Mifepristone, a Glucocorticoid Receptor Antagonist, Produces Clinical and Metabolic Benefits in Patients with Cushing's Syndrome

Maria Fleseriu, Beverly M. K. Biller, James W. Findling, Mark E. Molitch, David E. Schteingart, and Coleman Gross, on behalf of the SEISMIC Study Investigators

Oregon Health & Science University (M.F.), Portland, Oregon 97239; Massachusetts General Hospital (B.M.K.B.), Boston, Massachusetts 02114; Medical College of Wisconsin (J.W.F.), Milwaukee, Wisconsin 53226; Northwestern University Feinberg Medical School (M.E.M.), Chicago, Illinois 60611; University of Michigan (D.E.S.), Ann Arbor, Michigan 48109; and Corcept Therapeutics (C.G.), Menlo Park, California 94025

Context: Cushing's syndrome (CS) is a disorder associated with significant morbidity and mortality due to prolonged exposure to high cortisol concentrations.

Objective: Our objective was to evaluate the safety and efficacy of mifepristone, a glucocorticoid receptor antagonist, in endogenous CS.

Design and Setting: We conducted a 24-wk multicenter, open-label trial after failed multimodality therapy at 14 U.S. academic medical centers and three private research centers.

Participants: Participants included 50 adults with endogenous CS associated with type 2 diabetes mellitus/impaired glucose tolerance (C-DM) or a diagnosis of hypertension alone (C-HT).

Intervention: Mifepristone was administered at doses of 300-1200 mg daily.

Main Outcome Measures: We evaluated change in area under the curve for glucose on 2-h oral glucose test for C-DM and change in diastolic blood pressure from baseline to wk 24 for C-HT.

Results: In the C-DM cohort, an area under the curve for glucose ($AUC_{glucose}$) response was seen in 60% of patients ($P < 0.0001$). Mean $\pm$ SD glycated hemoglobin (HbA1c) decreased from 7.43 $\pm$ 1.52% to 6.29 $\pm$ 0.99% ($P < 0.001$); fasting plasma glucose decreased from 149.0 $\pm$ 75.7 mg/dl (8.3 $\pm$ 4.1 mmol/liter) to 104.7 $\pm$ 37.5 mg/dl (5.8 $\pm$ 2.1 mmol/liter, $P < 0.03$). In C-HT cohort, a diastolic blood pressure response was seen in 38% of patients ($P < 0.05$). Mean weight change was $-5.7 \pm 7.4\%$ ($P < 0.001$) with waist circumference decrease of -6.78 ± 5.8 cm ($P < 0.001$) in women and -8.44 ± 5.9 cm ($P < 0.001$) in men. Overall, 87% ($P < 0.0001$) had significant improvement in clinical status. Insulin resistance, depression, cognition, and quality of life also improved. Common adverse events were fatigue, nausea, headache, low potassium, arthralgia, vomiting, edema, and endometrial thickening in women.

Conclusions: Mifepristone produced significant clinical and metabolic improvement in patients with CS with an acceptable risk-benefit profile during 6 months of treatment. (***J Clin Endocrinol Metab* 97: 2039–2049, 2012**)

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Abbreviations: AE, Adverse event; AI, adrenal insufficiency; $AUC_{glucose}$, area under the curve for glucose; BDI, Beck Depression Inventory; CD, Cushing's disease; C-DM, patients with CS and T2DM/IGT; C-HT, patients with CS and a diagnosis of HTN; CI, confidence interval; CS, Cushing's syndrome; DBP, diastolic blood pressure; DRB, data review board; ET, early termination; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment of insulin resistance; HTN, hypertension; IGT, impaired glucose tolerance; mITT, modified intent-to-treat; MRI, magnetic resonance imaging; oGTT, oral glucose tolerance test; T2DM, type 2 diabetes mellitus.

