Poster no. GP185

Long-term treatment with metyrapone in four patients with Cushing's disease

Driessens N[1], Maiter D[2], Borensztein P[3], Jaspart A[3], Bostnavaron M[3], Beckers A[4]

[1]Endocrinology Department, Erasme Hospital, Brussels, Belgium; [2]Endocrinology Department, Saint-Luc Hospital, Brussels, Belgium; [3]HRA Pharma, Paris, France; [4]Endocrinology Department, Centre Hospitalier Universitaire de Liège, Liège, Belgium

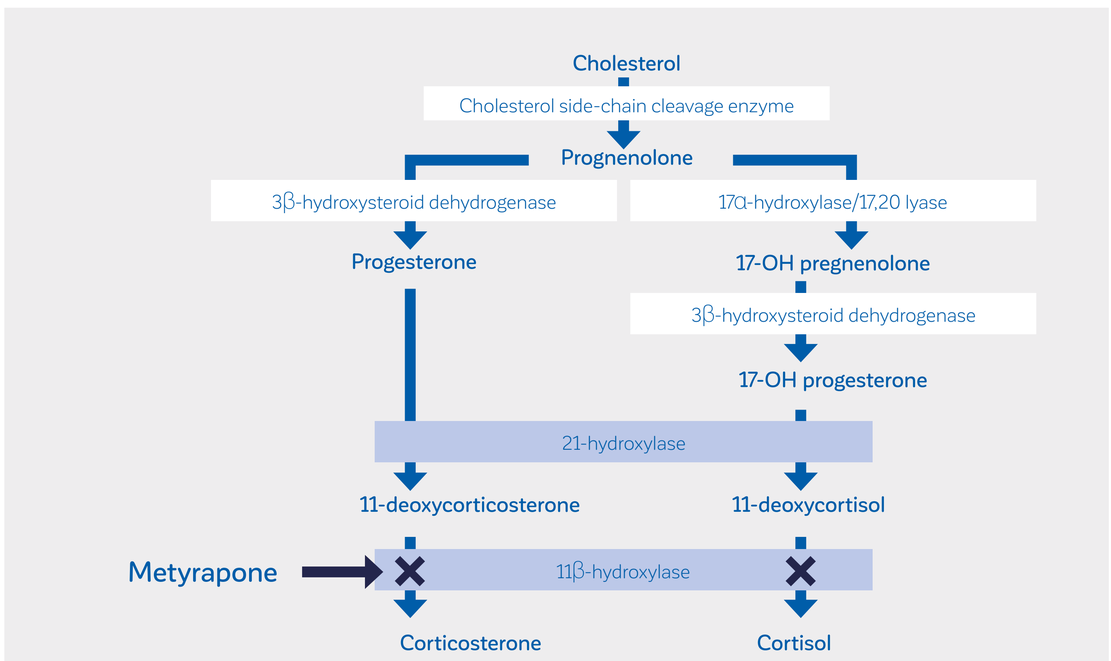
INTRODUCTION

- Cushing's disease (CD) is a severe disease, associated with an increased rate of comorbidities and mortality.[1]
- Remission rate after surgery of pituitary tumor is around 78%. Relapse occurs in 13% of patients within 10 years after surgery.[1]
- According to guidelines, patients who undergo noncurative surgery, or for whom surgery is not possible, require additional treatment, including medical therapies.[2]
- Metyrapone, inhibits 11β-hydroxylase enzyme, blocking the final step of cortisol synthesis in adrenal cortex (**Figure 1**). Daily dosage ranges from 250 to 6000 mg.[3]

Objective

- To report four cases of patients with CD receiving long-term treatment with metyrapone up to 24 months.

Figure 1: Mode of action of metyrapone

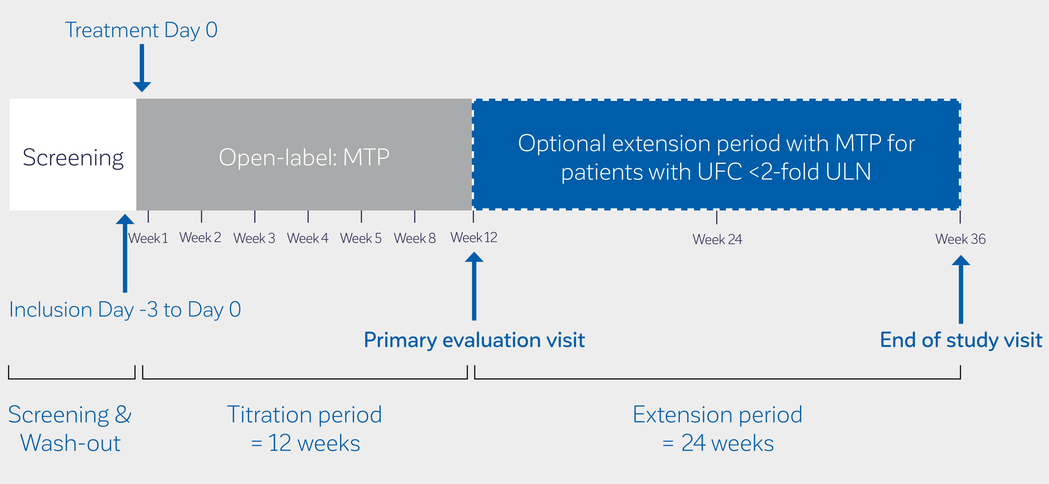


Adapted from: Kulstad EB, et al. *West J Emerg Med.* 2010;11(2):161–172. Creative Commons (CC BY-NC 4.0)

