Case Report

Biochemical and Radiological Changes in Liver Steatosis Following Mifepristone Treatment in Patients With Hypercortisolism

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Article Info

Article history:
Received 30 April 2021
Received in revised form 29 June 2021
Accepted 3 July 2021
Available online 12 July 2021

Key words:
Cushing syndrome
hypercortisolism
mifepristone
NAFLD

Abstract

Background: Nonalcoholic fatty liver disease (NAFLD) is the most common liver disorder in Western industrialized countries and may progress to liver injury. Cortisol is thought to play a role in the pathogenesis of NAFLD, and cortisol modulation has shown efficacy in preclinical models. However, published reports on the clinical effects of glucocorticoid receptor antagonist in these patients are limited.

Case Report: Two women (aged 66 and 60 years) with endogenous hypercortisolism presented with a history of hepatic steatosis, hypertension, type 2 diabetes mellitus, and dyslipidemia. Both patients declined adrenalectomy or pituitary tumor surgery, and treatment with mifepristone 300 mg daily was initiated. During mifepristone treatment (follow up durations ranging from 10 months to 5 years), improvements in hypercortisolism-related cardiometabolic abnormalities were observed, including the normalization of lipid levels and improvement of hyperglycemia. In both cases, follow-up imaging revealed resolution of fatty liver, which was supported by a decrease in liver enzymes on liver function tests. No adverse events were reported.

Discussion: NAFLD is frequently observed in patients with endogenous hypercortisolism. Improvement in liver function tests has previously been demonstrated in patients with hypercortisolism treated with mifepristone. The present cases showed, for the first time, radiological improvement of liver steatosis following mifepristone use in patients with hypercortisolism and NAFLD.

Conclusion: This case series demonstrated improvements in biochemical and imaging parameters of NAFLD in patients with hypercortisolism treated with mifepristone. Further research is needed to investigate the effects of glucocorticoid receptor modulation in fatty liver disease.

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hepatic vessels will appear white due to their increased density compared with the parenchyma. Both methods reveal pathologic changes in the liver and are diagnostically useful. Here, we present the cases of 2 patients with CS for whom medical therapy with the competitive GR antagonist mifepristone (approved by the U.S. Food and Drug Administration in 2012 for glycemic control in patients with CS) resulted in the remission of NAFLD, confirmed by changes in liver imaging and liver enzymes.

Case Report

Case 1: Mifepristone Treatment in a Woman With a Cortisol-Secreting Adrenal Adenoma and Hepatic Steatosis

A 66-year-old woman with a medical history of obesity, hypertension, and type 2 diabetes mellitus was diagnosed with CS caused by a benign left adrenal adenoma. At diagnosis, endocrine evaluation revealed an unusual overnight 1-mg dexamethasone suppression test and low adrenocorticotropic hormone (ACTH) (Table 1). Abdominal CT scan revealed hepatic steatosis with an attenuation value difference between liver and spleen of 38 Hounsfield units, consistent with moderate-to-severe steatosis (Fig. 1).

The patient declined adrenalectomy. She was wary of undergoing surgery, particularly as her diagnosis of ACTH-independent hypercortisolism from adrenal adenoma was new, and opted for medical treatment. After potential risks and benefits were discussed, she began treatment with mifepristone 300 mg daily. The patient was hospitalized due to a vertebral fracture (unrelated) shortly after beginning mifepristone treatment; subsequently, her dose was not titrated up because of the concern regarding the potential for edema that might complicate the risk of postfracture swelling. After 1 month of treatment, her aspartate transaminase, alanine transaminase, alkaline phosphatase, and total bilirubin levels (Table 1). Her blood pressure remained controlled with antihypertensive medications throughout the treatment. At baseline, her blood pressure was controlled with 4 antihypertensive medications. During mifepristone therapy, 2 of these medications were discontinued, and spironolactone was initiated preemptively to manage potential hypokalemia. Her total cholesterol and low-density lipoprotein levels were within the normal ranges at diagnosis but decreased during the treatment period, as did her hemoglobin A1C (HbA1c) level (Table 1), indicating improvement in the patient’s lipid and blood glucose profiles. Her triglyceride (TG) level normalized following several years of mifepristone treatment. These findings occurred in the context of no significant weight change (Table 1).

Case 2: Mifepristone Treatment in a Woman With Cushing Disease and Hepatic Steatosis

