P03.THU-035

Impact of Surgery or Medical Treatment With the Selective Glucocorticoid Receptor Modulator Relacorilant on Hypercoagulopathy in Patients With Cushing Syndrome

PRESENTER:
Chiara Simeoli MD, PhD
Contact: simeolichiara@gmail.com

Chiara Simeoli[1], Nicola Di Paola[1], Antonio Stigliano[2], Pina Lardo[2], Tara Kearney[3], Emese Mezosi[4], Ezio Ghigo[5], Roberta Giordano[6], Cary N. Mariash[7], Diane M. Donegan[8], Richard A. Feelders[9], Austin L. Hand[10], Andreas G. Moraitis[10], Rosario Pivonello[1]

[1]Dipartimento di Medicina Clinica e Chirurgia, Sezione di Endocrinologia, Università "Federico II" di Napoli, Naples, Italy; [2]Endocrinology, Sant'Andrea University Hospital, Sapienza University of Rome, Rome, Italy; [3]Salford Royal Foundation Trust, Salford, Manchester, UK; [4]1st Department of Internal Medicine, Clinical Center, University of Pecs, Pecs, Hungary; [5]Division of Endocrinology, Diabetology and Metabolism, University of Turin, Turin, Italy; [6]Department of Biological and Clinical Sciences, University of Turin, Turin, Italy; [7]Indiana University and Indiana University Health, Indianapolis, IN, USA; [8]Indiana University School of Medicine, Indianapolis, IN, USA; [9]Erasmus Medical Center, Department of Internal Medicine, Division of Endocrinology, Rotterdam, The Netherlands; [10]Corcept Therapeutics Incorporated, Menlo Park, CA, USA

Summary & Conclusions

- Studies have shown increased risk of venous thromboembolism (VTE) in patients with Cushing syndrome (CS) that persists for several months after successful surgery
- Studies suggest coagulation factors may transiently worsen after successful surgery, before the coagulation state normalizes
- A positive impact of medical treatment on coagulation factors had not previously been demonstrated
- We present improvements in coagulation markers, including factor VIII (fVIII), in patients with CS within an average of 6 months after curative surgery
- Medical treatment with the investigational drug relacorilant may have similar effects after 3–4 months
- Transient increases in fVIII immediately after surgery, as reported by Casonato et al., were absent with relacorilant. Instead, decreases were seen throughout the study
- A phase 3 study investigating the efficacy and safety of relacorilant in patients with hypercortisolism due to adrenal adenoma or hyperplasia (GRADIENT, NCT04038590) and an open-label extension study of relacorilant in patients with CS (NCT03604198) will include assessment of relacorilant's impact on coagulation factors
- Should data from these analyses support our findings, pretreatment with relacorilant (once approved for CS) may be of benefit to patients, particularly those at high risk of VTE, by potentially eliminating the postoperative rise in coagulation factors

The authors want to thank all those who participated in the studies: The study participants and their families, the investigators, and the sponsor team.

ENDO2023
JUNE 15–18, 2023 CHICAGO, IL

Scan QR code to download poster

Background

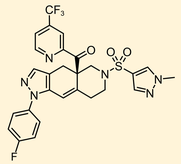
Hypercoagulability in Patients With Cushing Syndrome

- Hypercoagulability represents a significant concern in patients with CS, leading to elevated risk for thromboembolic events that contribute to cardiovascular morbidity and mortality[1-4]
- Increased synthesis of coagulation factors, particularly fVIII, which results in a shortening of the activated partial thromboplastin time (aPTT), contributes to the hypercoagulable state
- CS-mediated hypercoagulopathy appears to normalize within 6–12 months following curative surgery, but may worsen during the immediate postoperative period[5-7]
  - Casonato et al. (1999)[7] showed worsening hemostatic parameters in patients with Cushing disease within 1 month after surgery, independent of surgical outcome
  - Improvements began ~3 months after successful surgery and normalization occurred by 12 months
- This transient worsening may be due to increased inflammation following surgery. Additionally, the decrease in cortisol levels (and cortisol's anti-inflammatory effects) after successful surgery may also increase the coagulation cascade, which then normalizes over time

Relacorilant (CORT125134, Corcept Therapeutics)

- A selective glucocorticoid receptor modulator (SGRM) in development for the treatment of endogenous CS
- In a phase 2, open-label study in patients with CS (NCT02804750), relacorilant provided clinically meaningful changes in a number of cortisol-excess-related comorbidities, including hypertension and hyperglycemia, without undesirable antiprogesterone effects or drug-induced hypokalemia[8]

