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MIFEPRISTONE THERAPY SIGNIFICANTLY IMPROVED INSULIN RESISTANCE, GLYCEMIC CONTROL, AND WEIGHT LOSS IN A PATIENT WITH CUSHING DISEASE PREVIOUSLY TREATED WITH PASIREOTIDE

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ABSTRACT

Objective: Hypercortisolemia causes insulin resistance leading to hyperglycemia, hyperinsulinemia, and ultimately type 2 diabetes (T2DM) with increased cardiovascular morbidity and mortality. Patients with Cushing disease (CD) who are not surgical candidates or for whom surgery has failed may be treated with the somatostatin (SST) analog pasireotide (PASI, Signifor®, Novartis) to lower ACTH and cortisol production. However, SST analogs directly inhibit insulin secretion from pancreatic beta cells. Consequently hyperglycemia is a major factor limiting the use of PASI in patients with CD. In contrast, treatment with mifepristone (MIFE, Korlym®, Corcept Therapeutics), a competitive glucocorticoid receptor antagonist, has been shown to reduce hyperglycemia in patients with Cushing syndrome with a concomitant reduction/elimination of antidiabetic medications. To our knowledge this will be the first published case report on the effects of switching a patient with CD with hyperglycemia from PASI to MIFE.

Case Presentation and Results: A 46 yo woman with CD and a failed transsphenoidal surgery on PASI treatment (0.9 mg injection BID) for 14 months had poorly controlled T2DM (A1C 9.0%, FBG 248 mg/mL) despite treatment with several antidiabetic meds (Levemir [insulin detemir] 54 U QD, Humalog [insulin lispro] 24 U TID, Tradjenta [linagliptin] 5 mg QD and metformin 1000 mg/d). Despite a 5 lb loss of weight while on PASI, she still had a cushingoid appearance and weighed 258 lbs when she switched to MIFE. After 11 months of therapy with MIFE (300 mg QD titrated to 600 mg QD), glycemic control greatly improved (A1C 6.5%, FBG 136 mg/mL, fasting insulin 4.8 mU/L) on linagliptin alone. Hypokalemia was managed with spironolactone 50 mg BID. The patient reported a significant change in cushingoid appearance with a 40 lb weight loss and is no longer depressed.

Conclusion: Switching a patient with CD with uncontrolled hyperglycemia and T2DM from pasireotide to mifepristone led to a profound decrease in hyperglycemia along with a concomitant elimination of most antidiabetic medications, including exogenous insulin. Eliminating insulin injections along with a reduction of weight and improved appearance was life-altering for this patient

INTRODUCTION

- Hypercortisolemia causes insulin resistance, often leading to hyperglycemia and type 2 diabetes, with a concomitant increase in cardiovascular morbidity and mortality[1]
- Medical therapy in patients with persistent Cushing disease (CD) have generally targeted reducing circulating levels of cortisol as measured by urinary free cortisol (UFC)[2]
- Pasireotide (Signifor®, Novartis Pharmaceuticals), a somatostatin analog (SST), has been shown to lower adrenocorticotropic hormone (ACTH) and cortisol production but is limited by consequent hyperglycemia, likely through direct inhibition of insulin secretion, which is a class effect of SSTs[3]
- Mifepristone (Korlym®, Corcept Therapeutics), a glucocorticoid receptor (GR) competitive antagonist, is an alternative to treating cortisol levels by modulating cortisol activity and has been shown to improve hyperglycemia in patients with Cushing syndrome, including those with CD[4]

HYPOTHESIS

- Switching medical therapy from treatment directed at lowering cortisol levels (pasireotide) to treatment directed at inhibiting cortisol activity (mifepristone) may lead to clinical improvements in CD patients with persistent hypercortisolemia and hyperglycemia

Table 1. Demographic and Laboratory Results Before Mifepristone Treatment

Parameter	
Age, years	46
Gender	Female
Weight, lbs	258
Previous interventions	2x failed transsphenoidal surgeries Gamma knife radiation 14 months of pasireotide 0.9 mg SC BID
Urinary free cortisol	120 µg/24 hrs
ACTH	61.7 pg/mL

ACTH, adrenocorticotropic hormone.