Cushing's syndrome (CS), is a serious endocrine disorder that may be caused by a pituitary [Cushing's disease (CD)] or nonpituitary (ectopic) ACTH-secreting tumor or by an adrenal neoplasm. If inadequately treated, CS is associated with a 3.8- to 5.0-fold higher mortality than the general population (1–3). Regardless of cause, surgery is usually the treatment of choice; however, complete removal of the neoplasm may not be possible (4, 5). Adjunctive radiotherapy for CD may take years to control excess cortisol (6). Laparoscopic bilateral adrenalectomy represents another treatment option. No medical treatments were approved by the U.S. Food and Drug Administration for CS when the study was conducted, but off-label use of several medications is common, including dopamine agonists, somatostatin analogs, and the adrenal steroidogenesis inhibitors (ketoconazole, metyrapone, mitotane, and etomidate) (4, 7). Ketoconazole and mitotane are effective in many patients, but in CD, doses may need progressive increases due to escape from cortisol blockade. The tolerability of these drugs, especially at higher doses, limits their use in some patients (8, 9).

Mifepristone (11β-[*P*-(dimethylamino)phenyl]-17β-hydroxy-17-(1-propynyl)estra-4,9-dien-3-one) is a progesterone receptor antagonist that has glucocorticoid receptor antagonist activity at higher concentrations, with more than three times the binding affinity for the glucocorticoid receptor than dexamethasone (10, 11). It does not bind to the mineralocorticoid receptor (9). Case reports and small retrospective studies of mifepristone treatment in CS document improvements in abnormal glucose metabolism, psychiatric symptoms, and the somatic changes associated with CS; hypokalemia was the most commonly reported side effect (9, 12–25). Based on these preliminary findings, an open-label, prospective, multicenter, 6-month study of the safety and efficacy of mifepristone was conducted in patients with endogenous CS refractory to other therapies.

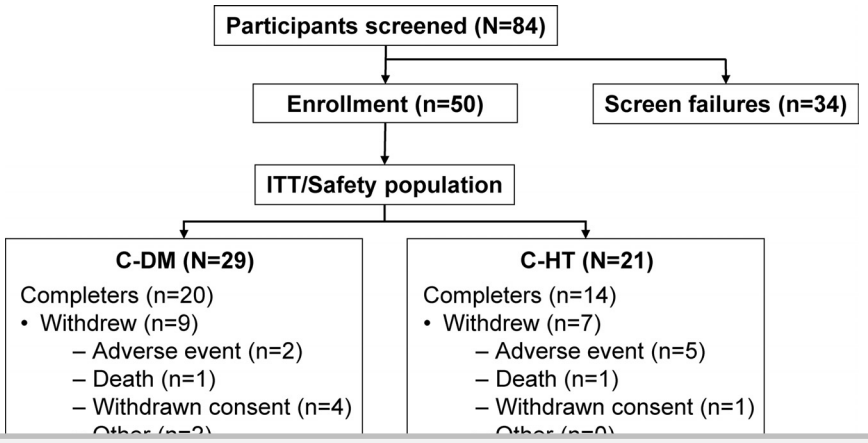
Patients and Methods

Patients

Adults with confirmed endogenous CS who had associated type 2 diabetes mellitus (T2DM), impaired glucose tolerance (IGT), or a diagnosis of hypertension (HTN) were enrolled (Fig. 1). Endogenous hypercortisolism was defined as elevated urinary free cortisol on at least two 24-h collections and elevated late-night salivary cortisol and/or lack of suppression with dexamethasone. T2DM was defined as a fasting plasma glucose (FPG) of at least 126 mg/dl (≥7.0 mmol/liter) on two measurements or a 2-h plasma glucose of at least 200 mg/dl (≥11.1 mmol/liter) after a 75-g oral glucose tolerance test (oGTT), and IGT was defined as 2-h oGTT glucose value of 140–199 mg/dl (7.8–11.0 mmol/liter). HTN was defined as systolic blood pressure over 140 mm Hg and/or diastolic blood pressure (DBP) over 90 mm Hg or pharmacologically treated HTN.

At least two of the following signs or symptoms of Cushing's were also necessary for inclusion: Cushingoid appearance (moon facies, dorsocervical fat pad, and plethora), increased body weight or central obesity, proximal muscle weakness, low bone mineral density (T score < -1.0), psychiatric symptoms, and skin changes (hirsutism, violaceous striae, or acne).