Relacorilant Structure



Objective

- Here, we evaluated the impact of treatment with relacorilant on coagulation parameters in patients with CS
- As recent surgical data are lacking, we also conducted a single-center, retrospective study to examine the effects of surgery on coagulation markers and to provide a historical cohort for comparison

1 Study Design and Methods

Surgical Study

- A retrospective, longitudinal cohort study in patients with endogenous CS treated at "Federico II" University of Naples, Italy, between 2004 and 2021
  - Coagulation markers (fVIII, von Willebrand factor [vWF], aPTT, and platelets) were assessed in 30 patients before curative surgery and after remission

Relacorilant Study

- An open-label, phase 2 study (NCT02804750) conducted between February 2017 and September 2018[8]
  - Patients with endogenous CS and uncontrolled hypertension and/or impaired glucose tolerance or type 2 diabetes mellitus received relacorilant at either a low dose (100–200 mg/day for 12 weeks) or high dose (250–400 mg/day for 16 weeks)[8]
  - Doses in each group were increased by 50 mg/day every 4 weeks[8]
- Coagulation markers (fVIII, vWF, aPTT, and platelets) were measured at baseline and at weeks 4, 8, 12, 16, and last observation in 34 patients
  - Additional ad-hoc assessments of coagulation factors VIII, IX, and X in patients with abnormal values at baseline were also conducted[8]

2 Results: Patients

- The majority of patients in the surgical and relacorilant studies had ACTH-dependent CS

Patient Demographic and Clinical Characteristics

	Surgical Study (n=30)	Relacorilant Study (n=34)
Age, years (mean ± SD)	51.3 ± 12.8	48.2 ± 13.3
Female, n (%)	24 (80.0)	24 (70.6)
Etiology, n (%)		
ACTH-dependent (pituitary or ectopic)	22 (73.3)	27 (79.4)
ACTH-independent (adrenal)	8 (26.7)	7 (20.6)
24-hour UFC, µg/24h xULN Mean ± SD	2.1x 615.6 ± 398.2[a]	4.2x 211.9 ± 234.3[b]
ACTH in patients with ACTH-dependent CS (mean ± SD)	80.4 ± 45.8[c] pg/mL	66.4 ± 28.6[d] pg/mL

To convert 24-hour UFC from µg/24 h to nmol/day, multiply by 2.76. To convert ACTH from pg/mL to pmol/L, multiply by 0.22.
[a]By immunoassay. Normal range: 21–292 µg/day.
[b]By tandem mass spectrometry. Normal range: <50 µg/day.
[c]By immunoassay. Normal range: 10–130 pg/mL.
[d]By immunochemiluminescent assay. Normal range: 6–50 pg/mL.
ACTH, adrenocorticotropic hormone; SD, standard deviation; UFC, urinary free cortisol; ULN, upper limit of normal.

3 Results: Surgical Study Outcomes

Surgical Outcomes

- Following surgical remission, mean UFC and ACTH normalized
- Mean (SD) time to remission post-surgery was 3.4 (2.4) weeks

Hemostatic Outcomes

- In the surgical study, significant mean changes from baseline were observed in aPTT, fVIII, and vWF; platelet count was unchanged
  - The mean (SD) time to hemostasis assessment was 6.2 (0.8) months

Changes in Hemostatic Parameters in the Surgical Study

	Baseline		In Remission		Change From Baseline	*P*-value
Mean ± SD	n	Mean ± SD	n	Mean ± SD		
fVIII, % [normal range 50–130]	30	161.9 ± 45.8	30	137.7 ± 40.4	-24.2	0.04
vWF, % [normal range 50–150]	24	150.5 ± 61.5	24	129.9 ± 38.4	-20.6	0.02
aPTT, sec [normal range 26–40]	30	28.5 ± 4.6	30	30.6 ± 3.4	+2.0	0.03
Platelet count, x10^9/L [normal range 130–400]	29	269.1 ± 60.5	29	261.1 ± 59.3	-8.0	ns

Wilcoxon signed-rank *P*-values were calculated to assess the mean changes from baseline.
aPTT, activated prothrombin time; fVIII, factor VIII; ns, not significant; vWF, von Willebrand factor.

