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

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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 ± 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 ($\geq$7.0 mmol/liter) on two measurements or a 2-h plasma glucose of at least 200 mg/dl ($\geq$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) $\geq$ 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 $\geq$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.

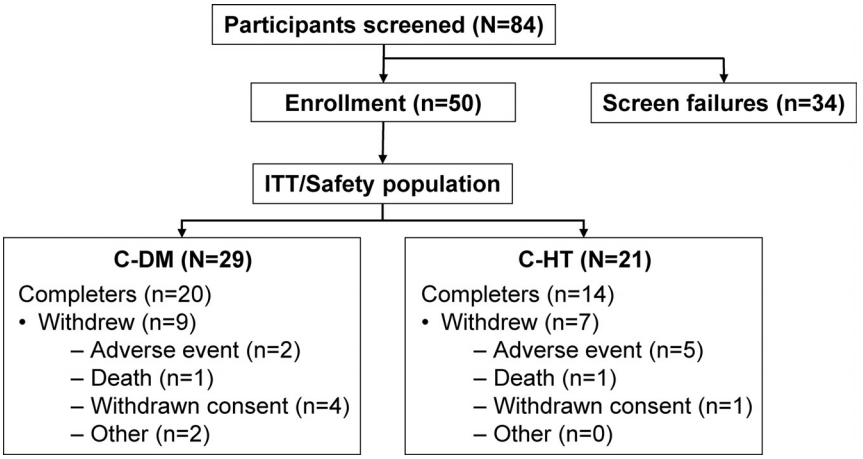

FIG. 1. Enrollment: ITT/safety population.

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 for the following adverse events (AEs): adrenal insufficiency (AI), severe hypokalemia,

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

Patients who took at least one dose of study medication comprised the safety population (n = 50). A modified intent-to-treat (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/dl·120 min (1146.4 mmol/liter·120 min)] as well as comparable reductions in plasma glucose levels (Fig. 2 and

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)

To convert values of ACTH to picomoles per liter, multiply by 0.22; urinary free cortisol (UFC) to nanomoles per 24 h, multiply by 2.759; cortisol to nanomoles per liter, multiply by 27.59.

