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MIFEPRISTONE REDUCED U500 INSULIN USAGE IN A PATIENT WITH CUSHING DISEASE AND NORMALIZED CONCOMITANT FATTY LIVER DISEASE AND RETINOPATHY

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ABSTRACT

Objective: Insulin resistance and type 2 diabetes mellitus (T2DM) are hallmarks of endogenous Cushing disease (CD). In some cases, T2DM is so severe it requires large doses of insulin that can only be given by using concentrated insulin (Humulin® R U500, Lilly). Mifepristone (MIFE, Korlym®, Corcept Therapeutics) is a competitive glucocorticoid receptor (GR) antagonist indicated for treating hyperglycemia secondary to hypercortisolism in patients with endogenous Cushing syndrome (CS). It has been shown to improve insulin sensitivity and reduce the need for insulin in controlling hyperglycemia. To our knowledge, this will be the first reported case of using mifepristone to decrease usage of high dose (U500) insulin to control severe T2DM in a patient with Cushing disease leading to resolution of fatty liver disease and normalization of liver enzymes.

Results or Case Presentation: A 40 yo woman with a 12 y history of CD (relapses from 2X TSS + γ-knife in 2003 & 2009 and an unsuccessful bilateral adrenalectomy [BLA] in 2012) presented with uncontrolled T2DM (HbA1c 11.5%, FBG 150 mg/dL on U500 Insulin [110 IU/d] and metformin ER [500 mg BID]), obesity (345 lbs), imaging proven fatty liver disease with elevated liver enzymes (AST 125 U/L, ALT 133 U/L; normal range 10-40 and 7-56, respectively), and retinopathy. Mifepristone therapy for 30 months (escalation from 300 mg/d to a final dose of 1200 mg/d) resulted in significant improvement in glycemic control (HbA1c 6.7%, FBG 102 mg/dL) and a reduction in insulin usage to 30 IU/d in combination with metformin ER. Also significant was a concomitant resolution of fatty liver disease (confirmed with imaging) and normalization of liver enzymes (AST 20 U/L, ALT 19 U/L).

Conclusion: Mifepristone treatment in this patient with CD with poorly controlled diabetes resulted in a significant decrease in the use of concentrated (U500) insulin to reestablish glycemic control and resolve accompanying fatty liver disease.

INTRODUCTION

- Insulin resistance and type 2 diabetes mellitus (T2DM) are prevalent in endogenous Cushing disease (CD)[1]
- Severe insulin resistance may require the use of concentrated insulin (Humulin R U500)[2]
- Both high circulating insulin levels and severe insulin resistance are risk factors for cardiovascular disease[3]
- Mifepristone (Korlym®, Corcept Therapeutics), a competitive glucocorticoid receptor (GR) antagonist, has been shown to improve hyperglycemia, improve insulin resistance, and reduce insulin requirements during treatment for Cushing Syndrome (CS)[4-6]

HYPOTHESIS

- In a case of recurrent CD with uncontrolled T2DM on high daily doses of U500 insulin, treatment with mifepristone would improve insulin resistance and hyperglycemia while reducing insulin

CASE PRESENTATION AND RESULTS

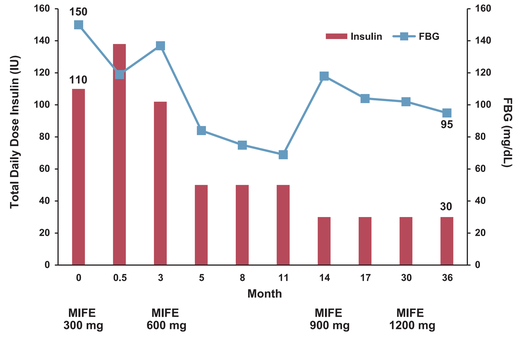
- 40-year-old woman with recurrent CD despite 2 transsphenoidal surgeries (2003, 2009), gamma knife (2003), and an unsuccessful bilateral adrenalectomy (BLA) (2012) (**Table 1**)
- Patient started on mifepristone 300 mg QD and titrated to 600 mg QD after 3 months. Patient was maintained on 600 mg QD for 12 months before increasing to 900 mg QD for an additional 16 months. Patient was then titrated to 1200 mg QD (time of abstract submission) and recently titrated to 1500 mg QD to seek further improvements.

Table 1. Demographic and Case Presentation

Age	40 yrs
Gender	Female
Weight	343 lbs
Fasting blood glucose	150 mg/dL
HbA1c	11.5%
Blood pressure	133/81 mmHg
Medications	Insulin (U500, 110 IU/d) Metformin ER (500 mg BID) Lisinopril (20 mg QD)
Liver enzymes	AST: 125 U/L (normal 10-40) ALT: 133 U/L (normal 7-56) Fatty liver indicated by imaging
Previous interventions	2x transsphenoidal surgeries Gamma knife radiation Bilateral adrenalectomy

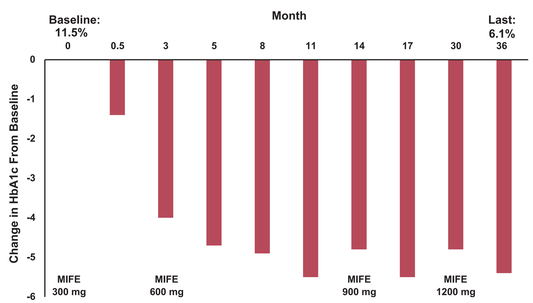
ALT, alanine transaminase; AST, aspartate transaminase.

Figure 1. Effect of Mifepristone on Insulin Usage and Fasting Blood Glucose



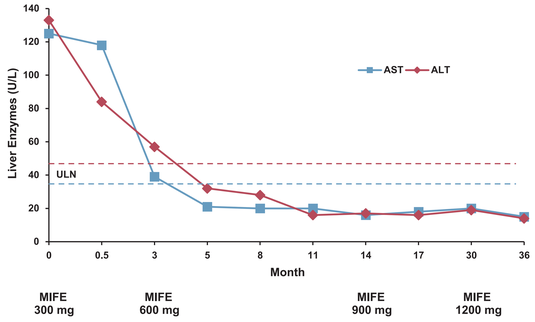
FBG, fasting blood glucose; MIFE, mifepristone.

Figure 2. Change in HbA1c From Baseline



MIFE, mifepristone.

Figure 3. Effect of Mifepristone on Liver Enzymes



ALT, alanine transaminase; AST, aspartate transaminase; MIFE, mifepristone; ULN, upper limit of normal.

OTHER NOTABLE CHANGES AND SAFETY

- Retinal microbleeds were no longer present after 18 months of mifepristone therapy
- Nausea was mild and resolved after 1 month
- Mild hypokalemia was treated with spironolactone (50 mg QD)

SUMMARY

- Mifepristone therapy greatly improved glycemic control (FBG decreased from 150 to 95 mg/mL, HbA1c decreased from 11.5 to 6.1% with a concomitant reduction of U500 insulin usage from 110 to 30 IU/d
- Liver enzymes improved in less than 1 year and were sustained. Later imaging confirmed normalization of fatty liver disease

CONCLUSIONS

- In persistent CD with severe insulin resistance and poorly controlled T2DM, competitive GR antagonism with mifepristone can significantly improve glycemic control while simultaneously decreasing the need for concentrated (U500) insulin

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DISCLOSURES

KAB: Consultant and speaker, Corcept Therapeutics

JJS: Employee, Corcept Therapeutics

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