4 Results: Relacorilant Study Outcomes

- In the relacorilant study, significant mean changes from baseline to last observed visit were reported in aPTT, fVIII, and platelet count; vWF was unchanged

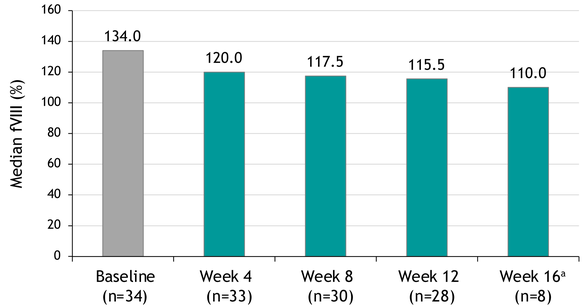
Changes in Hemostatic Parameters in the Relacorilant Study

	Baseline		Last Observed		Change From Baseline	*P*-value
	n	Mean ± SD	n	Mean ± SD		
fVIII, % [normal range 50–180]	34	143.0 ± 63.2	33	126.4 ± 50.2	-18.9	0.02
vWF, % [normal range 50–217]	34	145.8 ± 61.4	33	155.0 ± 65.3	+6.8	ns
aPTT, sec [normal range 22–34]	33	28.7 ± 10.5	32	28.4 ± 6.9	+1.5	<0.05
Platelet count, x10^9/L [normal range 130–400]	34	282.7 ± 75.7	34	213.9 ± 68.1	-68.8	<0.001

Wilcoxon signed-rank *P*-values were calculated to assess the mean changes from baseline.
aPTT, activated prothrombin time; fVIII, factor VIII; ns, not significant; vWF, von Willebrand factor.

- In the relacorilant study, median changes in fVIII over time showed decreases at each assessment interval through week 16

Median fVIII Levels During Relacorilant Treatment



For graphical representation, the median over time is displayed to minimize the effect outliers and smaller sample size have on the displayed data. fVIII, factor VIII.
[a]Week 16 data include only patients from the high-dose relacorilant treatment group.

- In the relacorilant study, significant improvements in other coagulation factors not collected in the surgical study were seen in patients with abnormal baseline values

Changes in Coagulation Factors in Patients With Abnormal Levels at Baseline in the Relacorilant Study

	Baseline		Last Observed		Change From Baseline	*P*-value
	n	Mean ± SD	n	Mean ± SD		
fVIII, % [normal range 50–180]	12	205.0 ± 61.0	12	150.8 ± 60.3	-54.2	<0.01
fIX, % [normal range 60–160]	10	182.7 ± 14.4	10	160.2 ± 31.1	-22.5	0.03
fX, % [normal range 70–150]	6	167.2 ± 14.8	6	147.0 ± 14.6	-20.2	0.03

fVIII, factor VIII; fIX, factor IX; fX, factor X.

References

1. Wagner J, et al. *Front Endocrinol*. 2018;9:805.
2. Świątkowska-Stodulska R, et al. *Endocr J*. 2015;62(8):687–94.
3. Pivonello R, et al. *Lancet Diabetes Endocrinol*. 2016;4(7):611–29.
4. Babic B, et al. *J Endocr Soc*. 2019;3(2):304–13.
5. Kastelan D, et al. *Clin Endocrinol*. 2013;78(1):102–6.
6. Ferrante E, et al. *J Endocrinol Invest*. 2022;45(1):9–16.
7. Casonato A, et al. *Blood Coagul Fibrinolysis*. 1999;10(3):145–51.
8. Pivonello R, et al. *Front Endocrinol*. 2021;12:662865.

Acknowledgements

Corcept Therapeutics provided a research grant for the surgical study. The phase 2 study was funded by Corcept Therapeutics. Funding for editorial, design, and production support for this poster was provided by Corcept to MedVal Scientific Information Services, LLC (Princeton, NJ, USA).

Disclosures

CS: Consultant/advisor: BresMed, Recordati; **NDP, AS, PL, EG, RG:** Nothing to disclose; **TK:** Other financial or non-financial interests: Corcept Therapeutics; **EM:** Research support: Corcept Therapeutics; Speaker: IBSA, Ipsen, Merck, Novartis, Pfizer, Recordati; **CNM:** Research support: Corcept Therapeutics; **DMD:** Consultant/advisor: Amryt, Corcept Therapeutics; Other financial or non-financial interests: Corcept Therapeutics; **RAF:** Consultant/advisor: Recordati; Research support: Corcept Therapeutics; Speaker: HRA Pharma, Recordati; **ALH:** Employee: Corcept Therapeutics; Stock ownership/options: Corcept Therapeutics; **AGM:** Employee: Corcept Therapeutics; **RP:** Consultant/advisor: BioPharma, BresMed, Corcept Therapeutics, HRA Pharma, Novartis, Pfizer, Recordati, Strongbridge; Research support (to institution): BioPharma, Camurus AB, Corcept Therapeutics, HRA Pharma, IBSA, Ipsen, Merck Serono, Neurocrine Biosciences, Novartis, Pfizer, Recordati, Shire, Strongbridge, Takeda.