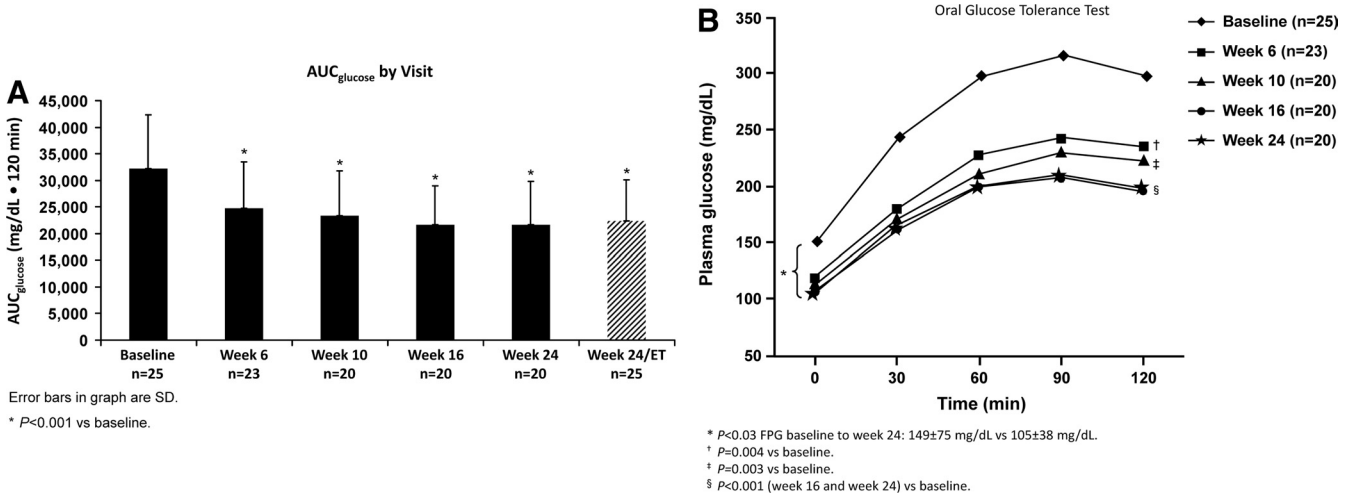

FIG. 2. Changes in glycemic parameters. A, Significant decreases in $AUC_{glucose}$ were observed in the C-DM cohort from baseline to each subsequent visit including wk 24/ET ($P < 0.001$). Data are shown as mean ± SD. B, Significant decreases were also seen in plasma and fasting plasma glucose ($P = 0.03$), 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.

[b] For overall clinical improvement (median DRB score +1) at any reviewed visit, the null hypothesis was to be rejected in favor of the alternative if the lower limit of the 95% exact one-sided binomial CI for the responder rate was at least 30%.

87.9%). The mean baseline HbA1c of 7.43 ± 1.52% in the C-DM group decreased to 6.29 ± 0.99% at wk 24/ET ($P < 0.001$) (Fig. 3A). Twelve C-DM patients had an HbA1c over 7% at baseline (mean 8.53 ± 1.11%); of these, nine achieved an HbA1c below 7%, including six reaching an HbA1c of 6% or below. C-DM and C-HT patients were insulin resistant and demonstrated rapid and significant improvements in $AUC_{insulin}$, which continued throughout the study (Fig. 3B); HOMA-IR demonstrated improvements in insulin sensitivity (Fig. 3C).

Weight and body composition

In the mITT population (n = 46), mean ± SD body weight change from baseline (99.5 kg) to wk 24/ET was −5.7 ± 7.4% ($P < 0.001$) (Fig. 4A). Twenty-four patients lost at least 5% of their baseline weight, 12 of whom lost at least 10%; 10 patients gained an average of 3.6 ± 3.9%. Waist circumference decreased by −6.8 ± 5.8 cm ($P < 0.001$) in women and −8.4 ± 5.9 cm in men ($P < 0.001$) (Fig. 4B). Mean percent total body fat declined by 3.6% by wk 24 ($P < 0.001$). Absolute fat mass declined by 13.9% ($P < 0.001$) for the total body, 15.6% ($P < 0.001$) for the trunk, and 17.1% ($P < 0.001$) for the abdominal region (Fig. 4C).

DBP and antihypertensive medications (C-HT and C-DM with HTN)

In addition to the 21 C-HT patients, 19 C-DM patients had a diagnosis of HTN at study entry; 42.5% (17 of 40) of these had a reduction in DBP of at least 5 mm Hg at wk 24/ET compared with baseline, and 27.5% had reductions in antihypertensive medications (50% of patients with a diagnosis of HTN were taking at least two antihyperten-

