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Tumor Shrinkage With Preoperative Relacorilant Therapy in Two Patients With Cushing Disease due to Pituitary Macroadenomas

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INTRODUCTION

- Transsphenoidal surgery (TSS) of the pituitary is the standard treatment for Cushing disease (CD), although patients with macroadenomas, particularly those with invasive tumors, have lower rates of surgical success and remission from hypercortisolism than patients with microadenomas[1]
- Relacorilant (CORT125134, Corcept Therapeutics) is a highly selective glucocorticoid receptor modulator in clinical development for the treatment of endogenous Cushing syndrome, or hypercortisolism, of all etiologies[2]
- Relacorilant demonstrates similar glucocorticoid receptor antagonistic effects as mifepristone (Korlym®), but without the anti-progesterone effects (abortifacient, endometrial thickening, vaginal bleeding) or mineralocorticoid effects (hypokalemia) of mifepristone[3]
- Results from an open-label phase 2 study (NCT02804750) indicated that treatment with relacorilant improved glycemic and blood pressure control in patients with endogenous hypercortisolism[4]
  - In the high-dose (up to 400 mg/day) relacorilant cohort, 50% of patients with hyperglycemia achieved improved glucose control, as shown by: ≥0.5% decrease in HbA1c, normalization or ≥50 mg/dL decrease in 2-hour oral glucose tolerance test (OGTT) glucose, or decrease in total daily insulin (≥25%) or sulfonylurea dose (≥50%)[5]
  - 63.6% of patients with uncontrolled hypertension achieved a ≥5 mmHg decrease in mean systolic and/or diastolic blood pressure, as measured by 24-hour ambulatory monitoring[5]
- Here we describe two patients with CD who were treated with relacorilant in the phase 2 study and who showed evidence of tumor shrinkage on posttreatment magnetic resonance imaging (MRI) performed after study completion

CASE PRESENTATION

- Two patients with de novo CD due to a macroadenoma were enrolled in the phase 2, multicenter, open-label, 12-week study of relacorilant for preoperative management
- At the conclusion of the study, patients underwent scheduled TSS surgeries
- Eligibility for the study included:
  - Patients aged 18-80 years with confirmed endogenous hypercortisolism as evidenced by ≥2 of the following:
    - 24-hour urinary free cortisol (UFC) above the upper limit of normal (ULN)
    - Late-night salivary cortisol above the ULN
    - Lack of cortisol suppression (>1.8 µg/dL serum cortisol) on either the overnight 1-mg or the 48-hour 2-mg dexamethasone suppression test
  - Impaired glucose tolerance or type 2 diabetes and/or uncontrolled or untreated hypertension
    - Impaired glucose tolerance and type 2 diabetes was determined by an OGTT
    - Hypertension was defined as mean systolic blood pressure of ≥130 mmHg and/or a diastolic blood pressure of ≥85 mmHg, as determined by ambulatory blood pressure monitoring
  - ≥2 clinical signs and symptoms of Cushing syndrome
  - Requirement for medical treatment for hypercortisolism
- If available, coronal postcontrast T1-weighted MRI obtained (as standard of care) up to 6 months before Day 1 and up to 1 month after the last relacorilant dose was reported

PATIENT HISTORY AND BASELINE CHARACTERISTICS

- **Patient 1** was a 50-year-old white woman with a pituitary macroadenoma measuring 10 x 6.3 mm on MRI
  - She presented with cushingoid features (moon face, dorsal and supraclavicular fat, plethora, central obesity, easy bruising, and striae) and had confirmatory biochemical tests (**Table 1**)
- **Patient 2** was a 43-year-old white man with a pituitary macroadenoma measuring 22 x 25 x 26 mm with suprasellar extension, right displacement of the pituitary stalk, and invasion of the left cavernous sinus on MRI
  - He also had cushingoid features and confirmatory biochemical tests (**Table 1**)

Table 1. Baseline Characteristics

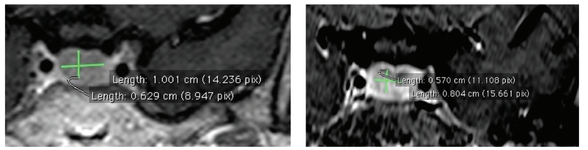
	Patient 1	Patient 2
Sex	Female	Male
Age, years	50	43
Weight, kg	105	92.5
Body mass index, kg/m^2	46.8	32.9
Biochemical findings		
ACTH, pmol/L	12.2	20.9
Late-night salivary cortisol, nmol/L	2.25	15.8
Urinary free cortisol, nmol/24 h	177.7	356.5

Normal laboratory ranges: ACTH, 1.3 to 11.1 pmol/L; late-night salivary cortisol, ≤2.5 nmol/L; urinary free cortisol, 11.1 to 138 nmol/24 h.
ACTH = adrenocorticotropic hormone.

