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

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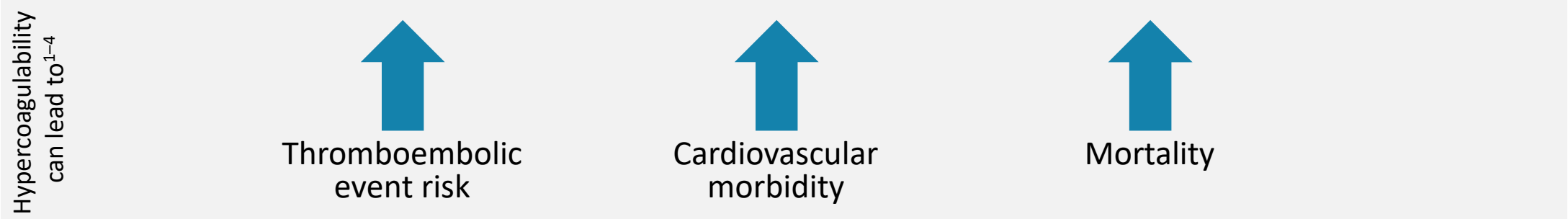
Disclosures

- Dr. Simeoli has been a consultant for BresMed and Recordati.

Hypercoagulability: A Significant Concern in Patients With Cushing Syndrome (CS)

- **Increased coagulation factor synthesis**, particularly fVIII, contributes to the hypercoagulable state



- Hypercoagulability typically **improves/normalizes 6–12 months after curative surgery**, but may **worsen immediately post-op**[5-7]
- Transient worsening in coagulation factors may be due to
  - **Increased inflammation** following surgery
  - **Decreased cortisol levels** (and cortisol's anti-inflammatory effects) after successful surgery

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.
fVIII, factor VIII; SGRM, selective glucocorticoid receptor modulator.

Study Aim & Patients

- We evaluated the impact of **curative surgery** or **medical treatment with relacorilant** on coagulation parameters in adult patients with CS

  - **Surgical study:** Retrospective, single-center, longitudinal cohort study conducted at "Federico II" University of Naples
  - **Relacorilant study:** Phase 2 prospective, multicenter, open-label study in patients with CS (NCT02804750)[8]
    - Relacorilant is a selective glucocorticoid receptor modulator in development for the treatment of endogenous CS

Patient Demographics 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	4.5x	4.2x
Mean ± SD	615.6 ± 398.2[a]	211.9 ± 234.3[b]
ACTH in patients with ACTH-dependent CS, pg/mL (mean ± SD)	80.4 ± 45.8[c]	66.4 ± 28.6[d]

[a]By immunoassay. NR: 35–135 µg/day. [b]By tandem mass spectrometry. NR: <50 µg/day.
[c]By immunoassay. NR: 10–130 pg/mL. [d]By immunochemiluminescent assay. NR: 6–50 pg/mL.

8. Pivonello R, et al. *Front Endocrinol*. 2021;12:662865.
ACTH, adrenocorticotropic hormone; CS, Cushing syndrome; NR, normal range; SD, standard deviation; UFC, urinary free cortisol; ULN, upper limit of normal.

Hemostatic Outcomes

- **Surgical study**
  - Significant changes were observed in **aPTT, factor VIII**, and von Willebrand factor
  - Platelet count was unchanged
- **Relacorilant study**
  - Significant changes were observed in **aPTT, fVIII,** and platelet count
  - Von Willebrand factor was unchanged
  - fVIII decreased over time with **no transient increase**
  - **Improvements in other coagulation factors** not collected in the surgical study were seen in patients with abnormal baseline values

	Baseline		In Remission / Last Observed		Change From Baseline (*P*-value)
	N	Mean ± SD	N	Mean ± SD	
Surgical Study					
fVIII, % Normal: 50–130	30	161.9 ± 45.8	30	137.87 ± 40.4	-24.4 **0.04**
vWF, % Normal: 50–150	24	150.5 ± 61.5	24	129.9 ± 38.4	-20.6 **0.02**
aPTT, sec Normal: 26–40	30	28.5 ± 4.6	30	30.6 ± 3.4	+2.0 **0.03**
Platelet count, x10^9/L Normal: 130–400	29	269.1 ± 60.5	29	261.1 ± 59.3	-8.0 ns
Relacorilant Study					
fVIII, % Normal: 50–130	34	143.0 ± 63.2	33	126.4 ± 50.2	-18.9 **0.02**
vWF, % Normal: 50–150	34	145.8 ± 61.4	33	155.0 ± 65.3	+6.8 ns
aPTT, sec Normal: 26–40	33	28.7 ± 10.5	32	28.4 ± 6.9	+1.5 **<0.05**
Platelet count, x10^9/L Normal: 130–400	34	282.7 ± 75.7	34	213.9 ± 68.1	-68.8 **<0.001**

Wilcoxon signed-rank *P*-values calculated to assess the mean changes from baseline to remission (surgical study) or baseline to last observation (relacorilant study). In the relacorilant study, data were missing in some patients for baseline or last observed; change from baseline is missing for patients with either baseline or last observed missing data.

aPTT, activated prothrombin time; fVIII, factor VIII; SD, standard deviation; vWF, von Willebrand factor.

Summary & Conclusions

- Hypercoagulability is a significant concern in patients with Cushing syndrome
  - A positive impact of medical treatment on coagulation factors had not previously been demonstrated
- **We presented improvements in coagulation markers, including fVIII, within ~6 months of curative surgery**
- **Medical treatment with relacorilant may have similar effects after 3–4 months**
  - Transient increases in fVIII, as previously reported, were absent with relacorilant
  - 2 ongoing studies[9-10] continue to assess relacorilant's impact on coagulation factors
  - Should these studies confirm our findings, pretreatment with relacorilant may potentially eliminate the post-operative rise in coagulation factors

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9. Phase 3 study of relacorilant in patients with hypercortisolism due to adrenal adenoma or hyperplasia (GRADIENT, NCT04038590). 10. Phase 2/3 extension study of relacorilant in patients with CS (NCT03604198). fVIII, factor VIII.