


Mifepristone as Bridge or Adjunct Therapy in the Management of Challenging Cushing Disease Cases

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ABSTRACT: Establishing a definitive diagnosis of Cushing disease (CD), given its clinical and biochemical heterogeneity, initiating effective treatment to control the effects of hypercortisolism, and managing recurrence are challenging disease aspects to address. Mifepristone is a competitive glucocorticoid receptor antagonist that is approved in the US by the Food and Drug Administration to control hyperglycemia secondary to endogenous hypercortisolism (Cushing syndrome) in patients who have glucose intolerance or type 2 diabetes mellitus and have failed surgery or are not candidates for surgery. Herein, we describe 6 patients with CD who received mifepristone as adjunct/bridge therapy in the following clinical settings: to assess clinical benefits of treatment for suspected recurrent disease, to control hypercortisolism preoperatively for severe disease, to control hypercortisolism during the COVID-19 pandemic, and to provide adjunctive treatment to radiation therapy. The patients were treated at multiple medical practice settings. Mifepristone treatment in each of the described cases was associated with clinical improvements, including improvements in overall glycemia, hypertension, and weight loss. In addition, in one case where biochemical and radiological evidence of disease recurrence was uncertain, clinical improvement with mifepristone pointed toward likely disease recurrence. Adverse events associated with mifepristone reported in the 6 cases were consistent with those previously reported in the pivotal trial and included cortisol withdrawal symptoms, anti-progesterone effects (vaginal bleeding), hypothyroidism (treated with levothyroxine), and hypokalemia (treated with spironolactone). These cases show how mifepristone can potentially be utilized as a therapeutic trial in equivocal cases of CD recurrence; as a presurgical treatment strategy, particularly during the COVID-19 pandemic; and as bridge therapy, while awaiting the effects of radiation.

KEYWORDS: Cushing disease, mifepristone, recurrence, radiation therapy, presurgical, bridge therapy

MESH TERMS: Cushing Syndrome, Recurrence, Radiation

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Introduction

Cushing disease (CD) is a serious endocrine disorder characterized by hypercortisolism caused by chronic adrenocorticotropic hormone (ACTH) hypersecretion from tumors of pituitary origin (primarily adenomas).¹ Morbidities associated with CD may include diabetes mellitus, obesity, dyslipidemia, infection, myopathy, hypertension, thrombosis, hypokalemia, psychosis, depression, and fatigue.^{2–4} Given the clinical and biochemical heterogeneity of the disease,^{5–8} establishing a definitive diagnosis remains challenging,^{9,10} as does initiating effective treatment to control symptoms,¹¹ and manage disease recurrence.¹² When diagnosis is delayed and/or treatment is suboptimal, mortality is increased, with death commonly attributed to sepsis, cardiovascular events (eg, myocardial infarction, stroke, pulmonary embolism), or other systemic complications.⁴

Once CD is diagnosed, the optimal first-line treatment, if feasible, is transsphenoidal adenomectomy.^{11,13} The median rate of remission following initial transsphenoidal surgery (TSS) is 78.7%; however, rates vary widely.¹³ A recent large, multicenter, retrospective US study of adult patients with CD reported a remission rate of only 41% with initial pituitary

surgery despite being operated on by experienced surgeons.² Regardless, even in patients who achieve surgical remission, recurrence of hypercortisolism remains a lifelong risk.¹³ Among patients who obtained initial remission, disease recurrence rates range from 0 to 65.6% (median rate 10.6%).¹³ The 5-year recurrence rate for hypercortisolism among patients with CD who achieve immediate surgical remission is 26%.¹⁴

While prompt surgical intervention is warranted, uncontrolled comorbidities are associated with surgical risks (eg, infections, thromboembolic events).^{13,15} Furthermore, the emergence of coronavirus disease-2019 (COVID-19), along with regional measures to reduce transmission (eg, stay-at-home orders, holds on elective procedures, travel restrictions) and clinical guidance to mitigate the risk of transmission in patients with Cushing syndrome (CS),^{16–18} may warrant surgical delays.

Radiation therapy may be used in cases of disease persistence, surgical failure, or disease relapse, with a reported mean remission rate of up to 70.7%;¹³ however, onset of treatment effect may be delayed for years with this treatment modality, and hypopituitarism is a common side effect that can occur years following treatment.^{13,19} Medical therapies, including



pituitary-directed drugs, steroid synthesis inhibitors, and glucocorticoid receptor-directed drugs, are another feasible option to treat persistent CD following failed surgery,^{11,13} to manage disease recurrence,^{11,13} to preempt surgical complications by controlling severe hypercortisolism,¹³ and to bridge the delay of radiation effects.^{11,13} Although published data are lacking, medical treatment may also be useful for confirming symptomatic recurrent hypercortisolism prior to surgical intervention in patients with equivocal biochemical and radiological findings,^{20,21} and treating patients during the COVID-19 pandemic when it may be appropriate to delay transsphenoidal pituitary surgery.^{16-18,22} Each drug is associated with a specific safety and efficacy profile.