A 60-year-old woman with a medical history of obesity, hypertension, and type 2 diabetes mellitus (Table 2) was diagnosed with severe ACTH-dependent CS due to a pituitary macroadenoma (measuring 12 × 13 × 13 mm). The optic chiasm was not abutted. Baseline laboratory testing revealed abnormally high levels of urinary free cortisol, late-night salivary cortisol, ACTH, and suppressed cortisol after 1-mg dexamethasone suppression test (Table 2). Liver function tests (LFTs) revealed markedly elevated liver enzymes and dyslipidemia. The patient declined surgery because she had previously undergone bariatric surgery and was wary of additional surgical procedures. She was also concerned about potential diabetes-related complications affecting her postoperative course. After the potential risks and benefits of treatment were discussed, she began mifepristone therapy at 300 mg daily. The patient was hospitalized due to a vertebral fracture (unrelated) shortly after beginning mifepristone treatment; subsequently, her dose was not titrated up because of the concern regarding the potential for edema that might complicate the risk of postfracture swelling. After 1 month of treatment, her aspartate transaminase, alanine transaminase, alkaline phosphatase, and total bilirubin levels decreased dramatically (Table 2). She did not report any adverse events during treatment. After approximately 10 months of treatment with mifepristone, her liver steatosis was significantly reduced as determined by decreased liver echogenicity and increased portal enhancement (Fig. 2) accompanied by normalization of her liver enzymes (Table 2). The patient’s body mass index also decreased, placing her weight in the normal category; her

| Parameter                          | Baseline | 5-y follow-up |
|------------------------------------|----------|---------------|
| Age, y                             | 66       | 71            |
| Weight, kg                         | 74.93    | 74.48         |
| Body mass index, kg/m²             | 31.2     | 31.1          |
| HbA1c, % (mmol/mol)                | 6.7 (50) | 6.3 (45)      |

| Cortisol following 1-mg DST, μg/dL (reference value, <1.8 μg/dL) | 2.34 |
| ACTH, pg/mL (reference range, 7.2-63.3 pg/ml)                     | 6.4  |
| DHEA-S, μg/dL (reference range, 20.4-186.6 μg/dL)                 | 36.9 |
| Lipids, mg/dL                                                      |      |
| Triglycerides                                                     | 173  |
| Total cholesterol                                                | 166  |
| Low-density lipoprotein                                          | 97   |

Liver function tests

- AST, U/L (reference range, 0-37 U/L) | 17 |
- ALT, U/L (reference range, 12-78 U/L) | 35 |
- Albumin, U/L (reference range, 3.2-4.8 U/L) | 3.9 |
- Alkaline phosphatase, U/L (reference range, 46-116 U/L) | 82 |
- Total bilirubin, mg/dL (reference range, 0.0-1.0 mg/dL) | 0.6 |
- Computed tomography imaging attenuation values (HU) | 38 |

Abbreviations: ACTH = adrenocorticotropic hormone; ALT = alanine transaminase; AST = aspartate transaminase; DHEA-S = dehydroepiandrosterone sulfate; DST = dexamethasone suppression test; HbA1c = hemoglobin A1C; HU = Hounsfield unit.

Table 1
Case 1: Baseline and Follow-Up Patient Characteristics, Laboratory Findings, and Imaging Findings.

| Parameter                          | Baseline | 5-y follow-up |
|------------------------------------|----------|---------------|
| Lipids, mg/dL                      |          |               |
| Triglycerides                      | 173      | 116           |
| Total cholesterol                  | 166      | 156           |

Liver function tests

- AST, U/L (reference range, 0-37 U/L) | 17 |
- ALT, U/L (reference range, 12-78 U/L) | 35 |
- Albumin, U/L (reference range, 3.2-4.8 U/L) | 3.9 |
- Alkaline phosphatase, U/L (reference range, 46-116 U/L) | 82 |
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Abbreviations: ACTH = adrenocorticotropic hormone; ALT = alanine transaminase; AST = aspartate transaminase; DHEA-S = dehydroepiandrosterone sulfate; DST = dexamethasone suppression test; HbA1c = hemoglobin A1C; HU = Hounsfield unit.

Table 1
Case 2: Baseline and Follow-Up Patient Characteristics, Laboratory Findings, and Imaging Findings.
dyslipidemia resolved, as shown by the impressive decreases in TG, total cholesterol, and low-density lipoprotein levels; her blood pressure normalized; and her HbA1c level decreased (Table 2). Following 14 months of mifepristone treatment, she underwent transsphenoidal surgery. She did not experience any postsurgical adrenal insufficiency and has had no additional weight loss to date.

**Discussion**

NAFLD has been described as the liver manifestation of metabolic syndrome. Numerous risk factors for NAFLD have been proposed, including insulin resistance, which leads to the accumulation of TG and free fatty acids in the liver. Elevated glucocorticoid levels have also been implicated in the development and progression of NAFLD. Administration of mifepristone to obese mice fed a high-fat diet reduced liver injury and resulted in improved insulin sensitivity. The investigational selective GR modulator miri-corilant exhibits high activity in liver tissue and has been shown to successfully reverse and prevent liver steatosis in mouse models of NAFLD.

