot be initially localized, which occurs in 12% to 19% of patients with EAS[3,4]
- EAS-associated tumors express somatostatin receptors (sst), enabling the use of somatostatin analogs for tumor localization and targeted treatment to reduce ACTH secretion and control hypercortisolism[5,6]; however, the success rates vary[5,7]
- Prior in-vitro and in-vivo studies have shown a glucocorticoid-dependent down-regulation of sst in EAS-associated tumors and up-regulation during treatment with the glucocorticoid receptor (GR) antagonist mifepristone[8-11]
  - The addition of mifepristone in 2 patients with EAS resulted in post-treatment changes in sst expression, enabling subsequent positive tumor localization with [^{111}In]pentetreotide scintigraphy (Octreoscan)[11]
- Mifepristone (Korlym®, Corcept Therapeutics) is approved for patients with all forms of CS who have diabetes or glucose intolerance and have failed or are not candidates for surgery
- In addition to improvement in diabetes and/or hypertension, significant clinical improvement was noted in 87% of patients with CS treated with mifepristone in the 24-week, open-label, multicenter Study of the Efficacy and Safety of Mifepristone in the Treatment of Endogenous Cushing's Syndrome (SEISMIC) trial[12]
  - Because of the GR antagonism with mifepristone treatment, ACTH and cortisol levels can remain elevated or further increase
- We describe a patient with EAS who had increased therapeutic response to octreotide long-acting release (LAR) therapy, a potent sst subtype 2 agonist, following the addition of mifepristone during the SEISMIC trial

HISTORY OF PRESENT ILLNESS

- A 30-year-old male with EAS subsequent to metastatic pancreatic NET presented for enrollment in the 24-week, phase III SEISMIC study
- Prior treatment history included surgical resection, ketoconazole, and chemotherapy, which were not successful in maintaining resolution of hypercortisolism
- 3 months prior to enrollment in SEISMIC, octreotide LAR was initiated and increased to 30 mg every month (maximum dose)
  - Partial biochemical response in plasma ACTH (decreased from 517 to 345 pg/mL) was noted with octreotide LAR, but clinical signs of CS remained
- Cushingoid features (eg, fat pads, moon facies, purple striae, muscle weakness), hypertension, diabetes, and severe depression (Beck Depression Inventory-II [BDI-II] score 32) were present at SEISMIC baseline
- Cortisol levels were elevated (serum cortisol 46 µg/dL, urinary free cortisol [UFC] 2250 µg/d, late-night salivary cortisol 1.71 µg/dL) at study baseline

TREATMENT COURSE

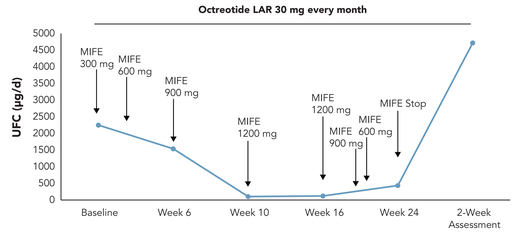
- Patient enrolled in SEISMIC trial and subsequent long-term extension (LTE) trial (**Figure 1**)

Figure 1. SEISMIC and long-term extension study design

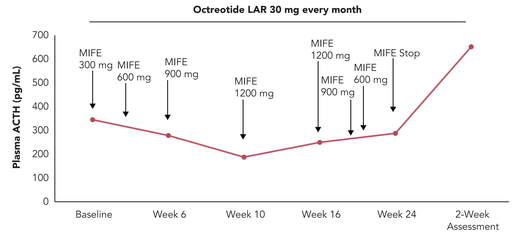
- Mifepristone was initiated at 300 mg and titrated to 1200 mg
  - Octreotide LAR (30 mg every month) was continued throughout the duration of SEISMIC
- During 24 weeks of mifepristone and octreotide LAR treatment, UFC and ACTH levels declined to below baseline levels (**Figure 2**)

Figure 2. Cortisol and ACTH concentrations during SEISMIC

a. UFC



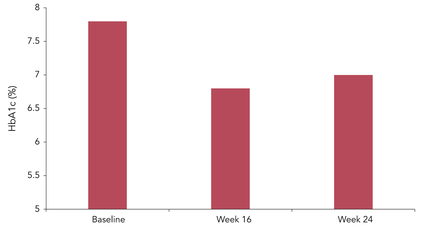
b. Plasma ACTH



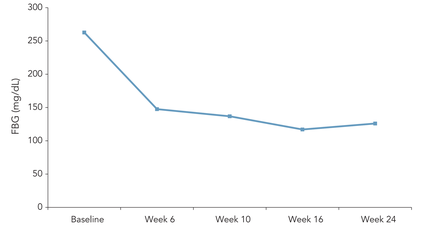
- Improvement in fasting blood glucose (FBG) and hemoglobin A1c (HbA1c) was also observed (**Figure 3**)
  - Insulin therapy was discontinued by week 4

Figure 3. Glycemic parameters during SEISMIC

a. HbA1c



b. FBG



- By week 12, cushingoid features resolved
- By week 20, the patient reported severe fatigue, resulting in reduction of mifepristone dose to 900 mg and later to 600 mg daily
  - Patient reported feeling better upon reduction of mifepristone dose
- Patient's BDI-II depression score improved from 32 (severe) to 12 (minimal depression) by week 24
- At week 24, the patient was taken off mifepristone (per study protocol), followed by a 6-week off-drug evaluation period
- Patient's UFC and ACTH began to rise following discontinuation of mifepristone, despite ongoing octreotide LAR (**Figure 2**)
  - After 2 weeks, UFC and ACTH increased to 4716 µg/d and 652 pg/ml, respectively
- 12 days after mifepristone was stopped, clinical signs and symptoms of CS returned
- Patient elected to enroll in LTE study of mifepristone; octreotide LAR was discontinued 2 months later due to the development of diarrhea

SUMMARY AND CONCLUSIONS

- Prior studies have shown glucocorticoid-induced down-regulation of sst in EAS-associated tumors and up-regulation during mifepristone treatment
- In the case presented here, the addition of mifepristone to ongoing octreotide LAR led to a substantial reduction in ACTH and cortisol in a patient with previously resistant EAS; mifepristone was generally well-tolerated
- Discontinuation of mifepristone after 24 weeks of treatment resulted in an abrupt rise in cortisol and ACTH, despite ongoing octreotide LAR treatment
- Mifepristone may provide synergistic efficacy when administered in combination with octreotide in patients with EAS, most likely via up-regulation of sst previously down-regulated by hypercortisolemia

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DISCLOSURES

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RJA is a consultant for Corcept Therapeutics.

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