Mifepristone is a competitive GR antagonist approved by the US Food and Drug Administration for adult patients with endogenous hypercortisolism (CS), including CD, who have glucose intolerance or type 2 diabetes mellitus and have failed or are not candidates for surgery.²³ Mifepristone is not a treatment for type 2 diabetes mellitus in patients without endogenous hypercortisolism. Clinically significant improvement with mifepristone was achieved in 87% of patients in the SEISMIC study.²⁴ Treatment and adverse effects associated with mifepristone include cortisol withdrawal symptoms, antiprogesterone effects, changes in thyroid function, and hypokalemia.²⁴

We present a series of 6 patients with CD from multiple centers in whom mifepristone therapy was used as adjunct/bridge therapy in the following clinical settings: to assess clinical benefits of treatment for suspected recurrent CD, for preoperative control of hypercortisolemic effects, and as an adjunctive treatment to radiation therapy. These cases detail unique treatment courses for complex clinical scenarios that healthcare providers may encounter when managing patients with CD.

Consent

Institutional Review Board approval was not required by the 3 pituitary centers where these cases were documented. Informed consent was obtained from each patient. Laboratory and diagnostic findings for all cases are presented in the tables.

Cases

Case 1: Mifepristone as part of a strategy to detect recurrence and assess clinical benefit of treatment

A 34-year-old woman, diagnosed 3 years prior with CD when she developed weight gain, acne, hirsutism, amenorrhea, and altered cognition, presented with concerns of recurrence. At her initial diagnosis, no pituitary lesion was seen on magnetic resonance imaging (MRI); however, inferior petrosal sinus sampling (IPSS) indicated a central source of ACTH, and pituitary surgery was successfully performed. Pathology confirmed an ACTH-positive pituitary adenoma. She developed postoperative adrenal insufficiency, and the function of her

hypothalamic-pituitary-adrenal (HPA) axis returned after being on hydrocortisone replacement for 2 years.

At recent presentation, her symptoms included profound fatigue, cognitive and mood changes, nausea, night sweats, amenorrhea, and weight gain (Table 1). Repeated 1-mg dexamethasone suppression testing (DST) demonstrated unsuppressed cortisol, but 24-hour urinary free cortisol (UFC) and late-night salivary cortisol (LNSC) were normal (Table 1). Her pituitary MRI revealed no detectable abnormalities, but given the return of signs/symptoms similar to her initial presentation at diagnosis and the 1-mg DST cortisol results, medical therapy with mifepristone was initiated (300 mg/day for 2 weeks titrated to 300 mg/day and 600 mg/day on alternating days) for presumptive recurrence of CD. Within 8 weeks of treatment, she reported improvement in symptoms of nausea, fatigue, and cognitive disturbance. After 4 months of treatment, mifepristone was discontinued for 2 weeks for repeat biochemical testing and for assessment of symptom recurrence. A 1-mg DST and a dexamethasone-suppressed corticotropin-releasing hormone stimulation test (Dex-CRH) were both indicative of CD recurrence, whereas UFC, LNSC, and repeat pituitary MRI were all normal (Table 1). She reported a return of her symptoms during the 2 weeks off mifepristone; therefore, mifepristone was restarted, which was followed by resolution of symptoms. The abatement and return of symptoms while being on and off mifepristone suggested recurrent CD. She continued treatment for 7 months but experienced vaginal bleeding as a result of the antiprogesterone effects of mifepristone. The patient eventually elected to undergo a bilateral adrenalectomy (BLA) to treat her recurrent CD, as she wished to avoid the risks of hypopituitarism with fractionated radiation in the absence of visible tumor. She now receives glucocorticoid and mineralocorticoid replacement therapy to treat her adrenal insufficiency.

Case 2: Mifepristone prior to pituitary surgery in a patient with bilateral pulmonary emboli

A 36-year-old man presented with fatigue, ecchymoses, muscle wasting, facial swelling, and palmar erythema. Additionally, he was found to have new-onset type 2 diabetes (65 units/day of insulin initiated), resistant hypertension despite treatment with 4 antihypertensives, and severe hypokalemia (200 mg spironolactone and 160 mEq potassium chloride initiated) (Table 2). He was receiving anticoagulation therapy for extensive deep venous thromboses and pulmonary emboli. Biochemical testing confirmed the suspicion of severe hypercortisolism based on markedly elevated UFC and abnormal 1-mg DST (Table 2). MRI of the pituitary gland revealed a subtle, 6-mm hypoenhanced area. However, given the patient's abrupt development of hypercortisolism, with an extremely elevated 24-hour UFC of 13,943 µg/day (38,483 nmol/day), there was concern that the patient may have an ectopic source of ACTH production. Because of concerns

Table 1. Case 1: Diagnostic strategy to detect CD recurrence.

