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IMPROVING GLYCEMIC CONTROL WITH MIFEPRISTONE IN CUSHING SYNDROME PATIENTS MAY LEAD TO SIGNIFICANT WEIGHT-LOSS

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ABSTRACT

Background: Obesity is a prominent feature of Cushing syndrome (CS), with 70%-80% of patients overweight or obese. Most patients seek advice due to rapid weight gain. Prolonged exposure to hypercortisolemia leads to insulin resistance, hyperglycemia, weight gain, and cardiovascular complications. Medical therapy is usually aimed at reducing the degree of hypercortisolemia. However, durable normocortisolemia is difficult to achieve with steroidogenesis inhibitors and somatostatin analogs, and does not always translate into meaningful improvements in glycemic control or weight-loss. Glucocorticoid receptor antagonism with mifepristone (MIFE, Korlym®, Corcept Therapeutics) offers an alternative mechanism of action. In the pivotal SEISMIC trial (n=46), average weight-loss was 5.7%, mean FPG decreased from 149 to 104 mg/dL and HbA1c from 7.43% to 6.29% despite increases in cortisol levels. We present four CS cases with weight-loss ≥8% on MIFE therapy.

Case Presentations: Case 1: 37-yo woman (adrenal CS) lost 30 lbs (352 to 322 lbs; 8.5%) after 3 mo on MIFE 600 mg/d. There was a significant decrease in HbA1c (7.3% to 6.4%) and FBG (206 to 112 mg/dL) without changes in antidiabetic medications (sitagliptin 100 mg, metformin 1000 mg/d). **Case 2:** 46-yo woman (pituitary CS) lost 40 lbs (258 to 218 lbs; 15.5%) after 11 mo on MIFE 600 mg/d. Both HbA1c (9.0% to 6.5%) and FBG (247 to 136 mg/dL) decreased, while Levemir (54 IU/d), Humalog (24 IU TID), and metformin (1000 mg/d) were stopped, and linagliptin (5 mg/d) was continued. **Case 3:** 55-yo woman (pituitary CS) lost 45 lbs (220 to 175 lbs; 20%) after 9 mo on MIFE 600 mg/d. Both HbA1c (7.5% to 6.6%) and FBG (153 to 129 mg/dL) decreased without changes in antidiabetic medications (sitagliptin 100 mg/d). **Case 4:** 45-yo woman (pituitary CS) lost 50 lbs (178 to 128 lbs; 28%) after 23 mo on MIFE 1200 mg/d. Patient has had T1DM since 25 yo and is on an insulin pump (lispro). Both HbA1c (9.9% to 7.3%) and FBG (300 to 110 mg/dL) decreased, along with the insulin daily requirement.

Conclusion: These cases illustrate a significant weight-loss in parallel with a significant improvement in glycemic control by treatment with a glucocorticoid receptor antagonist (MIFE) in patients with DM. In all cases, there was no intensification of antidiabetic regimen, and the weight-loss was greater than previously reported in SEISMIC. Further research is needed to understand the metabolic benefits of long-term treatment with MIFE in patients with CS.

INTRODUCTION

- Obesity is a prominent feature of Cushing syndrome (70%-80%)[1]
- Insulin resistance, hyperglycemia, and weight gain are consequences of hypercortisolism and often lead to cardiovascular complications[2]
- Medical therapy in CS with steroidogenesis inhibitors or somatostatin analogs is directed at reducing cortisol levels but does not always result in clinical improvements in diabetes and weight-loss[3,4]
- Conversely, competitively antagonizing the glucocorticoid receptor (GR) with mifepristone (Korlym®, Corcept Therapeutics) therapy to inhibit cortisol activity has been shown to decrease insulin resistance, hyperglycemia, and weight in CS[5-7]

