

IMMEDIATE AND SUSTAINED IMPROVEMENTS IN A CUSHING’S SYNDROME PATIENT WITH PRIMARY MACRONODULAR ADRENAL HYPERPLASIA TREATED WITH MIFEPRISTONE

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ABSTRACT

Background: Bilateral adrenalectomy is the standard treatment for bilateral macronodular adrenal hyperplasia (BMAH). It allows for rapid and permanent reversal of hypercortisolism but obliges the patient to receive life-long steroid replacement. Additionally, the permanent effects of mineralocorticoid and glucocorticoid deficiency expose the patient to the risks of adrenal insufficiency, including substantially increased morbidity and mortality. Medical therapies are being more commonly administered for a limited time prior to adrenalectomy. Herein, we present a patient receiving long-term treatment with mifepristone (MIFE, Korlym®, Corcept Therapeutics), a glucocorticoid receptor antagonist, for the treatment of BMAH-related Cushing’s syndrome (CS).

Case: A 54 y/o woman presented with cushingoid features and extreme weakness requiring a cane. Her medical history included uncontrolled diabetes (A1c 8.5%), HTN (141/88 mmHg) despite taking 6 antihypertensive medications, obesity (240 lbs, BMI 43 kg/m²), dyslipidemia, congestive heart failure, COPD, sleep apnea, chronic renal insufficiency, and hyperthyroidism. Abdominal CTs revealed diffused bilateral enlargements of the adrenal glands with density ranging from 2-20 HU, which were stable compared to previous imaging studies. Hormonal testing resulted in multiple suppressed ACTHs (<5 pg/mL), normal UFCs (18.2, 21.3 µg/24hr [nl=4-50]), unsuppressed 1-mg DST of 18.8 µg/dL, and low normal DHEA-S of 36 µg/dL [nl=8-188].

Diabetic meds: Novolin sliding scale, Lantus 20 U QHS. Anti-HTN meds: amlodipine 10 mg QD, carvedilol 25 mg BID, furosemide 40 mg QD, hydralazine 50 mg TID, lisinopril 5 mg QD, clonidine 0.2 mg QD.

Adrenalectomy was refused by the patient. Ketoconazole was rejected due to hepatic injury contraindication and potential for therapeutic escape. Mifepristone (MIFE) 300 mg/d was initiated and titrated to 600 mg/d.

After 2 weeks of treatment, the patient’s daily log recorded improvements in BP and fasting blood glucose, and 3 lbs weight loss. At 6 months, her A1c was 5.8% and she had lost 11 lbs. After 1 year, she had lost 28 lbs (12% of her baseline weight), with BP 130/84 mmHg, A1c 5.6%, and discontinuation of Lantus. Her daily log revealed well controlled daily glucose levels.

Conclusion: Our observation suggests that MIFE was a well-tolerated and efficacious option in this patient with CS due to BMAH when surgical intervention was not desired. GI-related adverse events (nausea, vomiting) were manageable with adjustment in dose and the beneficial effects were apparent and sustained

INTRODUCTION

- Bilateral adrenalectomy followed by life-long steroid replacement is the standard treatment for bilateral macronodular adrenal hyperplasia (BMAH)
- Bilateral adrenalectomy allows for rapid and permanent reversal of hypercortisolism but exposes the patient to the risks of adrenal insufficiency, including increased morbidity and mortality
- Medical therapies are more frequently being administered prior to adrenalectomy
- However, when surgery is refused by the patient, life-long medical therapy is required
- We describe a patient with Cushing’s syndrome resulting from BMAH who is receiving long-term treatment with mifepristone (Korlym®, Corcept Therapeutics), a competitive glucocorticoid receptor antagonist

CASE

- A 54-year-old woman presented with cushingoid features and extreme weakness requiring a cane
- Her medical history included uncontrolled diabetes (on sliding scale insulin and Lantus 20 U QHS), hypertension, obesity, dyslipidemia, congestive heart failure, COPD, sleep apnea, chronic renal insufficiency, and hyperthyroidism
- Abdominal CTs revealed diffused bilateral enlargements of the adrenal glands (**Figure 1**) with density ranging from 2-20 HU; enlargements were stable compared to previous imaging studies
- Clinical presentation, laboratory testing (**Table 1**), and adrenal imaging confirmed Cushing’s syndrome diagnosis
- Adrenalectomy was refused by the patient and ketoconazole was rejected due to hepatic injury contraindication and potential for therapeutic escape
- Mifepristone 300 mg/d was initiated and titrated to 600 mg/d