| Case summary: | <p>Presentation: 34-year-old woman with history of CD (TSS 3 years prior) presented with profound fatigue, changes in cognition and mood, nausea, night sweats, and 69.8 kg weight gain in 1 year (BMI 28.5 mg/kg²). Pituitary MRI negative; biochemical assessments equivocal.</p> <p>Treatment course: Mifepristone started (300 mg/day titrated to alternating 300/600 mg/day). After 8 weeks, symptoms improved. After 4 months, treatment paused for repeat testing, revealing abnormal 1-mg DST and Dex-CRH results. During 2-week pause, symptoms returned. Mifepristone restarted and symptoms abated. After 7 months of treatment, she experienced vaginal bleeding and underwent BLA.</p> | | |
|--------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| BIOCHEMICAL FINDINGS | INITIAL CD DIAGNOSIS | BEFORE MIFEPRISTONE (3 YEARS AFTER TSS) | RETEST AFTER MIFEPRISTONE PAUSE |
| Cortisol after 1-mg DST, µg/dL (normal <1.8 µg/dL) | 22 pre-op; 4 post-op | 2.8-6.1 | 5.1 |
| UFC, µg/d (normal 3.5-45 µg/d) | 159 | 19 | 19 |
| LNSC, µg/dL (normal <0.10 µg/dL) | | <0.05 | 0.07 |
| ACTH, pg/mL (normal 10-60 pg/mL) | 29 | 15 | 28 |
| Dex-CRH, cortisol, µg/dL (normal post-15 min: <2.5 µg/dL); ACTH, pg/mL (normal post-15 min: <27 pg/mL) | | | -5 min: cortisol 1.9; ACTH 9.1 0 min: cortisol 1.8; ACTH 8.8 15 min: cortisol 4.5; ACTH 28 30 min: cortisol 8.8; ACTH 26 45 min: cortisol 93; ACTH 31 60 min: cortisol 11; ACTH 38 |

To convert cortisol and LNSC to nmol/L, multiply by 276. To convert UFC to nmol/d, multiply by 2.76. To convert ACTH to pmol/L, multiply by 0.22.

Abbreviations: ACTH, adrenocorticotropic hormone; BMI, body mass index; CD, Cushing disease; Dex-CRH, dexamethasone-suppressed corticotropin-releasing hormone stimulation test; DST, dexamethasone suppression test; HbA1c, glycated hemoglobin; LNSC, late-night salivary cortisol; TSS, transsphenoidal surgery; UFC, urinary free cortisol.

Table 2. Cases 2 and 3: Presurgical symptom control.

| | CASE 2 | CASE 3 |
|-------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Case summary: | <p>Presentation: 36-year-old man presented with fatigue, ecchymoses, muscle wasting, facial swelling, and palmar erythema.</p> <p>Past medical history/work-up: New-onset T2DM (HbA1c 10% [79.5 mmol/mol]); uncontrolled hypertension (BP 140/95 mmHg); severe hypokalemia (2 mEq/L). Patient was receiving anticoagulation for extensive venous thromboses and bilateral pulmonary emboli.</p> <p>Treatment course: Mifepristone was started (300 mg/d) for 5 wk before surgery. During treatment, patient lost 6.8 kg; several medications were eliminated or reduced. Mifepristone discontinued. Patient underwent TSS 2 wk later.</p> | <p>Presentation: 59-year-old woman (BMI 33.61 kg/m²) presented with unexplained bruising, abdominal striae, lower extremity edema despite furosemide, proximal weakness necessitating a motorized scooter and cane for ambulation, progressively worsening memory, concentration, and irritability; hirsutism; alopecia; and an infected joint on left index finger that required amputation.</p> <p>Past medical history: T2DM (HbA1c 6.9% [47.6 mmol/mol]), controlled hypertension (BP 105/70 mmHg); hyperlipidemia, osteoporosis, nephrolithiasis, obesity, chronic cellulitis, and recent sepsis resulting from abscess development after lumbar spine surgery for spinal stenosis.</p> <p>Treatment course: Mifepristone was started (300 mg/d). Treatment paused twice for scheduled surgeries. Treatment resumed for 11 months. Antihypertensive and antidiabetic medications except metformin were discontinued. She lost 11.3 kg. Levothyroxine started for hypothyroidism; spironolactone started for hypokalemia. After 11 months, mifepristone increased to 600 mg for cushingoid symptoms. 6 months later, underwent IPSS (positive); MRI revealed pituitary lesion. Underwent TSS.</p> |
| BIOCHEMICAL FINDINGS | | |
| Serum cortisol, µg/dL (normal 7-25 µg/dL) | 71 Increased from 53 to 98 after CRH stimulation | — |

(Continued)

Table 2. (Continued)

| CASE 2 | | CASE 3 | | | | |
|--------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------|
| Cortisol after DST, $\mu\text{g/dL}$ | 1-mg DST: 46 (normal $<1.8\mu\text{g/dL}$) | 1-mg DST: 25 (normal $<1.8\mu\text{g/dL}$; dexamethasone level 265 ng/dL, normal 140-295 ng/dL) | 8-mg DST: 6.7 (normal $>50\%$ suppression of serum cortisol; dexamethasone $>1000\text{ng/dL}$, normal 1600-2850 ng/dL) | | | |
| UFC $\mu\text{g/d}$ (normal $<45\mu\text{g/d}$) | 13943 | 121.6 | | | | |
| LNSC, $\mu\text{g/dL}$ (normal $<0.09\mu\text{g/dL}$) | — | 1.35 | | | | |
| ACTH, pg/mL | 190 (normal 10-60 pg/mL) Increased from 98 to 1198 after CRH stimulation | 102 after 1-mg DST 18 after 8-mg DST (normal 7.2-63.3 pg/mL) | | | | |
| MEDICATIONS | BEFORE MIFEPRISTONE | DURING MIFEPRISTONE | 1.5Y POSTSURGERY | BEFORE MIFEPRISTONE | DURING MIFEPRISTONE | 1Y POSTSURGERY |
| | <ul style="list-style-type: none"> Insulin 65 units/d Losartan Hydralazine Amlodipine Metoprolol KCl 160 mEq/d Spironolactone 200 mg | <ul style="list-style-type: none"> Insulin 5 units/d Hydralazine Amlodipine KCl 40 mEq/d | <ul style="list-style-type: none"> Amlodipine Spironolactone 100 mg/d | <ul style="list-style-type: none"> Metformin Dulaglutide Glimepiride Lisinopril Amlodipine Atorvastatin | <ul style="list-style-type: none"> Metformin Atorvastatin Spironolactone Levothyroxine | <ul style="list-style-type: none"> Hydrocortisone Metformin Atorvastatin |