Patients were excluded for poorly controlled diabetes mellitus [glycated hemoglobin (HbA1c) ≥ 11%], poorly controlled HTN (>170/110 mm Hg), use of drugs to treat hypercortisolism within 1 month of baseline (mitotane for adrenal carcinoma was allowed if on stable dose ≥1 month before entry), uncorrected hypokalemia, or uncontrolled hypothyroidism or hyperthyroidism; also excluded were women with a uterus who required anticoagulants or had hemorrhagic disorders, endometrial hyperplasia, carcinoma, or polyps. Increases or additions of antihyperglycemic medications during the study were not permitted for patients with T2DM/IGT. For patients with HTN, increases or additions of antihypertensive medications were not permitted with the exception of mineralocorticoid receptor antagonists, which were allowed for treating hypokalemia, a known side effect of mifepristone (9). Changes in or initiation of antidepressant or lipid-lowering medications were not allowed.



The study was approved by the institutional review board at each center and was registered with www.clinicaltrials.gov (NCT00569582). All patients provided written informed consent.

Design

This was a 24-wk, open-label, multicenter study of mifepristone administered as a single daily oral dose. Treatment began at 300 mg/d; if no significant clinical improvement was noted by the investigator, doses could be increased to 600 mg/d on d 14, 900 mg/d at wk 6, and 1200 mg/d at wk 10. Dose interruption and reduction were specified in the protocol

and vaginal bleeding. Temporary glucocorticoid rescue for suspected AI was also allowed.

Assessments

The primary endpoint for patients with CS and T2DM/IGT (C-DM cohort) was the change in area under the curve for glucose ($AUC_{glucose}$) on oGTT from baseline to wk 24. Response was defined as at least a 25% decrease in $AUC_{glucose}$, an amount considered clinically meaningful improvement in glucose control (26). $AUC_{glucose}$ was used because both patients with T2DM and patients with IGT were enrolled, and HbA1c and FPG would not be uniformly applicable. In patients receiving medications for diabetes, administration occurred before the oGTT (other than short-acting insulin and glucagon-like peptide-1 analogs). The primary endpoint for patients with CS and a diagnosis of HTN (C-HT cohort) was the change in DBP from baseline to wk 24; response was defined as DBP decrease of at least 5 mm Hg (mean of two sequential readings). Patients with both T2DM/IGT and HTN were included only in the C-DM cohort.

Key secondary endpoints included clinical response graded by an independent data review board (DRB) at wk 6, 10, 16, and 24 compared with baseline. The DRB consisted of three CS experts who evaluated the following assessments: glucose homeostasis, blood pressure, lipids, weight and body composition change, clinical appearance (acne, hirsutism, striae, and Cushingoid appearance) (27, 28) as rated by the investigators, strength, and neuropsychological [Beck Depression Inventory (BDI)-II and Trail Making Test] (29–31) and quality of life [Short-Form 36 Health Survey version 2 (SF-36)] (32) parameters. The DRB also reviewed standardized photographs of 34 consenting patients. Visit number after baseline and mifepristone dose were blinded. Each DRB member categorized patient overall status at follow-up visits as worse (−1), unchanged (0), or having clinically significant improvement (+1) from baseline. If the reviewers' median score was +1, the patient was considered to have clinical improvement.

Blood, urine, and saliva samples were analyzed by a central laboratory (Quest Diagnostics, Collegeville, PA). $AUC_{glucose}$ and $AUC_{insulin}$ were determined using the linear trapezoidal rule; homeostatic model assessment of insulin resistance (HOMA-IR) was calculated (33). Urinary and salivary cortisol levels were assayed with liquid chromatography tandem mass spectrometry [normal ranges, respectively, are 2–42.4 μg/24 h (5.5–117 nmol/24 h) and ≤0.09 μg/dl (2.5 nmol/liter)]; serum cortisol [normal range is 4–22 μg/dl (110–607 nmol/24 h)], and ACTH (normal range is 5–27 pg/ml (1.1–5.9 pmol/liter) for females and 7–50 pg/ml (1.5–11 pmol/liter) for males] were measured with immunochemiluminometric assay.