Figure 1. Bilateral Macronodular Adrenal Hyperplasia

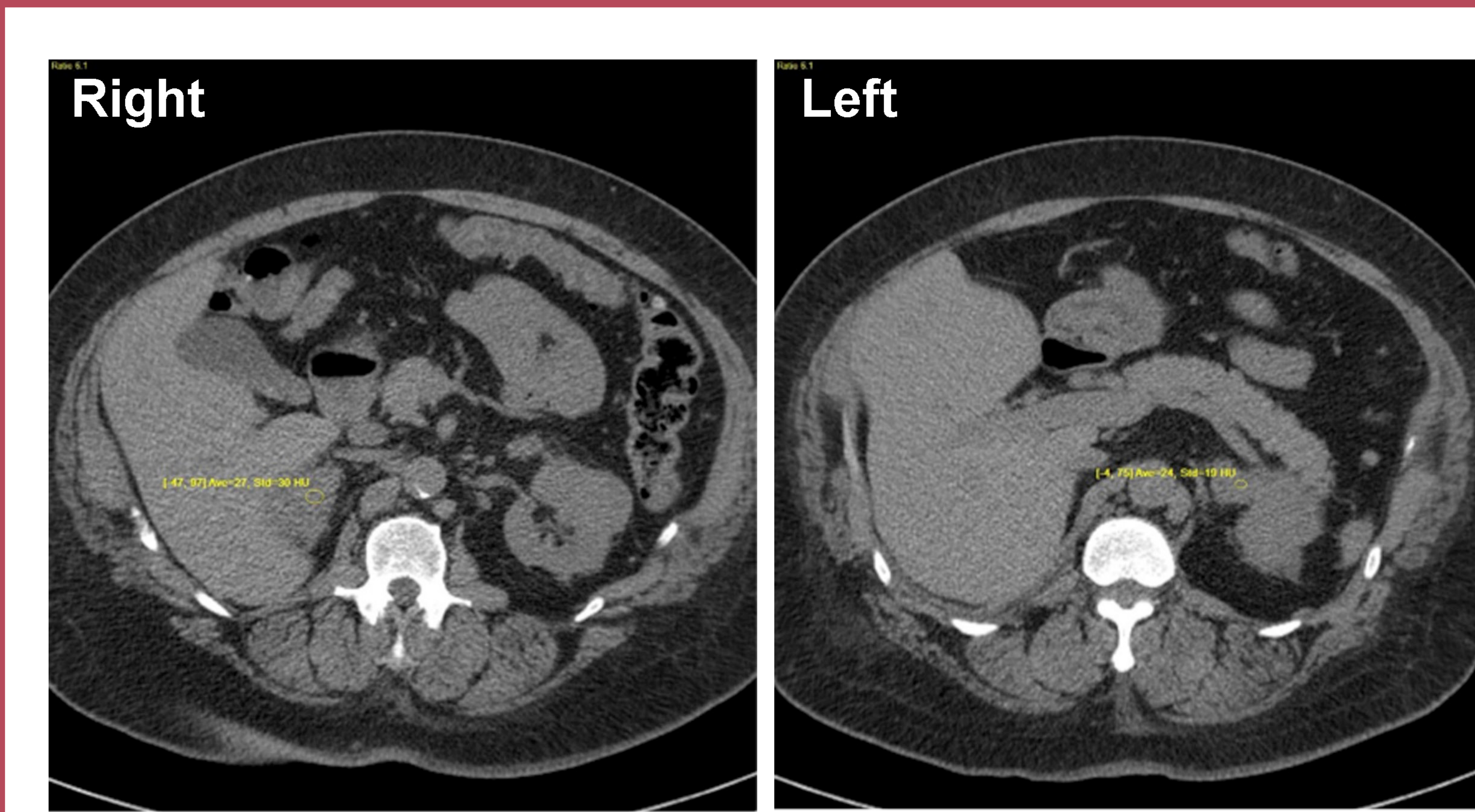


Table 1. Hormonal Testing Results		
	Results	Normal range
ACTH	<5 pg/mL, multiple suppressed results	
UFCs	18.2 µg/24hr; 21.3 µg/24hr	4-50 µg/24hr
1-mg DST	18.8 µg/dL	<1.8 µg/dL
DHEA-S	36 µg/dL	8-188 µg/dL

RESULTS WITH MIFEPRISTONE

- After 2 weeks of treatment, the patient’s daily log showed improvements in blood pressure and fasting blood glucose, as well as a 3-lb weight loss
- At 6 months, her A1c was 5.8% and she had lost 11 lbs (**Figures 2 and 3**)
- After 1 year, she had lost 28 lbs (12% of her baseline weight), with BP 130/84 mmHg, A1c 5.6%, and discontinuation of Lantus (**Figure 3**)
 - Her daily log revealed well controlled daily glucose levels
- At 1.5 years, the patient had lost 51 lbs (**Figure 2**), had an A1c of 5.7% (**Figure 3**), a blood pressure of 137/81 mmHg, and was using fewer medications to control blood pressure (**Table 2**)
- GI-related adverse events (**Table 3**) were manageable with adjustment in dose