To convert cortisol and LNSC to nmol/L, multiply by 27.6. To convert dexamethasone to pmol/L, multiply by 25.48. To convert UFC to nmol/d, multiply by 2.76. To convert ACTH to pmol/L, multiply by 0.22.

Abbreviations: ACTH, adrenocorticotropic hormone; BP, blood pressure; BMI, body mass index; CRH, corticotropin-releasing hormone; DST, dexamethasone suppression test; HbA1c, glycated hemoglobin; KCl, potassium chloride; LNSC, late-night salivary cortisol; MRI, magnetic resonance imaging; T2DM, type 2 diabetes mellitus; TSS, transsphenoidal surgery; UFC, urinary free cortisol.

about suspending anticoagulation for IPSS, the patient instead underwent corticotropin-releasing hormone (CRH) stimulation, which showed an ACTH increase of $>50\%$ from baseline, suggestive of CD. The following month, when the patient's extensive clot burden had stabilized, he underwent IPSS, which confirmed a central source of hypercortisolism.

Because of the severity of his disease, mifepristone 300 mg/day was administered for 5 weeks prior to surgery to improve his preoperative status. During this treatment period, he lost 6.8 kg, his insulin requirement decreased to 5 units/day, losartan and metoprolol were discontinued, and his potassium supplementation decreased to 40 mEq/day.

Mifepristone was discontinued 2 weeks prior to pituitary surgery without a significant increase in glucose parameters or blood pressure. Sublabial TSS was performed, and an ACTH-positive adenoma was resected from the left lateral aspect of his pituitary gland. The patient was started on empiric hydrocortisone therapy (20 mg in the morning, 10 mg in the afternoon) immediately after surgery as per institutional protocol.

Postoperatively, insulin, hydralazine, and potassium were discontinued, and his spironolactone dose was reduced to 100 mg/day. Postoperative MRI revealed surgical changes with the previously described hypoenhanced lesion no longer visible. During the 1-month postsurgical endocrine follow-up visit, the patient's 8 a.m. cortisol was 4.6 $\mu\text{g/dL}$ (127.0 nmol/L) and ACTH was 21.2 pg/mL (4.7 pmol/L). Hydrocortisone was tapered and stopped 18 months after his pituitary surgery. The patient has remained in remission from CD for 4 years after surgery.

Case 3: Mifepristone prior to pituitary surgery in a patient with recent sepsis

A 59-year-old woman reporting multiple symptoms (Table 2) presented for evaluation of possible CS. Her past medical history included type 2 diabetes, hypertension, hyperlipidemia, osteoporosis, nephrolithiasis, obesity, chronic cellulitis, and recent sepsis (Table 2).

Her biochemical work-up was consistent with hypercortisolism (Table 2), but radiographic studies revealed no evidence of a pituitary adenoma. Because of her susceptibility to infections, inability to heal, and recent sepsis, she was considered too high of a procedural risk for IPSS or other invasive procedures. Medical therapy with mifepristone was initiated at 300 mg/day. After 2 weeks of mifepristone treatment, her glimepiride was discontinued. Mifepristone was temporarily discontinued to allow urgent surgery on an infected left knee. Mifepristone was held for 11 days prior to the surgery, resumed 9 days postsurgery at 300 mg every other day for 1 month, and increased to 300 mg/day for 2 months. She temporarily discontinued mifepristone treatment again 2 weeks before a scheduled right knee surgery for another infection; treatment was resumed 9 days postsurgery at 300 mg every other day for 1 week and then was increased to 300 mg/day. Over the course of mifepristone treatment for 11 months at 300 mg/day, all antihypertensive and antidiabetic medications except metformin were discontinued. The patient lost 11.3 kg and reported resolution of her cushingoid signs/symptoms. She developed hypothyroidism (initiated levothyroxine) and hypokalemia (initiated spironolactone 25 mg). She was able to heal from both knee surgeries and ambulate independently.

After 11 months, some cushingoid symptoms returned, and mifepristone was increased to 600 mg/day. After 6 additional months, the patient was reevaluated with an IPSS (positive), and a hypoenhanced lesion within the left aspect of her pituitary gland measuring 2 × 2 × 3 mm became visible on MRI. With her overall health improvement on mifepristone and improved surgical candidacy, she underwent TSS, which removed an ACTH-positive left pituitary adenoma. Postoperatively, her nadir cortisol level was 1.3 µg/dL (35.9 nmol/L), which was suggestive of disease remission. At discharge, she required hydrocortisone 20 mg twice daily. At 3 months postoperatively, her hydrocortisone replacement was tapered to physiologic dosing (20 mg daily) and levothyroxine was discontinued. After 1 year postoperatively, she remains on hydrocortisone (10–20 mg daily) and metformin (glycated hemoglobin [HbA1c] 6.5% [47.5 mmol/mol]).

