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Impact of Mifepristone on Liver Function and Liver Steatosis in Patients With Cushing Syndrome

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Disclosures

HEE: Speaker, Amgen, Boehringer Ingelheim, Corcept Therapeutics, Lilly.
AGM, JB: Employees, Corcept Therapeutics.

Summary & Conclusions

- These data suggest that mifepristone is effective in improving liver function and decreasing liver steatosis in patients with endogenous CS
- Improvement in NAFLD was accompanied by improvement in insulin resistance and glycemic control

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Introduction

Non-alcoholic fatty liver disease (NAFLD)

- Affects 80 to 100 million people in the United States[1]
- Can progress to liver injury; more than a quarter of adults with NAFLD are presumed to have nonalcoholic steatohepatitis (NASH)[2]
- A feature of metabolic syndrome[3]
- Frequently seen in patients with endogenous Cushing syndrome (CS)[3]

Mifepristone (Korlym®, Corcept Therapeutics), a glucocorticoid receptor antagonist:

- Is FDA-approved for the treatment of hyperglycemia in patients with endogenous CS[4]
- Has shown beneficial effects in preclinical models of fatty liver disease, including reduced liver injury, improved insulin sensitivity, and increased plasma adiponectin concentrations[5,6]
- Is associated with improvements in liver steatosis in case reports of patients with CS and NAFLD[7,8]
  - Resolution of fatty liver based on imaging and reduction in liver enzymes on liver function tests (LFTs) observed in 2 patients treated with mifepristone[8]
  - Normalization of liver enzymes reported in 1 patient with CS and long-standing NAFLD following mifepristone treatment[7]

Objectives

- To report the case of a patient with CS and liver steatosis in whom treatment with mifepristone was accompanied by resolution of liver steatosis on imaging and reduction in liver enzymes
- To present data on the effects of mifepristone on liver enzymes from the phase 3 SEISMIC study

1 Case Presentation

- 36-year-old woman with CS associated with:
  - Uncontrolled type 2 diabetes mellitus, obesity, major depressive disorder, hyperlipidemia, and hypertension

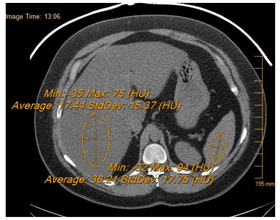
Baseline assessments

Weight, lb	198
BMI, kg/m^2	32
HbA1c, % (normal 5.0%-6.5%)	11.5
Lipids, mg/dL	
Total cholesterol (normal <200 mg/dL)	204
HDL (normal >50 mg/dL)	35
Triglycerides (normal <150 mg/dL)	307
Liver function tests	
ALT, U/L (normal 6-42 U/L)	40
AST U/L (normal 8-36 U/L)	31
Alkaline phosphatase U/L, (normal 41-114 U/L)	124
Albumin, g/dL (normal 3.6-4.8 g/dL)	3.9
Total bilirubin, mg/dL (normal 0.2-0.9 mg/dL)	0.4

ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index, HbA1c, glycated hemoglobin; HDL, high-density lipoprotein.

2 Baseline Imaging

- Imaging performed for abdominal pain showed liver steatosis despite normal LFTs



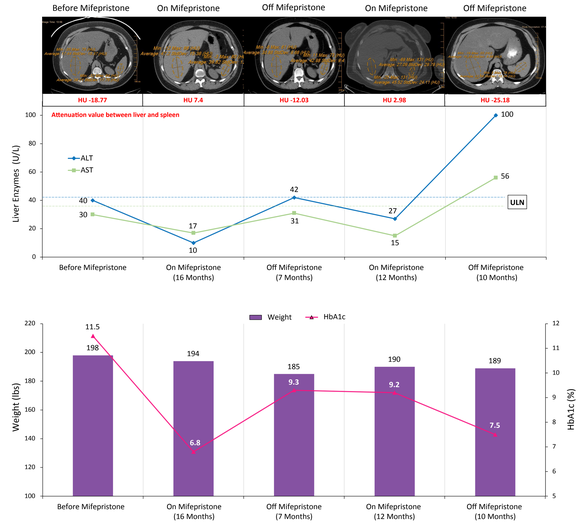
Abdominal computed tomography (CT) scan without contrast

- CT imaging measures the attenuation value of liver parenchyma (expressed in Hounsfield units [HU]), which is compared to the spleen (internal control)
- Under normal conditions, liver density in HU is higher than spleen density
- Difference in liver to spleen density before mifepristone was -18.77 HU

3 Treatment Course

- Patient treated with mifepristone intermittently for 3 years
  - Treatment was paused several times for various reasons
- Following 16 months on treatment:
  - Imaging showed resolution of liver steatosis, as shown by measurement of HU
  - Labs showed significant reductions in ALT and AST to levels typically seen in healthy individuals with no liver steatosis
- 7 months off mifepristone:
  - Imaging (HU) showed recurrence of liver steatosis
  - Labs showed increases in ALT and AST to pre-treatment levels
- 12 months after treatment resumed:
  - Imaging (HU) showed resolution of liver steatosis
  - Labs showed reductions in ALT and AST levels
- 10 months off mifepristone:
  - Imaging (HU) showed recurrence of liver steatosis
  - Labs showed increases in ALT and AST levels above the upper limits of normal

Abdominal CT imaging without contrast, liver enzymes, weight, and HbA1c during intermittent mifepristone treatment

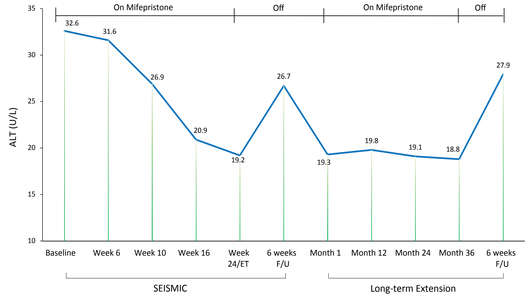


ALT, alanine transaminase; AST, aspartate transaminase; HbA1c, glycated hemoglobin; HU, Hounsfield units; ULN, upper limit of normal.

4 SEISMIC (NCT00569582) and Long-term Extension Study (NCT00936741)

- 50 patients with CS received mifepristone as part of the SEISMIC study,[9] and 30 continued into the long-term extension
  - ALT levels during SEISMIC:
    - Decreased during the 24-week treatment phase
    - Reversed during the 6-week follow-up phase (off mifepristone)
  - ALT levels during long-term extension:
    - Decreased during 36 months of treatment
    - Reversed during the 6-week follow-up phase (off mifepristone)

ALT trend during the SEISMIC and long-term extension study



ALT upper limit of normal: 48 U/L. ALT, alanine transaminase; ET, end of treatment; F/U, follow-up.

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