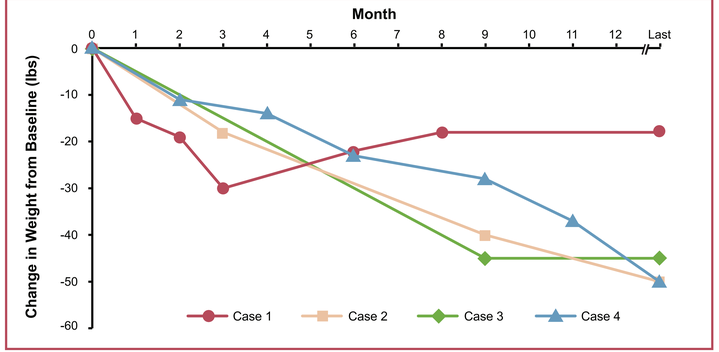
CASE PRESENTATIONS

Table 1. Baseline Characteristics and Treatment with Mifepristone

Baseline Characteristics	Case 1	Case 2	Case 3	Case 4
Age/Sex	37/F	46/F	55/F	45/F
Etiology	Adrenal	Pituitary	Pituitary	Pituitary
Weight (lbs)	352	258	220	178
FBG (mg/dL)	206	247	153	300
HbA1c (%)	7.3	9.0	7.5	9.9
Antidiabetic medications	Sitagliptin 100 mg Metformin 1000 mg/d	Levemir 54 IU/d Humalog 24 IU TID Linagliptin 5 mg/d Metformin 1000 mg/d	Sitagliptin 100 mg QD	Lispro insulin pump
Mifepristone Treatment				
Duration of mifepristone treatment	9 mo	12 mo	36 mo	26 mo
Final dose	900 mg/d	1200 mg/d	600 mg/d	1200 mg/d

F, female; FBG, fasting blood glucose; HbA1c, glycated hemoglobin; TID, 3x/day; QD, once a day.

Figure 1. Change in Weight



	Baseline (lbs)	Last Follow up (lbs)
Case 1	352	334
Case 2	258	208
Case 3	220	175
Case 4	178	128

Figure 2. Change in Glycated Hemoglobin (HbA1c)

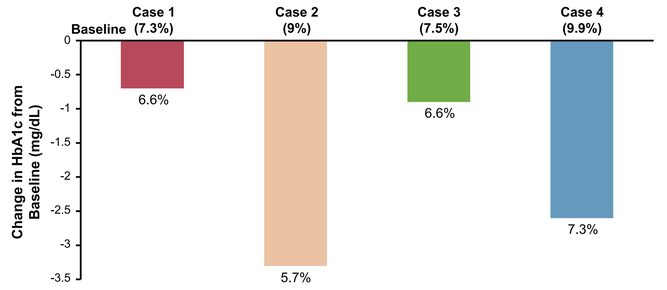
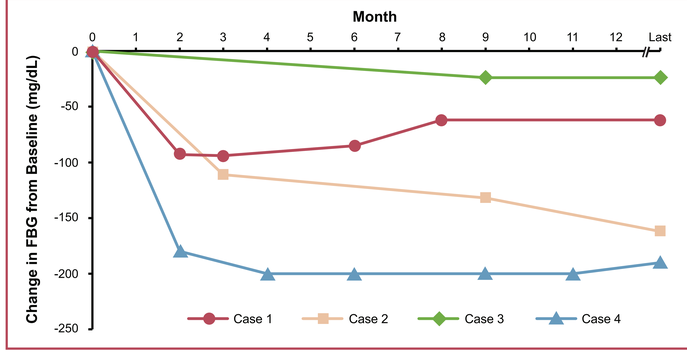


Figure 3. Change in Fasting Blood Glucose (FBG)



	Baseline (mg/dL)	Last Follow up (mg/dL)
Case 1	206	144
Case 2	247	85
Case 3	153	129
Case 4	300	110

DISCUSSION

- Clinically meaningful weight loss achieved during a 24-week study of mifepristone (SEISMIC) for CS (7.7%; 16.9 lbs) persisted for an additional 2 years in patients who remained on therapy[5,6]
- Significant decreases in average FPG (149.0 to 104.7 mg/dL) and average HbA1c (7.43 to 6.29%) were also observed in SEISMIC accompanied by reductions in antidiabetic medications in 7 out of 15 patients[5]
- An analysis by Wallia et al[7] suggested that rapid improvement in insulin sensitivity from a direct effect of glucocorticoid receptor antagonism is responsible for early weight loss
- Our cases demonstrate that substantial improvement in glycemic control and weight in patients with both type 1 and type 2 diabetes mellitus can be attained using mifepristone in CS

CONCLUSION

In patients with Cushing syndrome, treatment with a competitive glucocorticoid antagonist, mifepristone, can have a profound effect on glycemic control and weight loss. Further research is needed to determine how these metabolic benefits will impact cardiovascular morbidity and mortality.

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DISCLOSURES

AGI, NGG, and GSW: Served as consultants to Corcept Therapeutics.

JGO: Speaker for Corcept Therapeutics.

TCJ: Nothing to disclose.

JJS: Employee of Corcept Therapeutics.

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