Case 4: Mifepristone during the COVID-19 pandemic

A 53-year-old woman with ACTH-dependent CS was referred from her local endocrinologist for a telehealth consultation during the COVID-19 pandemic. The patient had a long history of type 2 diabetes, hypertension, and obesity. Her endocrinologist had locally pursued an evaluation for CS the previous year following multiple admissions for recurrent lower extremity cellulitis. Baseline ACTH level was 82 pg/mL (18.0 pmol/L), cortisol was 37.1 µg/dL (1024 nmol/L), and 1-mg DST revealed an unsuppressed 8 a.m. cortisol level (17.5 µg/dL [483 nmol/L]). Imaging, including an MRI of the brain and computed tomography (CT) of the chest and abdomen, did not reveal any tumor.

Her local endocrinologist initiated mifepristone and titrated up to 300 mg twice daily along with spironolactone 200 mg daily. After 3 months of treatment, she lost 13.6 kg, and her insulin dosage decreased from 80 units of glargine twice a day and 60 units of aspart 3 times a day with meals to 40 units of glargine twice daily and less than 10 units of aspart with meals. Her blood pressure control improved, and she was able to discontinue 2 of her antihypertensive medications.

Because of the COVID-19 pandemic, further management options at the tertiary care center were discussed with the patient via telehealth. One option included additional testing, involving discontinuation of mifepristone followed by IPSS and possible pituitary surgery. However, achieving surgical remission in the absence of a visible tumor was considered challenging. The patient had additional concerns about pursuing surgery given the uncertain course of the COVID-19 pandemic. Moreover, the need for postsurgical assessment and management, which often includes a steroid taper until recovery of endogenous pituitary and adrenal function is confirmed, would require additional office visits, unnecessarily exposing the patient to potential COVID-19 infection. Since her comorbidities had improved during mifepristone treatment, an alternative option to continue medical management of hypercortisolism and reconsider IPSS, repeat MRI, and possible surgery in the following year was discussed. After reviewing her options, she elected to continue mifepristone.

Case 5: Mifepristone prior to gamma knife (GK) radiosurgery

A 21-year-old woman presented with possible recurrent CD. Two years prior, she was diagnosed with CD in the context of morbid obesity, hypertension, poorly controlled type 2 diabetes, and acanthosis nigricans. At that time, her 24-hour UFC was elevated at 107 µg/day (295 nmol/day), LNSC was 0.586 µg/dL (16.2 nmol/L), DHEAS was 853 µg/dL (23 µmol/L), and ACTH was 88 pg/mL (19 pmol/L). MRI revealed a subtle area of hypoenhancement in the far-right lateral aspect of her pituitary gland contacting the medial aspect of the cavernous internal carotid artery, which decreased in size following TSS. Her surgical specimen stained positive for ACTH and had a low MIB-1 labeling index.

Three months after TSS, she had lost 9 kg, and her menstrual cycle had returned. She was tapered to a single medication for hypertension, her insulin requirements had diminished (30 units/day), and her total daily dose of hydrocortisone was 15 mg daily.

However, 10 months post TSS, she had regained 13.5 kg (total weight 145 kg; body mass index [BMI] 60.8 kg/m²) and her blood pressure (BP) (147/83 mmHg; spironolactone, hydrochlorothiazide, lisinopril) and glycemic control (HbA1c 9.8% [83.6 mmol/mol]) had worsened. Her 24-hour UFC measurements ranged between 75 and 85 µg/day (207.0–234.6 nmol/day).

After discussing treatment options for recurrent CD, the patient elected to undergo GK radiosurgery for the residual tumor in her right cavernous sinus. She was counseled on the potential implications of radiosurgery for future fertility and anterior pituitary hormone function. One month prior to radiosurgery, mifepristone was initiated at 300 mg/day and was titrated to 900 mg/day over 12 months as bridge therapy until the effects of radiosurgery could be demonstrated. During mifepristone treatment, her insulin requirements decreased from 130 to 22 units/day, while her HbA1c decreased from 9.8% (83.6 mmol/mol) to 6.5% (47.5 mmol/mol). She lost 18 kg over 12 months. Hypokalemia developed during mifepristone treatment and was managed with spironolactone 100 mg twice/day and potassium chloride 40 mEq 3 times/day. She remained on 3-drug antihypertensive therapy during mifepristone treatment, with sporadic hypertension associated with antihypertensive medication nonadherence. Two years after radiosurgery, the residual tumor in the right cavernous sinus (measuring 9 mm anteroposterior \times 5 mm transverse \times 3 mm craniocaudal on baseline postsurgical imaging) regressed and was nearly undetectable on 3T MRI.

While stereotactic radiosurgery improved her tumor burden, she did not experience glucocorticoid withdrawal or further clinical improvement (eg, reduction in insulin requirement or weight), indicating persistent ACTH production. She did not acquire any new anterior pituitary hormonal deficits following GK radiosurgery. She remained on mifepristone 900 mg daily and contemplated undergoing BLA at last contact.