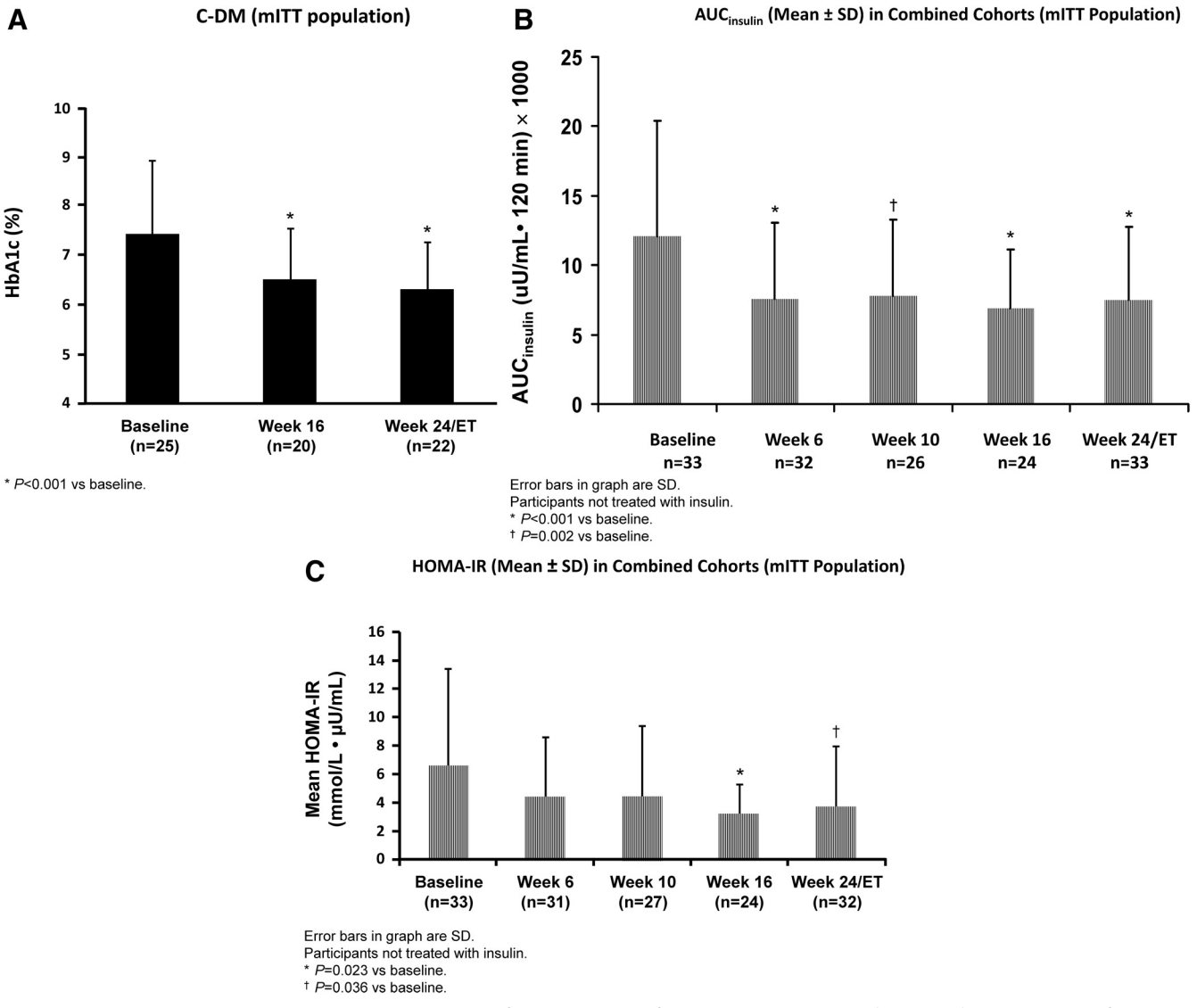

FIG. 3. Changes in glucose-related outcomes. A, HbA1c significantly decreased from baseline to wk 24/ET ($P < 0.001$); B and C, a significant reduction in $AUC_{insulin}$ (B) and significant improvements in HOMA-IR (C) were also observed. Data are shown as mean ± SD. To convert insulin values to picomoles per liter, multiply by 6.945.