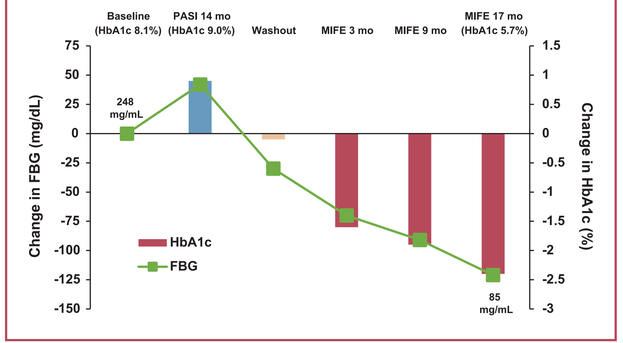
Table 2. Glucose Control Before and After Mifepristone Treatment

Parameter	Baseline With Pasireotide	With Mifepristone
HbA1c	9.0%	5.7%
Fasting blood glucose	248 mg/mL	85 mg/mL
Antidiabetic medications	Insulin detemir (Levemir) 54 units QD	Discontinued
	Insulin lispro (Humalog) 24 units TID	Discontinued
	Linagliptin (Tradjenta) 5 mg QD	
	Metformin 1000 mg/d	Discontinued

HbA1c, glycated hemoglobin.

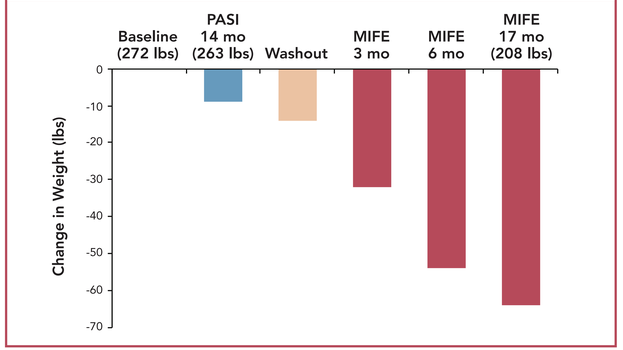
- Patient was started on mifepristone 300 mg QD and was titrated to 600 mg QD in 2 weeks
- Patient was maintained on 600 mg QD for 11 months and then titrated to 1200 mg QD to seek further improvements
- Notable clinical changes on mifepristone:
  - Patient no longer depressed by month 11 of mifepristone
  - Patient no longer required a cane for ambulation by month 11 of mifepristone
  - Steady decrease in FBG to 85 mg/mL and HbA1c to 5.7% by month 17 of mifepristone (**Figure 1**)
  - Steady decrease in weight to 208 lbs by month 17 of mifepristone (**Figure 2**)

Figure 1. Changes in FBG and HbA1c



FBG, fasting blood glucose; HbA1c, glycated hemoglobin; MIFE, mifepristone; PASI, pasireotide.

Figure 2. Changes in Weight



MIFE, mifepristone; PASI, pasireotide.

SAFETY

- Low potassium and edema after 2 weeks of mifepristone was treated by adding spironolactone (50 mg BID)
- Insulin was reduced by 50% when mifepristone was started, and insulin was stopped completely after 4 months of treatment with mifepristone
- Nausea was mild and resolved within 1 month

SUMMARY

- Switching to mifepristone therapy (600 mg QD for 11 months):
  - Greatly improved glycemic control (HbA1c 6.5%, FBG 136 mg/mL, fasting insulin 4.8 mU/L), with concomitant discontinuation of insulin and metformin
  - Led to significant weight loss (40 lbs) with loss of cushingoid appearance and an improvement in strength to where the patient no longer needed a cane
  - Patient reported that she was no longer depressed and has maintained a normal mood
- Increasing mifepristone dose (to 1200 mg QD for an additional 6 months):
  - Further improved glycemic control (HbA1c 5.7%, FBG 85 mg/mL)
  - Led to additional weight loss (to 208 lbs)

CONCLUSIONS

- Switching medical therapy in persistent CD from a treatment directed at lowering cortisol levels to a treatment directed at reducing cortisol activity can lead to a profound improvement in hyperglycemia, allowing the discontinuation of almost all antidiabetic medications
- In this case, discontinuation of insulin injections, a significant loss of weight, and increased strength with improved appearance and mobility provided a profound improvement in the patient's quality of life

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DISCLOSURES

JGO: Speaker, Corcept Therapeutics.
JJS: Employee, Corcept Therapeutics.

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