Case 6: Mifepristone after GK radiosurgery

A 32-year-old woman presented for evaluation of persistent CD following an unsuspected diagnosis of CD approximately 1 year prior during an evaluation for bilateral galactorrhea. Among her many cushingoid symptoms, she reported precipitous weight gain (38 kg in 1 year), edema, visual disturbances, skin lesions, and recurrent infections. Also present were hyperprolactinemia (prolactin 45.6 ng/mL [2.0 nmol/L], upper limit of normal [ULN] 26.0 ng/mL [1.1 nmol/L]) and unsuppressed cortisol levels after 1-mg DST. Brain MRI revealed a pituitary mass measuring 1.8 \times 2.1 \times 1.6 cm with left cavernous sinus invasion and compression of her optic chiasm.

After undergoing TSS that removed an ACTH-positive pituitary adenoma, her cortisol levels did not drop sufficiently. The patient desired surgery rather than medical treatment. Future fertility was not a concern for her; therefore, a total hypophysectomy was undertaken. Postsurgical cortisol was 5.23 μ g/dL (144.3 nmol/L), and hydrocortisone replacement 20 mg twice daily was prescribed. She noted improvements in dermatological lesions, edema, and vision (left eye); however, she developed growth hormone deficiency (received growth hormone 0.2 mg), diabetes insipidus (received desmopressin 0.2 mg), hypothyroidism (received levothyroxine 150 μ g/day), and hypogonadism. Her hydrocortisone dose was 15 mg/day.

Six months after surgery, the patient was found to have prediabetes, hypertension, and weight gain, as well as various symptoms and laboratory measures characteristic of CD recurrence (Table 3). Brain MRI revealed a residual enhancing tumor within the left aspect of the sella and the left cavernous sinus with encasement of the left internal carotid artery of approximately 75% of its circumference. The residual tumor measured maximally 1.4 \times 1.7 \times 1.4 cm and extended minimally into the suprasellar space.

She underwent GK radiosurgery, and 2 weeks later, mifepristone was initiated at 300 mg/day as adjuvant therapy. After 1 month of treatment, her potassium was 3.6 mmol/L (normal range 3.5 mmol/L–5.2 mmol/L); 50 mg/day spironolactone was initiated. Free thyroxine decreased to 1.27 ng/dL (16.34 pmol/L; normal range 0.82–1.77 ng/dL [10.6–22.8 pmol/L]), so levothyroxine was increased to 175 μ g/day. She experienced mild symptoms of cortisol withdrawal, which resolved 2 months later, and mifepristone was titrated to 600 mg/day. She experienced more significant cortisol withdrawal symptoms (nausea, vomiting, and diarrhea), and her dose was reduced to 450 mg/day. She continued mifepristone for 8 additional months. During treatment, she experienced resolution of prediabetes (HbA1c 5.5% [36.6 mmol/mol]) and hypertension (BP 113/75 mmHg), and lost weight (BMI decreased from 52.01 to 41.71 kg/m²).

Although ACTH and cortisol were expected to increase on mifepristone treatment, her levels decreased (Table 3), suggesting GK radiosurgery success; hence, mifepristone was discontinued. Follow-up brain MRI 1 year after GK radiosurgery demonstrated that her residual tumor decreased in size and enhancement intensity. Ten months after discontinuing mifepristone, her ACTH remained normal, and cortisol remained low, although the cortisol increased after a cosyntropin stimulation test (Table 3). Blood pressure (BP 103/64 mmHg) and glucose control (FPG 68 mg/dL [3.8 mmol/L]) remained normal.

Discussion

The management of CD is often complicated by the potential risks of infection, uncontrolled diabetes, and/or hypertension, which may increase periprocedural risks.¹³ Postoperative management of residual unresectable tumor, persistent hypercortisolism, or disease recurrence requires interventions and considerations regarding more invasive treatments (eg, BLA, total hypophysectomy, radiation) to achieve sustained remission.¹³ The COVID-19 pandemic has further affected patient care and complicated treatment decisions. Recent guidance recommends deferring extensive laboratory and imaging diagnostic work-up and transphenoidal pituitary surgery during the pandemic depending on the patient's clinical disease severity and lack of visual symptoms; they suggest incorporation of virtual telehealth visits to aid in the diagnosis and management of patients.^{17,18} These cases from 3 pituitary centers provide real-world examples for how mifepristone can be used as adjunct/bridge therapy in challenging clinical

Table 3. Case 6: Bridging therapy for radiosurgery for recurrent CD.

| Case summary: | <p>Presentation: 32-year old woman with history of CD (post TSS, total hypophysectomy 1 y prior) presented with weight gain (BMI 52.01 kg/m²), scalp lesions, dorsocervical and supraclavicular fat deposition, facial rounding, hirsutism, pulsating headaches, edema, anxiety, poor memory, and low energy.</p> <p>Work-up: Prediabetes (HbA1c 6.5% [47.5 mmol/mol]) and hypertension (BP 132/78 mmHg, treated with triamterene/hydrochlorothiazide). MRI positive for residual tumor.</p> <p>Treatment course: Patient underwent GK radiosurgery followed by mifepristone (300 mg/day titrated to max-tolerated dose of 450 mg/day). After 1 mo, spironolactone added for low-normal potassium (3.6 mmol/L). Levothyroxine increased to 175 µg/day. During the following 10 months of treatment, her prediabetes (HbA1c 5.5%) and hypertension (BP 113/75) resolved, and she lost weight (BMI 41.71 kg/m²). ACTH and cortisol decreased; mifepristone was discontinued. MRI showed decrease in residual tumor size. Ten months after mifepristone discontinuation, BP (103/64 mmHg) and glucose control (FPG 68 mg/dL) remained normal.</p> | | |
|-------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------|----------------------------------------------------|
| BIOCHEMICAL FINDINGS | BEFORE GK RADIOSURGERY/ MIFEPRISTONE | DURING MIFEPRISTONE BRIDGE (AFTER RADIOSURGERY) | POST-MIFEPRISTONE |
| Serum cortisol, µg/dL (normal 7-25 µg/dL) | 12.3, 21, 23.9 | 7.4 | 7.3 15.3 after cosyntropin stimulation test |
| LNSC, µg/dL (normal <0.09 µg/dL) | 0.16, 0.41, 0.44, 0.31 on repeat testing | — | — |
| ACTH, pg/mL (normal 7.2-63.3 pg/mL) | 99 | 47.9 | 34.0 |