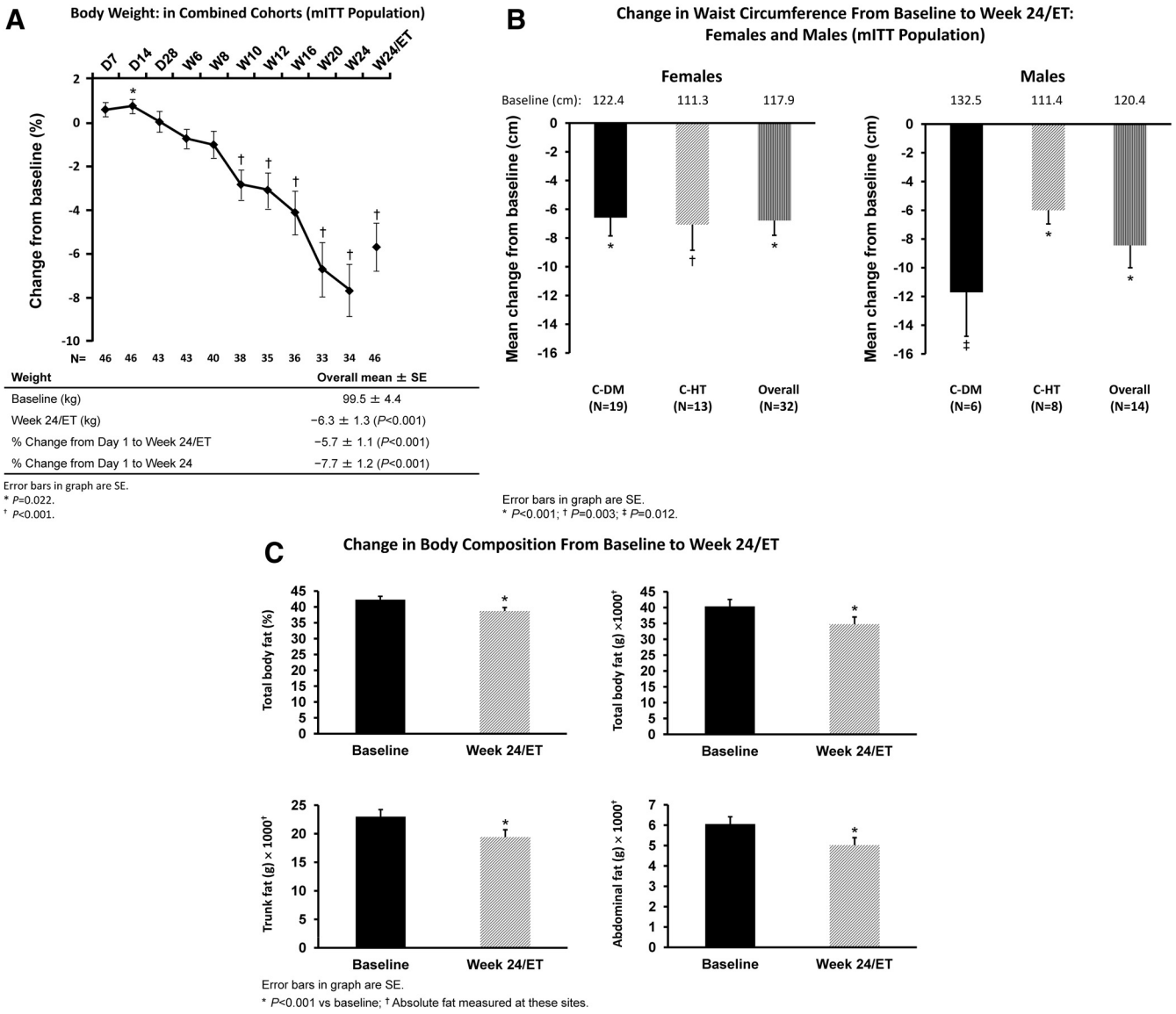

FIG. 4. Changes in weight and body composition. Results demonstrated a significant reduction in body weight from baseline to wk 24/ET ($P < 0.001$) (A), significant decreases in overall waist circumference for females and males ($P < 0.001$) (B), and improvements in body composition (C). Data are shown as mean ± SE.