PATIENTS AND METHODS

- PROMPT is an international European Phase III/IV study that commenced in 2015 (ClinicalTrial.gov registry: NCT02297945).
- PROMPT is the first prospective study to document the safety and efficacy of metyrapone using modern assay techniques, in endogenous Cushing's syndrome over 36 weeks.
- In Belgium, four patients with CD (three women and one man) were treated with metyrapone for the duration of the 9-month PROMPT study.
- One patient had received prior medical treatment with ketoconazole and cabergoline and three patients had received prior pituitary surgery.
- Metyrapone was individually titrated during the first 3 months of PROMPT based on urinary free cortisol (UFC) and/or serum cortisol performed at each visit (**Figure 2**).
- UFC measurements during the study was performed centrally by liquid chromatography tandem–mass spectrometry (LC-MS/MS) method.
- An extension period of 6 months was proposed for patients whose mean UFC normalized or did not exceed twice the upper limit of normal (ULN = 165 nmol/24h) (**Figure 2**).
- All four patients benefited after study end from further therapy with metyrapone through a medical need program. Three patients were treated for an additional 15 months (total 24 months) and one patient for an additional 12 months (total 21 months).

Figure 2: Study design



MTP: metyrapone; UFC: urinary free cortisol; ULN: upper limit of normal

RESULTS

- Centralized UFC measurements (LC-MS/MS method) showed:
  - Baseline mean UFC value of 768 nmol/24h [range: 291–1244] fell below ULN after 3 and/or 9 months of treatment in three patients.
  - Baseline mean UFC of the fourth patient decreased by more than 50% after 9 months of therapy to 235 nmol/24h.
- Control of UFC levels was maintained during the study with a metyrapone dosage of between 500 mg and 5750 mg, divided into 3–4 intakes per day (**Table 1**).
- Adrenocorticotropic hormone (ACTH) remained unchanged after the first 3 months of therapy, except for one patient who needed 5750 mg/day of metyrapone (3.2-fold increase in ACTH, **Table 1**). The baseline mean UFC was also the highest in this patient.
- Three patients maintained control of UFC levels after 24 months of treatment (as at December 2017).
- Despite maintaining disease control with metyrapone, the fourth patient (Patient #2) decided after 21 months of treatment to undergo bilateral adrenalectomy.

Table 1: Efficacy results per patient during the PROMPT study

	Patient 1	Patient 2	Patient 3	Patient 4
Age (years)	34	51	56	45
Mean UFC baseline (nmol/24h)*	1244	291	358	695
Mean UFC Week 12 (nmol/24h)	294	139	67	333
Mean UFC Week 36 (nmol/24h)	127	68	97	235
ACTH baseline (ng/L)†	56	10	36	10
ACTH Week 12 (ng/L)	180	6	44	11
Metyrapone baseline (mg/day)	1500	500	750	750
Metyrapone Week 36 (mg/day)	5750	1250	750	2500

*UFC ULN: 165 nmol/24h; †ACTH ULN: 46 ng/L
ACTH: adrenocorticotropic hormone; UFC: urinary free cortisol; ULN: upper limit of normal

SAFETY AND TOLERABILITY

- Four patients had fatty deposits before treatment, which resolved in three of the patients; two patients developed bruising, which resolved in both patients.
- Patients experienced transient mild to moderate AEs during the 9 months of the PROMPT study: nausea (n=1), fatigue (n=2), tiredness (n=2), dizziness (n=1), migraine (n=1), loss of appetite (n=1) and arthralgia (n=1) (**Table 2**).
- Safety and tolerability were acceptable during the extension period after the 9-month study. Only one woman (Patient #3) developed hirsutism after one year of treatment, treated with cyproterone acetate. No acne was observed.

Table 2: Number of adverse events experienced per patient during the PROMPT study

Adverse event	Patient 1	Patient 2	Patient 3	Patient 4
Nausea				1
Fatigue			1	1
Tiredness	1	1		
Dizziness				1
Migraine				1
Loss of appetite		1		
Arthralgia			1	

CONCLUSION

- Metyrapone showed good efficacy with control of cortisol based on mean UFC.
- Metapyrone has an acceptable safety and tolerability profile in the long-term management (up to 24 months) of four patients with CD.

Acknowledgments and disclosures

N Driessens, D Maiter and A Beckers have each received research grants from HRA Pharma. A Jaspart, P Borensztein and M Bostnavaron are full-time employees of HRA Pharma.

This study and poster development was funded by HRA Pharma.

References

1. Pivonello R, et al. *Endocr Rev.* 2015;36(4):385–486
2. Nieman LK, et al. *J Clin Endocrinol Metab.* 2015;100(8):2807–2831
3. HRA Pharma UK & Ireland Ltd. Metopirone® (metyrapone) capsules 250mg. Summary of Product Characteristics. December 2016. https://www.medicines.org.uk/emc/product/4092 (Accessed: April 2018)

Presented at the 20th European Congress of Endocrinology, 19–20 May 2018, Barcelona, Spain.