AEs were reviewed every visit, and patients were monitored with vital signs, physical exams, and blood tests; transvaginal ultrasounds were conducted at baseline, wk 24 [or early termination (ET)], and 6 wks after last dose. Pituitary magnetic resonance imaging (MRI) was performed at screening and at wk 10 and 24 (or ET) in patients with CD. Body composition was measured using dual-energy x-ray absorptiometry at baseline and wk 24 or ET using Hologic (Bedford, MA) or GE Lunar (Madison, WI) instruments; results were submitted to a central reading site for quality control and analysis.

Statistics

(mITT) population (patients who received ≥30 d of study medication) was used for analyses of efficacy (n = 46). The completer population included participants who completed through wk 24 and were at least 80% compliant with study medication (n = 33).

Because there was no placebo group in this study, a responder analysis was conducted. Responder rates were tested against an *a priori* threshold of 20%, which was chosen based on very low spontaneous response rates in this patient population (<5%) (34). The null hypothesis was to be rejected if the lower bound of the one-sided binomial 95% confidence interval (CI) of responder rates was over 20%. Because mifepristone blocks rather than lowers cortisol, alternative quantitative endpoints (other than cortisol) were assigned at study entry based on inclusion in either C-DM or C-HT cohorts. Two abnormal oGTTs were required for inclusion in the C-DM group; patients with a diagnosis of HTN and without T2DM/IGT were included in the C-HT group. For statistical analysis, response was defined as at least 25% reduction in $AUC_{glucose}$ for C-DM patients or at least 5 mm Hg reduction in DBP in C-HT patients comparing baseline with wk 24/ET. For patients who did not complete the study or have an ET visit, the last available data were used. ANOVA and *t* tests were used for analyses of other endpoints. Nonparametric statistical testing was employed for nonnormally distributed data. Change in oGTT curves over the course of the study was modeled by a hierarchical linear mixed model that took into consideration the correlation within subjects. SAS statistical software versions 9.1.3 and 9.2 (Cary, NC) were used. Data are shown as mean ± SD unless otherwise stated.

Results

Patients

From January 2008 to January 2011, 50 patients with CS were enrolled at 17 U.S. centers; 34 completed the study. Forty-three patients had a pituitary source of CS (42 with unsuccessful pituitary surgery, 18 with pituitary radiation, and one without previous surgery), four had ectopic ACTH secretion, and three had adrenal cortical carcinoma. Baseline characteristics are detailed in Tables 1 and 2. The mean dose ± SD at the final study visit was 732 ± 366 mg/d. Twenty-two subjects received the maximum dose of 1200 mg/d. Dose interruptions occurred in 42% of patients with median duration of 2 d (range 1–39 d). There were 18 dose reductions in 12 patients; reductions occurred most commonly in 300-mg decrements (317 ± 114 mg).

Primary efficacy analyses

Patients with T2DM/IGT

In the C-DM mITT population, $AUC_{glucose}$ decreased by at least 25% on oGTT in 15 of 25 (60%) patients from baseline to wk 24/ET (95% CI lower bound 42%, $P < 0.0001$) with a median decrease of 36% [30330.0 mg/dl·120 min (1683.3 mmol/liter·120 min) to 20655.0 mg/

TABLE 1. Demographics and body measurements at baseline (ITT/safety population)