sive medications at baseline). Overall, 52.5% (95% CI = 36.13–68.49%) had either a response in DBP or a reduction in antihypertensive medications (Table 3). However, there were no significant differences in mean systolic blood pressure and DBP from baseline to wk 24/ET among C-HT patients (129.5 ± 16.3/82.9 ± 11.4 *vs.* 129.9 ± 19.0/82.8 ± 13.2 mm Hg) or in C-DM patients with a diagnosis of HTN (137.7 ± 24.0/86.4 ± 15.3 *vs.* 132.2 ± 16.7/82.4 ± 13.2 mm Hg). Eight of 12 patients with DBP of at least 90 mm Hg at study entry had a reduction of at least 5 mm Hg (median decline −14 mm Hg, range −26.5 to −5.5 mm Hg); only one (C-DM patient) of the eight received additional antihypertensive therapy. AEs of increased blood pressure were reported in 12 patients, nine (75%) of whom had evidence of mineralocorticoid receptor activation (edema, hypokalemia, and/or need for spironolactone to control hypokalemia).

Mood, cognition, and quality of life

Median BDI-II depression scores improved in the mITT population (baseline 14.5, range 0–49; wk 24/ET 9.5, range 0–36; $P < 0.001$). For patients with at least mild depression at baseline (BDI-II ≥ 14, n = 24), median BDI-II scores improved from 23 (range 14–49) to 12 (range 0–34) ($P < 0.001$). Cognition scores were measured by the Trail Making Test at wk 24/ET; there were improvements in both Trail A (median decrease of 4.0 sec, $P < 0.01$) and Trail B (median decrease of 12 sec, $P < 0.01$). Quality of life improved at wk 24/ET as measured by SF-36 mental composite scores (mean 40.0 ± 14.5 *vs.*

45.4 ± 12.5, $P = 0.01$) and physical composite scores (mean 34.9 ± 11.0 *vs.* 39.1 ± 10.8, $P = 0.02$).

Hormone and pituitary MRI scan changes

During mifepristone treatment, 72% of the 43 patients with CD had at least a 2-fold increase in ACTH, cortisol, or both; 28% had smaller increases. These changes were observed early (by d 14), plateaued from wk 10–24, and declined to baseline levels at the follow-up visit 6 wk after discontinuation of mifepristone. Increases in ACTH of at least 2-fold were observed in 62.8% of patients; 33.6% had lesser increases, and 4.7% had no change. Late-night salivary cortisol increased 7.92-fold (1.43) at wk 16, and urinary free cortisol increased 7.70-fold (15.29) at wk 24/ET. At the 6-wk follow-up visit, ACTH and cortisol (serum and urine) declined to near baseline levels. Patients with ectopic ACTH secretion did not demonstrate increases in ACTH and cortisol in response to mifepristone.

Pituitary MRIs were obtained in 41 CD patients; 17 had visible tumors, 10 of which were macroadenomas, and the remaining 24 did not have demonstrable tumors after surgery. MRIs were stable at wk 10 and 24 in all cases except one. This patient had an aggressive pituitary tumor at baseline that was increased in size at wk 10, leading to treatment discontinuation.

Safety

Overall, AEs were reported in 88% of patients during mifepristone treatment, most commonly nausea (48%), fatigue (48%), headache (44%), decreased blood potassium (34%), arthralgia (30%), vomiting (26%), peripheral edema (26%), HTN (24%), dizziness (22%), decreased appetite (20%), and endometrial thickening (20%). The majority of AEs were considered mild or moderate. Seven patients discontinued mifepristone because of an AE; fatigue was the only cause of discontinuation for more than one patient (n = 2). Interruptions or reductions in mifepristone due to AEs, most commonly nausea (n = 6), occurred in 40% of patients; there were interruptions or reductions for protocol-specified events in four subjects (two for AI, one for severe hypokalemia, and one for vaginal bleeding). After dose interruption or reduction before wk 10, there were increases in dose in one of four and two of five patients, respectively; after wk 10, dose escalation did not occur after an interruption for an AE except in a single patient. Four patients experienced progression of preexisting metastatic malignancy that resulted in death.