To convert cortisol and LNSC to nmol/L, multiply by 27.6. To convert UFC to nmol/d, multiply by 2.76. To convert ACTH to pmol/L, multiply by 0.22.

Abbreviations: ACTH, adrenocorticotropic hormone; BP, blood pressure; BMI, body mass index; CD, Cushing disease; FPG, fasting plasma glucose; GK, gamma knife; HbA1c, glycated hemoglobin; LNSC, late-night salivary cortisol; MRI, magnetic resonance imaging; TSS, transsphenoidal surgery; UFC, urinary free cortisol.

care settings to treat hypercortisolism while other treatment decisions are being considered.

Mifepristone as part of a strategy to detect recurrence and assess clinical benefit of treatment

Although the 2008 Endocrine Society guidelines outline the investigative strategy for the diagnosis of CD,⁹ currently no clear consensus exists regarding the most appropriate test(s) for the diagnosis of recurrent CD.^{10,25} The management of patients who present with recurrent, but not definitive clinical features in the context of equivocal biochemical is particularly challenging.²¹ The use of a therapeutic trial in patients with suspected CD recurrence who have equivocal biochemical workup, in order to determine if a more definitive treatment approach should be considered, has been previously proposed and warrants further prospective clinical evaluation.^{20,21}

Therapeutic trials to establish/support a diagnosis have long been used for other endocrinopathies; for example, spironolactone has been used historically as an empirical treatment to distinguish primary from secondary aldosteronism and to predict who might benefit from adrenal surgery;²⁶ and prednisone and methimazole have been used to treat amiodarone-induced thyroiditis when the type (type 1, type 2, mixed type) is in question.²⁷

In Case 1, the patient presented with recurrence of her presenting features of CD and demonstrated lack of suppression on two 1-mg DSTs, but had normal LNSC and 24-hour UFC, suggesting

early disease recurrence. A therapeutic trial of mifepristone was initiated, which resulted in symptomatic improvement. With time, repeated testing confirmed recurrent CD and the patient opted to undergo BLA to avoid hypopituitarism with fractionated radiation or total hypophysectomy. Although BLA offers definitive treatment of hypercortisolism, it results in permanent adrenal insufficiency, requiring lifelong glucocorticoid and mineralocorticoid replacement.¹³ While the use of a therapeutic trial in equivocal cases of CD is an area that requires further study, this case shows that medical treatment with mifepristone to manage symptoms may be useful during the ongoing evaluation of therapeutic options for recurrent or persistent CD, with awareness that treatment goals and patient preferences may change over time.

Medical therapy as preoperative treatment to control hypercortisolemic effects

Mortality from uncontrolled CD-associated hypercortisolism is largely attributed to cardiovascular disease and its consequent events, thrombotic events resulting from a hypercoagulable state, and/or systemic infections that often lead to fulminant septicemia.²⁸⁻³¹ Reducing the risk of such sequelae is vital, given that surgery tends to amplify these risks.^{13,15} Susceptibility to opportunistic infections due to glucocorticoid-induced immunosuppression is characteristic of CD^{4,32} and can be improved with effective treatment.^{4,33} However, to date, data supporting the potential benefits of preoperative treatment of hypercortisolism on surgical outcomes are lacking.³⁴

Case 2 illustrates the ability of mifepristone to control the effects of severe hypercortisolism and reduce the risk of perioperative complications in a patient with CD who presented with resistant hypertension, history of pulmonary emboli, and diabetes. The patient's disease manifestations were effectively stabilized and hypokalemia was effectively managed with spironolactone, enabling the patient to undergo the preferred surgical intervention. In the SEISMIC trial that included 50 adult participants on mifepristone therapy for CS, 44% developed hypokalemia, which responded to potassium supplementation (10–420 mEq daily) and the use of mineralocorticoid antagonist therapy (spironolactone: 50–400 mg daily).²⁴