Characteristic	C-DM (n = 29)	C-HT (n = 21)	Overall (n = 50)
Sex [n (%)]			
Male	7 (24.1)	8 (38.1)	15 (30.0)
Female	22 (75.9)	13 (61.9)	35 (70.0)
Race [n (%)]			
Black or African-American	6 (20.7)	2 (9.5)	8 (16.0)
White	23 (79.3)	19 (90.5)	42 (84.0)
Ethnicity [n (%)]			
Hispanic or Latino	2 (6.9)	2 (9.5)	4 (8.0)
Not Hispanic or Latino	27 (93.1)	19 (90.5)	46 (92.0)
Age (yr)			
Mean ± SD	44.4 ± 13.71	46.7 ± 8.83	45.4 ± 11.85
Median	41.0	46.0	45.0
Range	26–71	26–67	26–71
Height (cm)			
Mean ± SD	168 ± 12.11	166 ± 8.84	167 ± 10.81
Median	168	163	166
Range	143.5–190.5	154.0–185.4	143.5–190.5
Weight (kg)			
Mean ± SD	105 (33.54)	91.4 (21.10)	99.5 (29.55)
Median	102	88.2	92.4
Range	61.3–198.7	62.7–150.5	61.3–198.7
BMI (kg/m^2)			
Mean ± SD	37.4 (11.18)	33.4 (7.44)	35.7 (9.90)
Median	35.1	31.8	33.5
Range	24.1–66.4	24.5–53.6	24.1–66.4
Waist circumference, cm			
Mean ± SD	124 (21.73)	111 (15.77)	119 (20.31)
Median	120	104	115
Range	97.9–178.4	88.5–153.5	88.5–178.4
Etiology of CS			
CD [n (%)]	24 (82.8)	19 (90.5)	43 (86.0)
Ectopic ACTH [n (%)]	3 (10.3)	1 (4.8)	4 (8.0)
Adrenal cancer [n (%)]	2 (6.9)	1 (4.8)	3 (6.0)

The C-DM group included subjects with T2DM and/or IGT at screening and d 1 as determined by two or more abnormal oGTT. The C-HT group included subjects with a diagnosis of HTN at screening but without T2DM and/or IGT.

Table 3). Similar reductions in $AUC_{glucose}$ were observed in the C-DM ITT and completer populations. The most common doses among responders at wk 24/ET were 600 mg (40%) and 1200 mg (40%), followed by 300 mg (13.3%) and 900 mg (6.7%). In exploratory analyses we found no relationship between the incremental change in dose from baseline and $AUC_{glucose}$ (see Supplemental Fig. 1, published on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org).

Patients with HTN

In the C-HT mITT cohort, eight of 21) patients (38.1% achieved the primary endpoint of at least 5 mm Hg decline in DBP (95% CI lower bound 21%, $P < 0.05$; Table 3). Four patients (two responders) received spironolactone during the study; one nonresponder was on spironolactone at entry and remained on a stable dose throughout the study.

Secondary endpoints

Clinical improvement

The overall clinical improvement response rate as assessed by the DRB in the mITT population was 87% (95% CI lower bound 76%, $P < 0.0001$); response rates were similar in the C-DM and C-HT cohorts (Table 3). Thirty-three patients

TABLE 2. Biochemistry at baseline (ITT/safety population)

	CD	Ectopic ACTH	Adrenal cancer	Overall
Biochemistry				
ACTH (pg/ml)	63 (51)	153 (140.3)		66 (66)
24 h UFC (μg/24 h)	139 (137)	2471 (3266)	812 (559)	366 (1049)
Serum cortisol (μg/dl)	21.2 (6.0)	42.6 (14.3)	37.4 (15.4)	23.9 (10.0)
Late-night salivary cortisol (μg/dl)	0.29 (0.29)	1.90 (2.26)	1.02 (0.58)	0.47 (0.83)