In patients with hypercortisolism, mifepristone is effective in treating the metabolic manifestations of excess cortisol. In the SEISMIC trial, substantial reductions in the levels of fasting plasma glucose,

**Table 2**

| Parameter | Baseline | 10-mo follow-up |
|-----------|----------|-----------------|
| Age, y    | 60       | 61              |
| Weight, kg| 77.56    | 67.22           |
| Body mass index, kg/m² | 27.6 | 23.9 |
| Blood pressure, mm Hg | 165/96 | 126/73 |
| HbA1c, % (mmol/mol) | 8.4 (68) | 8.0 (64) |

**Liver function**

| Parameter | Baseline | 1-mo follow-up | 10-mo follow-up |
|-----------|----------|----------------|-----------------|
| AST, U/L (reference range, 10-35 U/L) | 395 | 25 | 21 |
| ALT, U/L (reference range, 6-29 U/L) | 579 | 43 | 11 |
| Albumin, U/L (reference range, 3.6-5.1 U/L) | 3.8 | 4.1 | 4.2 |
| Alkaline phosphatase, U/L (reference range, 37-153 U/L) | 538 | 168 | 72 |
| Total bilirubin, mg/dL (reference range, 0.2-1.2 mg/dL) | 0.53 | <0.3 | 0.5 |

**Abbreviations:** ACTH = adrenocorticotropic hormone; ALT = alanine transaminase; AST = aspartate transaminase; DHEA-S = dehydroepiandrosterone sulfate; DST = dexamethasone suppression test; HbA1c = hemoglobin A1C; Len Maj = length major; Len Min = length minimum; LNSC = late-night salivary cortisol; M = mean; Max = maximum; Min = minimum; P = perimeter; SD = standard deviation; UFC = urinary free cortisol.

**Fig. 1.** Precontrast computed tomography scans of liver steatosis before (A) and after mifepristone treatment (B). Red boxes show the mean attenuation values calculated from regions of interest (white (A) and green ovals (B) indicate the region of interest). After mifepristone treatment, fatty liver was reversed. A – area; HU – Hounsfield unit; Len Min – length minimum; Len Maj – length major; M – mean; Max – maximum; Min – minimum; P – perimeter; SD – standard deviation.
enzymes levels dramatically decreased, and during treatment with mifepristone, the patient elevated LFTs and con...ation of hepatic steatosis via imaging. During treatment with mifepristone, the patient’s lipids and liver enzymes levels dramatically decreased, and findings of follow-up imaging revealed a reduction in liver fat. In both cases, mifepristone treatment improved glucose metabolism as demonstrated by reductions in HbA1c levels.

Studies in other patient populations have been conducted to investigate the effect of mifepristone on metabolic parameters. In healthy postmenopausal women, 2 weeks of mifepristone treatment improved insulin sensitivity. Improvement in glycemic measures was also shown in a cohort of patients with type 2 diabetes mellitus who were treated with a combination of mifepristone and metyrapone. Gross et al evaluated the efficacy of mifepristone in healthy men in preventing weight gain induced by antipsychotic medication and found that the treatment reduced body weight and TG and fasting plasma insulin levels. Additionally, short-term mifepristone therapy (duration of 9 days) in overweight and obese individuals with pre- or mild diabetes resulted in improved adipose tissue and hepatic insulin sensitivity.

Because mifepristone antagonizes the progesterone receptor, it is also indicated as an abortifacient. Undesirable treatment-related adverse events in women receiving mifepristone for CS include endometrial hypertrophy and vaginal bleeding caused by the drug’s interaction with the progesterone receptor. For this reason, to specifically target the GR, newer therapeutics have been developed, such as the investigational selective GR modulator relacorilant, which is currently in phase 3 clinical trials. In a recently completed phase 2 trial (NCT02804750), patients with CS treated with relacorilant experienced decreases in alanine transaminase and aspartate transaminase levels. In a phase 3 trial, the patients being studied have severe hypercortisolism caused by any endogenous etiology (Glucocorticoid Receptor Antagonism in the Treatment of Cushing Syndrome [GRACE], NCT03697109). In the second phase 3 trial, patients with less severe hypercortisolism due to cortisol-secreting adenomas are being studied (Glucocorticoid Receptor Antagonism in the Treatment of Hypercortisolism in Patients With Cortisol-secreting Adrenal Adenomas or Hyperplasia [GRADIENT], NCT04308590).

Conclusion

This case series has demonstrated, for the first time, improvements in both the biochemical and imaging parameters of NAFLD in patients with hypercortisolism treated with mifepristone. Further studies, including studies with selective GR modulators, will provide additional data on the potential clinical benefit of cortisol modulation in fatty liver disease.

Acknowledgment

We thank Dr Ha Evans for her interpretation of the imaging results. We also thank Nicole Day, PhD, and Sarah Mizne, PharmD, of MedVal Scientific Information Services, LLC, for medical writing and editorial assistance. Medical writing and editorial assistance to prepare this manuscript for publication were funded by Corcept Therapeutics. This manuscript was prepared according to the International Society for Medical Publication Professionals’ “Good Publication Practice for Communicating Company-Sponsored Medical Research: GPP3.”

Author Contributions

J.C.P., A.G.M., and J.K.B. interpreted the data, revised the manuscript for intellectual content, and approved the final version to be submitted.
Disclosure

J.C.P. is an employee of Wilmington Health, an advisor to Corcept Therapeutics, and a promotional speaker for AstraZeneca and Corcept Therapeutics. A.G.M. and J.K.B. are employees of Corcept Therapeutics.

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