Case 3 describes a complicated patient with high susceptibility to infectious complications, who, after mifepristone treatment, was able to undergo 2 knee surgeries without worsening infection or development of sepsis. She experienced further clinical benefit with mifepristone prior to surgery for CD that included improvements in ambulatory capacity, and glyce-mic and blood pressure control. In line with our case series, there have been other reports of symptom management benefits with the use of mifepristone in patients with hypercortisolism prior to surgery.^{13,35–37} Additionally, in Case 3, the pituitary tumor became visible during the interval period of medical therapy, allowing more targeted surgery, which may increase the likelihood of long-term remission. Mifepristone has been shown to increase ACTH levels.³⁸ The increase in ACTH levels with mifepristone and its effects on ACTH-secreting tumor progression is not yet well understood. Follow-up data from the SEISMIC study noted both regression and progression of pituitary tumors with mifepristone treatment.³⁸ Regression occurred in 2 patients (1 macroadenoma after radiotherapy and 1 microadenoma), and progression occurred in 3 patients with macroadenomas (2 after radiotherapy). Progression has also occurred in a patient with an initial nonvisible tumor; however, whether tumor growth was related to the drug or the natural history of the pituitary adenoma itself is unknown.³⁸

Case 4 describes a patient diagnosed with ACTH-dependent CS during the COVID-19 pandemic. No tumor had been visualized, and her comorbidities were being medically managed with mifepristone therapy. Preoperative counseling for pituitary surgery included detailed discussion about the postoperative likelihood of remission and hypopituitarism, the experience of steroid withdrawal symptoms, and the management of a potentially long glucocorticoid taper until endogenous pituitary function resumes. Telehealth consultation has improved our ability to communicate with patients and direct therapy during the uncertainty of the COVID-19 pandemic, especially when considering travel and surgery at tertiary pituitary specialty care centers. With the additional risk concerns for COVID-19 transmission and complications during the pandemic, patients and providers may consider medical therapy for CD more often as a presurgical option,^{16–18,22}

particularly when a tumor is not visible. In this case, the patient was able to discuss management options via telehealth and subsequently decided to continue medical treatment of her hypercortisolism while planning to reconsider additional testing in another year, with the hope that during the interval period, the tumor may become visible on follow-up imaging, as occurred in Case 3. This case demonstrates the importance of shared decision-making when treating patients with hypercortisolism and shows that it can occur successfully using telehealth medicine during the COVID-19 pandemic. Interval preoperative medical therapy might also facilitate postoperative recovery of the HPA axis, decreasing the need for or duration of glucocorticoid replacement therapy after surgery as described in adrenal CS.³⁶ However, one must consider the potential effects of preoperative medical treatment on the interpretation of surgical success, as medical treatment may confound the immediate postoperative cortisol assessment.³⁴

Medical therapy during the latency interval of radiotherapy

The mean time to initial remission varies from 3 to 58.3 months with stereotactic radiotherapy^{13,19,39} and from 10.2 to 24 months with conventional radiotherapy,^{13,40,41} thus, adjuvant medical therapy during this latency period is essential. In Cases 5 and 6, mifepristone was administered as adjunct therapy to radiation therapy. Case 5 describes a patient with recurrent disease, and Case 6 describes a patient with incomplete response following pituitary surgery. Treatment with mifepristone led to a reduction in weight and HbA1c in both cases, as well as resolution of hypertension in the latter. In Case 5, hypokalemia developed but was adequately managed with potassium supplementation and spironolactone. In Case 6, spironolactone was initiated during mifepristone treatment after a low-normal potassium level (3.6 mEq/L) was recorded, in order to proactively prevent an episode of hypokalemia, since mifepristone can exacerbate the risk of hypokalemia.²⁴ A similar proactive approach to mitigating the risk of hypokalemia has been suggested based on consensus recommendations for the management of patients treated with mifepristone from clinical practice.⁴² These recommendations included consideration of potassium supplementation and concomitant spironolactone for patients with baseline potassium levels less than 4 mEq/L followed by monitoring during and after mifepristone titration.⁴² The patient in Case 6 also had a history of central hypothyroidism. Substantial increases in thyroid hormone requirement (median levothyroxine dose increase 1.83 times initial dose) have been documented during mifepristone treatment in patients with CD and central hypothyroidism.⁴³ Free thyroxine (T4) levels should be monitored in patients with central hypothyroidism before and during mifepristone treatment.⁴² In this case, a clinical treatment decision was made to slightly increase the patient's dose of levothyroxine during mifepristone treatment following an observed decrease in free T4 levels.

As ACTH levels typically increase during mifepristone treatment, when a decline in cortisol and ACTH levels was observed in Case 6, it was a signal that the GK radiotherapy had been successful, and mifepristone was discontinued. Whether mifepristone and its associated changes in ACTH affect the outcome of radiotherapy itself remains to be determined, and its adjunctive use before and after radiotherapy in patients with CD has yet to be formally studied.

Conclusions

This case series highlights the utility and effectiveness of mifepristone therapy in patients with CD in perisurgical and per-radiation settings, where its use alleviated various clinical manifestations, including improvements in glycemic and blood pressure control, and weight reduction. In particular, during the COVID-19 pandemic, mifepristone may also be considered to treat the effects of hypercortisolism when surgical delays occur. The potential for mifepristone to be used as a therapeutic trial in patients with suspected recurrent hypercortisolism whose presentation is mild or biochemically inconclusive until definitive diagnosis and therapeutic strategies can be implemented should be further evaluated in a large prospective clinical study.

Previous Presentation

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AYC, SM, EEK, JUM, DMD, and KCJY were in charge of the clinical care of the patients. AYC, SM, EEK, JUM, DMD, and KCJY contributed to the writing of the article, revised it critically for important intellectual content, approved the final version of the manuscript, and take public responsibility for appropriate portions of the content.

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