MRI RESULTS

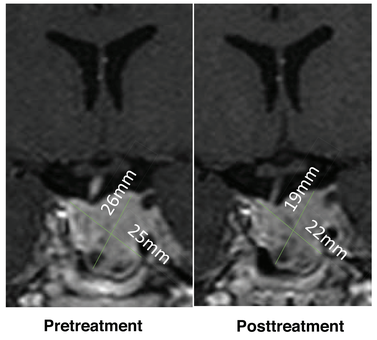
- Both patients received relacorilant at the following intervals:
  - Weeks 1-4: 100 mg/day
  - Weeks 5-8: 150 mg/day
  - Weeks 9-12: 200 mg/day
- After completing the 3-month study, preoperative MRIs revealed reduction in the size of their tumors
  - MRIs were performed within 2 weeks after the last dose of relacorilant
- The pituitary tumor for Patient 1 decreased from 10 x 6.3 mm prior to treatment to 8.0 x 5.7 mm after treatment with relacorilant (**Figure 1**)
- The pituitary tumor for Patient 2 decreased from 22 x 25 x 26 mm prior to treatment to 21 x 22 x 19 mm after treatment with relacorilant (**Figure 2**)
- Adrenocorticotropic hormone (ACTH) levels did not fluctuate and remained consistent with baseline (**Table 2**)

Figure 1. Patient 1: MRI of the Pituitary Macroadenoma Before and After 12 Weeks of Treatment With Relacorilant



Coronal post-contrast T1-weighted MR imaging obtained at diagnosis (left image) after administration of gadolinium showed a nodular lesion with reduced enhancement in the median and paramedian anterior part of the sellar region compatible with pituitary macroadenoma. It measured 10 x 6.3 mm. Pituitary MRI obtained 6 months later (right image), after 12 weeks of treatment with relacorilant, showed a reduction in the size of the macroadenoma (8.0 x 5.7 mm).

Figure 2. Patient 2: MRI of the Pituitary Macroadenoma Before and After 12 Weeks of Treatment With Relacorilant



Coronal post-contrast T1-weighted MR imaging obtained at diagnosis (left image) after administration of gadolinium showed a pituitary macroadenoma measuring 22 x 25 x 26 mm with suprasellar extension (bottom arrow), right displacement of the pituitary stalk (top arrow), and invasion of the left cavernous sinus. The tumor was isointense to the gray matter and slightly inhomogeneous for the presence of cystic changes in its lower aspect. MRI of the hypophysis obtained 6 months later (right image), after 12 weeks of treatment with relacorilant, showed a reduction in the size of the macroadenoma (21 x 22 x 19 mm) with decreased suprasellar extension (bottom arrow) and a recessed pituitary stalk (top arrow).

Table 2. ACTH at Baseline and Weeks 4, 8, and 12

	Patient 1	Patient 2
ACTH, pmol/L		
Baseline	12.2	20.9
Week 4	12.9	25.5
Week 8	13.3	30.2
Week 12	14.9	26.0

Normal laboratory ranges: ACTH, 1.3 to 11.1 pmol/L.
ACTH = adrenocorticotropic hormone.

DISCUSSION

- Pituitary imaging performed as part of the preoperative standard of care[6] revealed tumor shrinkage in two patients with macroadenomas treated for 3 months with relacorilant
- This unexpected finding will be further investigated in an ongoing phase 3 study with relacorilant (GRACE Study, NCT03697109)
- The reduction in the size of the macroadenomas may potentially be attributable to endogenous (hypothalamic) somatostatin via upregulation of somatostatin receptors type 2 (SSTR2), which are downregulated in patients with hypercortisolism[7]
- If this finding is confirmed, it may support the role of relacorilant as preoperative medical treatment for patients with CD with invasive macroadenomas

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DISCLOSURES

MT, DI, AP, PA, and RP served as investigators for this study.

AM: Employee, Corcept Therapeutics.

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