AI was reported in two patients. One occurred during an infection and responded to withdrawal of mifepristone; the other resolved with mifepristone withdrawal and dexamethasone administration (6–9 mg by mouth daily for 6 d). Neither episode was associated with hypoglycemia or hypotension, and mifepristone was restarted at a lower dose. Analysis of AEs and concomitant medications identified five other instances of two or more symptoms possibly consistent with AI during which glucocorticoids were administered. Dexamethasone doses for these episodes ranged from 2–8 mg daily in tapering amounts for 1–12 d. Vaginal bleeding was observed during the study in five premenopausal women. Prolonged metrorrhagia was observed in two of them after discontinuing mifepristone. Endometrial thickening was reported as an AE in 10 women. Three women underwent dilatation and curettage for unresolved endometrial thickening.

Twenty-two patients had a serum potassium level less than 3.5 mEq/liter (<3.5 mmol/liter), but only three experienced severe hypokalemia [≤2.5 mEq/liter (≤2.5 mmol/liter)] during mifepristone treatment, including one serious AE [potassium 2.1 mEq/liter (2.1 mmol/liter)]. Hypokalemia occurred in patients with both ACTH-dependent and independent CS. Four (one adrenal cancer and three ectopic ACTH) of seven patients with nonpituitary CS experienced hypokalemia during treatment. Hypokalemia was often associated with alkalosis and edema and generally responded to potassium replacement (10–420 mEq daily); all nonpituitary CS patients received potassium supplementation. Overall, spironolactone (50–400 mg daily) was used by 14 patients; it was started or increased in 11 patients for hypokalemia while taking mifepristone, including one patient with adrenal cancer and two patients with ectopic ACTH secretion. Reversible decreases in high-density lipoprotein cholesterol (HDL-C) and increases in TSH were observed. The mean change in HDL-C from baseline [62.3 ± 27.8 mg/dl (1.61 ± 0.72 mmol/liter)] to wk 24/ET was −14.2 ± 11.9 mg/dl (0.37 ± 0.31 mmol/liter) ($P < 0.001$); there were small declines in low-density lipoprotein cholesterol and triglycerides that were not statistically significant. Eight patients had undetectable TSH at baseline; of the remaining 42 patients, eight had increases in TSH above normal (three with TSH > 10 μU/liter, one with TSH of 32 μU/liter). Six weeks after mifepristone discontinuation, both HDL-C and thyroid function tests reverted to baseline levels.

Discussion

Cushing's syndrome is a complex endocrine condition with serious sequelae, including cardiovascular mortality, fractures, proximal myopathy, insulin-resistant hyperglycemia, and neuropsychiatric and neurocognitive disorders (35, 36). Transsphenoidal pituitary surgery with adenoma resection is initially successful in 65–90% of patients with ACTH-secreting microadenomas when performed by ex-

pert surgeons, but approximately 20–25% have persistent hypercortisolism or recurrence postoperatively; cure rates are lower and recurrence rates are higher for macroadenomas (4). Morbidity and mortality in patients with CD are related to cortisol excess and rarely to the ACTH-secreting pituitary tumor mass. When surgery fails to reverse hypercortisolemia, medical treatment can suppress cortisol overproduction and improve clinical manifestations. Bilateral adrenalectomy promptly resolves hypercortisolism but causes permanent adrenal cortical insufficiency mandating lifelong corticosteroid and mineralocorticoid replacement therapy. It may also decrease quality of life (5, 37) and can result in an enlargement of an ACTH-secreting pituitary tumor in 15–20% of cases (38). Patients with ectopic ACTH-secreting neoplasms or adrenocortical carcinoma often require control of hypercortisolism while waiting for definitive therapy or if definitive therapy is not feasible (39).

Mifepristone, a glucocorticoid receptor antagonist with binding affinity greater than dexamethasone and cortisol (10, 11), is rapidly absorbed orally, highly protein bound, and has a long half-life (40). The use of mifepristone in CS has been explored in case reports and/or small retrospective studies (9, 12–25). This is the largest prospective multicenter trial of mifepristone and demonstrates effectiveness in treating the clinical and metabolic derangements associated with hypercortisolism.