Figure 2. Persistent Weight Loss

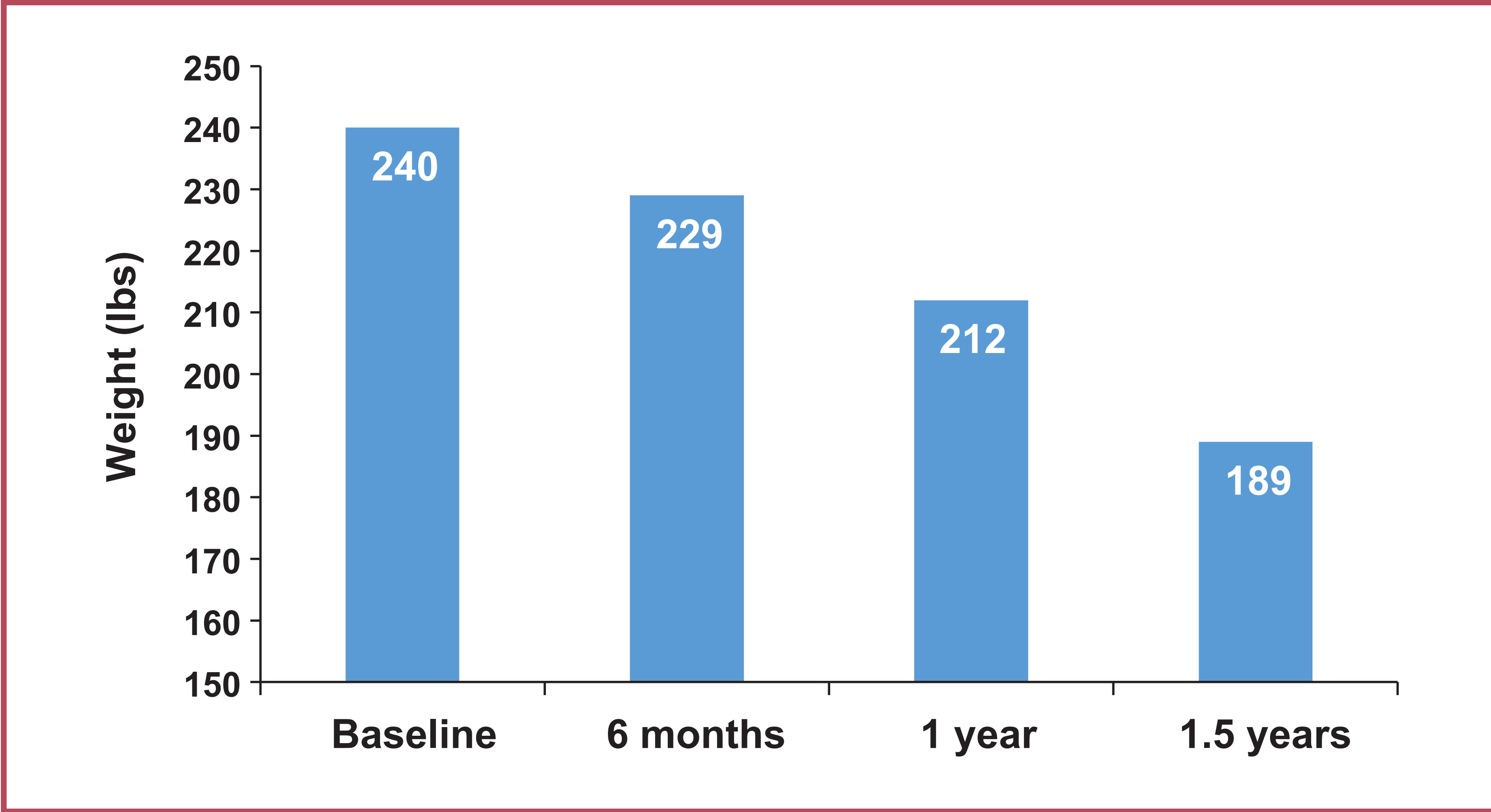


Figure 3. Improvements in Glycemic Control

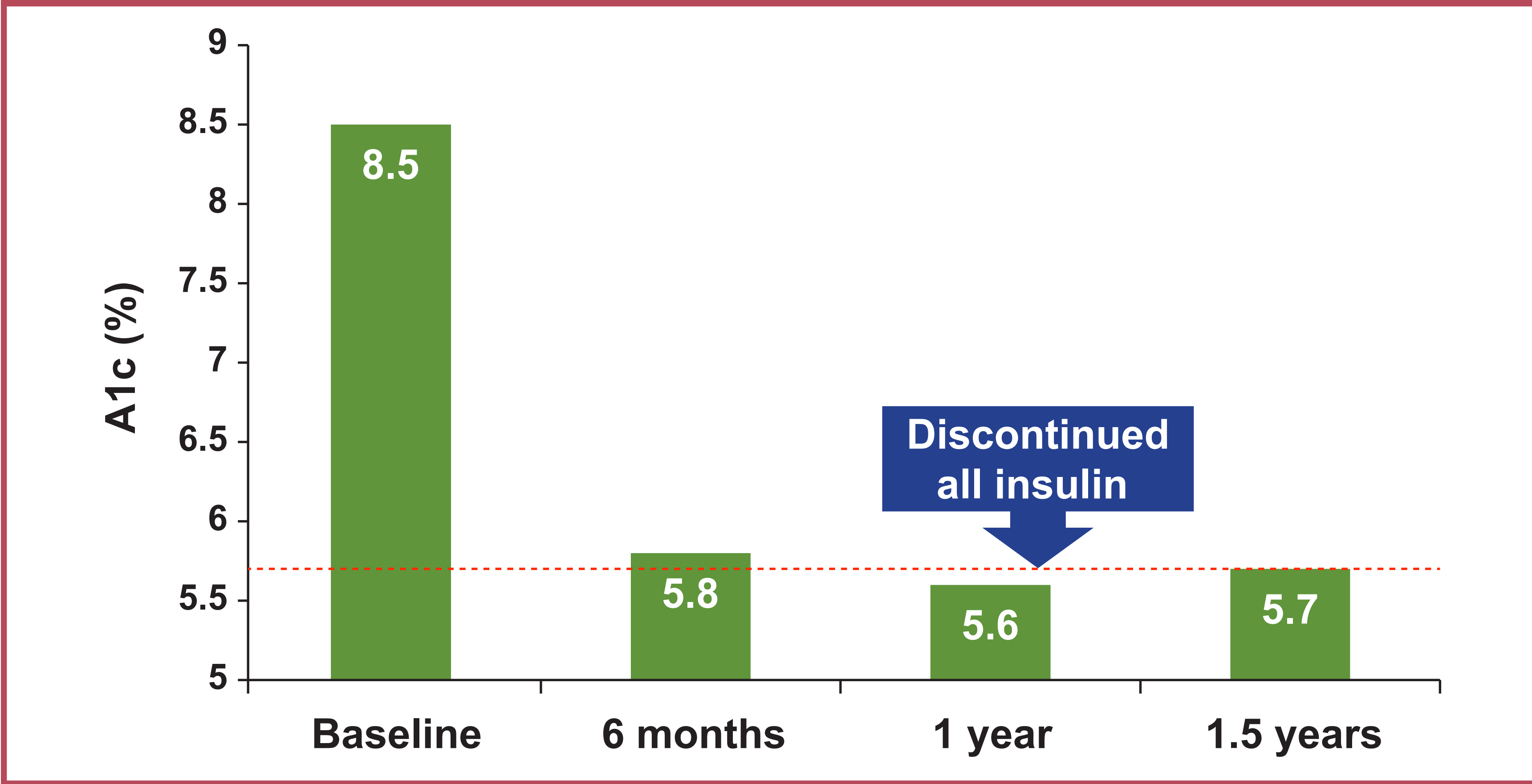


Table 2. Reductions in Blood Pressure and Use of Antihypertensives

	Baseline	1.5 years
BP	141/88 mmHg	137/81 mmHg
Medications	Amlodipine 10 mg QD Carvedilol 25 mg BID Furosemide 40 mtg QD Hydralazine 50 mg TID Lisinopril 5 mg QD Clonidine 0.2mg QD	Amlodipine 5mg QD — — — Lisinopril 5 mg QD Clonidine 0.2 mg QD Spironolactone 100 mg BID

Table 3. Adverse Events

Event	Management approach
• Gastrointestinal discomfort (nausea, vomiting, diarrhea)	Temporary reduction in mifepristone dose until resolution
• Fatigue and weakness	Resolved with increased spironolactone dose
• Hypokalemia	

SUMMARY

- Medical treatment with mifepristone may be an appropriate alternative to surgery in patients with Cushing’s syndrome due to BMAH
- Our case demonstrated that mifepristone was a safe and effective option for a BMAH patient wanting to avoid surgery, resulting in long-term and persistent clinical benefits

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DISCLOSURES

HEE: Speaker, Amgen, Boehringer Ingelheim, Corcept, Shire.
DN: Employee, Corcept.