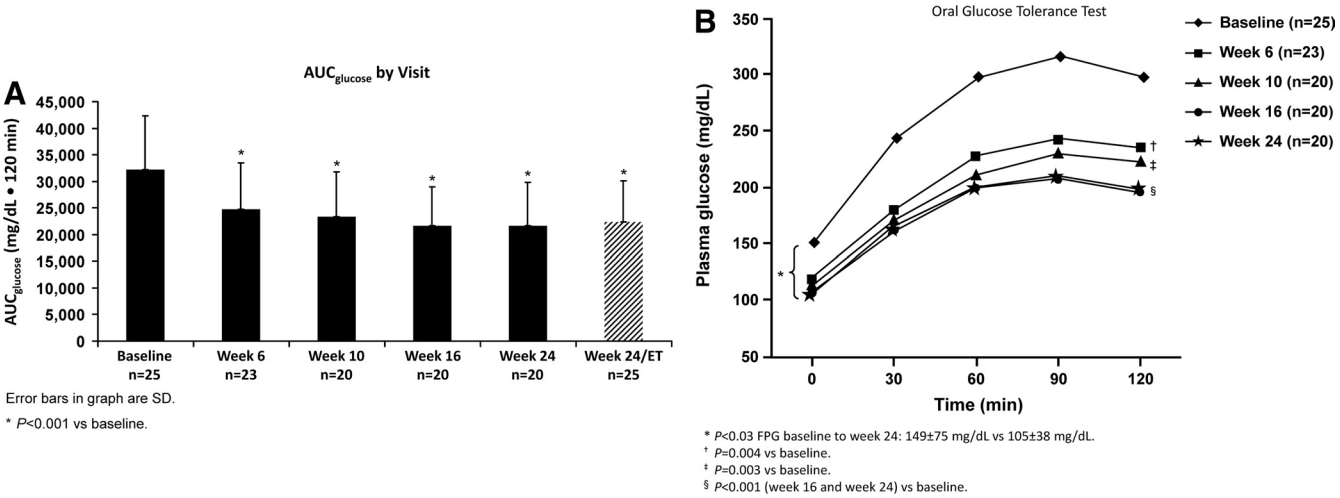


FIG. 2. Changes in glycemic parameters. A, Significant decreases in $AUC_{glucose}$ were observed in the C-DM cohort from baseline to each subsequent visit including wk 24/ET ($P < 0.001$). Data are shown as mean ± SD. B, Significant decreases were also seen in plasma and fasting plasma glucose ($P = 0.03$), as measured by oGTT from baseline to wk 24. The oGTT response curves at each visit were statistically different compared with baseline. Mean data are shown. To convert glucose values to millimoles per liter, multiply by 0.0555.

(72%) had a median score of +1 at wk 24 or ET. Eleven patients by wk 6 and another six patients by wk 10 had a median score of +1 with responses maintained throughout the remainder of the study (Initial clinical improvement response by dose and visit are shown in Supplemental Fig. 2). Three patients had a nonsustained improvement (median score of +1 decreased to 0 at wk 24 or ET). One patient was rated as being worse at the final visit (early termination at wk 10) than at baseline.

Other glucose-related endpoints

FPG decreased from 149.0 ± 74.7 mg/dl (8.3 ± 4.1 mmol/liter) at baseline to 104.7 ± 37.5 mg/dl (5.8 ± 2.1 mmol/liter) at wk 24 ($P < 0.03$). Antidiabetic medications were reduced in seven of 15 patients. Of 12 patients taking insulin, five reduced their daily dose by at least half. Eighteen of 25 C-DM patients (72%) had at least a 25% reduction from baseline in $AUC_{glucose}$ or a reduction in antidiabetic medication (95% CI = 50.6–

TABLE 3. Summary of responder analyses (mITT population)

Statistics (mITT population)	Responder [n (%)]	Nonresponder [n (%)]	Lower bound one-sided 95% exact binomial CI (%)	*P* value
C-DM (n = 25)				
Participants with or without a 25% reduction from baseline in $AUC_{glucose}$ at wk 24/ET	15 (60)	10 (40)	41.7	<0.0001
C-HT (n = 21)				
Participants who had ≥5 mm Hg reduction from baseline in DBP at wk 24/ET	8 (38.1)	13 (61.9)	20.6	<0.05
C-HT and C-DM with HTN at screening (n = 40)				
Participants who had ≥5 mm Hg reduction from baseline in DBP at wk 24/ET	17 (42.5)	23 (57.5)		
Participants who had a reduction in antihypertensive medications at wk 24/ET	11 (27.5)	29 (72.5)		
Participants who had either ≥5 mm Hg reduction from baseline in DBP or had a reduction in antihypertensive medications at wk 24/ET	21 (52.5)[a]	19 (47.5)		
Median clinical improvement score of +1 at any reviewed visit[b]				
Combined cohorts (n = 46)	40 (87.0)	6 (13.0)	75.9	<0.0001
C-DM (n = 25)	23 (92.0)	2 (8.0)	76.9	
C-HT (n = 21)	17 (81.0)	4 (19.0)	61.6	

[a] 95% CI = 36.1–68.5.

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