The two primary study endpoints were met: mifepristone significantly decreased $AUC_{glucose}$ during oGTT in patients with CS and T2DM or IGT and decreased DBP in a significant number of patients with CS and HTN. Significant decreases in FPG and HbA1c occurred in the C-DM cohort, and more than half the hypertensive patients in both groups had either an improvement in DBP or a reduction in antihypertensive medication. However, overall, there was no change in mean blood pressure from baseline to end of study.

As expected with a receptor-blocking strategy, ACTH and cortisol levels increased in patients with CD. Because high cortisol may not be completely inactivated by 11β-hydroxysteroid dehydrogenase type 2 in the kidney, excess cortisol may activate the mineralocorticoid receptor (41). This likely explains the increased blood pressure, hypokalemia, edema, and alkalosis seen in some patients; nine of the 12 patients with increased blood pressure were prescribed spironolactone.

Secondary endpoint results were noteworthy: mifepristone significantly decreased body weight, waist circumference, and body fat and increased insulin sensitivity. Clinically significant improvement was seen in 87% of patients, according to well-defined criteria used by the DRB. Moreover, 30 of the 34 patients who completed the 24-wk study elected to continue treatment with mifepristone.

Weight loss observed in the study may have been partially due to commonly experienced nausea and decreased appetite (see Supplemental Fig. 3) as well as to a direct result of glucocorticoid blockade. Moreover, it is not possible to discern whether these AEs result from medication or secondarily through a therapeutic effect of glucocorticoid withdrawal. Although clinically significant AI is a potential side effect of glucocorticoid receptor antagonism (9), it was uncommon during this study. Only two patients were reported to have AI; possible symptoms of AI including anorexia, nausea, lethargy, and dizziness occurred in five additional patients who also received glucocorticoids. It is important to note that cortisol elevations that occur in CD could be misleading and render the diagnosis of AI difficult. Without any available biochemical marker, these patients require close monitoring during treatment.

Decreased HDL-C and increased TSH were observed in some patients; these abnormalities resolved upon discontinuation of mifepristone. Because of its antiprogesterone effects, mifepristone has an impact on the endometrium characterized by thickening, with cystically dilated endometrial glands and features usually seen separately in normal proliferative and secretory endometrium (42). Ten women had AE of endometrial thickening, and abnormal vaginal bleeding occurred in five patients. An ongoing, long-term extension study will further characterize the safety profile of mifepristone in CS.

With the exception of a very aggressive tumor in one patient, there were no increases in tumor size, but it is important to note that the study duration was only 6 months. Data from longer-term use of mifepristone will be required to determine whether this risk is similar to that after bilateral adrenalectomy (38).

Limitations of the study include the lack of a placebo comparator group, the open-label design, exclusion of patients with *de novo* Cushing's who were candidates for surgery, and the small number of adrenal cancer and ectopic ACTH cases. The dosing scheme allowing investigators to use their clinical judgment regarding increasing mifepristone based on benefit *vs.* tolerance produced heterogeneity in management, which is a limitation of the study. Similarly, interruptions or reduction in the dose of mifepristone to manage AE produced additional dosing pattern heterogeneity. An assessment of dose response overall was therefore not possible.

Glucocorticoid receptor antagonism with mifepristone may offer a new approach to control the clinical manifestations of endogenous hypercortisolism in patients who have not responded to multimodal therapies. Although the side effect profile over 6 months is well characterized and

manageable with additional medications, the long-term efficacy and safety remain to be determined, particularly with regard to the need for potassium supplementation and/or mineralocorticoid receptor blockade and endometrial monitoring. Because mifepristone does not decrease cortisol production, measurement of this hormone should not be performed during treatment; careful monitoring by clinicians familiar with the mechanism of action of this unique agent is essential. Long-term data are needed to further define the role of mifepristone in the medical treatment of CS.

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