PROMPT: A prospective study to assess efficacy and safety of metyrapone in endogenous Cushing's syndrome

Nieman L1, Akinci B2, Beckers A3, Bolanowski M4, Hanzu FA5, Mezösi E6, Tönjes A7, Bostnavaron M8, Jaspart A9, Borenztein P8, Boscaro M3, Scaroni C9

1The National Institute of Diabetes and Digestive and Kidney Diseases, NIH, Bethesda, US; 2Division of Endocrinology and Metabolism, Ghent University Hospital, University of Ghent, Belgium; 3Department of Endocrinology, Diabetes and Isotope Therapy, Wroclaw Medical University, Wroclaw, Poland; 4Endocrinology and Nutrition Department, Hospital Clinic, Division of Endocrinology and Nutritional Metabolism, University of Barcelona, Barcelona, Spain; 5Endocrine Unit, Endocrinology Department, Hospital Clinic Universitari, Barcelona, Spain; 6Division of Endocrinology and Metabolism, Dokuz Eylul University, Izmir, Turkey; 7Endocrinology Department, Centre Hospitalier Universitaire de Liege, Liege, Belgium; 8Department of Endocrinology, Diabetes and Isotope Therapy, Wroclaw Medical University, Wroclaw, Poland; 9Endocrinology and Nutrition Department, Hospital Clinic Universitari, Barcelona, Spain; 10Endocrine Unit, Endocrinology Department, Hospital Clinic Universitari, Barcelona, Spain.

INTRODUCTION

- Metyrapone blocks cortisol production by inhibiting 3β-hydroxysteroid dehydrogenase of 11-deoxycortisol, the last step of cortisol synthesis. (Figure 1)
- Based on observational retrospective studies published over more than 50 years, metyrapone is approved for the treatment of endogenous Cushing's syndrome (CS) in 15 European countries.
- PROMPT is the first prospective study to document the safety and efficacy of metyrapone using modern assay techniques.

Figure 1: Mode of action of metyrapone

METHODS

Patients
- Adult patients with a new diagnosis of endogenous CS of any etiology (except advanced adrenal carcinoma) or recurrent or persistent Cushing's disease (CD) after transsphenoidal surgery (TSS), were eligible if three baseline urine free cortisol (UFC) values measured over 24 hours were at least 50% above the upper limit of normal (ULN=165 nmol/24h).

Study design (Figure 2)
- The international European Phase III PROMPT study commenced in 2015 (ClinicaTrials.gov registry: NCT02395945).
- This single-arm, open-label, multicenter trial is ongoing in seven countries: Belgium, Germany, Hungary, Italy, Poland, Spain, Turkey

Figure 2: Study design

ENDPOINTS

- The primary endpoint is to assess the efficacy of metyrapone to normalize mUFC after 12 weeks of treatment.
- Secondary endpoints are:
  - Assessment of the efficacy of metyrapone to normalize serum and salivary cortisol after 12 weeks and UFC after 24 weeks;
  - Assessment of changes in clinical symptoms of CS, systolic and diastolic blood pressure, and quality of life (Cushing-QoL and Tübingen CD QoL inventory);
  - Assessment of safety and tolerability, including adverse events (AEs) and Ferriman-Gallwey score of hirsutism in women;
  - Assessment of impact of metyrapone blockade on circulating lipids, glucose, adrenocorticotropic hormone (ACTH), 11-deoxycortisol, deoxycorticosterone, renin/renin activity, androstenedione, 11-deoxycorticosterone sulfate and total testosterone levels;
  - Estimation of time to 50% reduction of UFC, eosinophilia, clinical and biochemical improvements.
- Exploratory endpoints include factors predicting success and response relationships.

Figure 3: Mean mUFC at baseline and at Week 12 in the initial 28 patients

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

Table 1: Metyrapone titration scheme

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Initial MTP dose</th>
<th>MTP dose change</th>
<th>UFC at baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline UFC ≤ 5 ULN</td>
<td>750 mg/day</td>
<td>Increase by 250–500 mg/day</td>
<td>≤ 5 x ULN</td>
</tr>
<tr>
<td>Moderate CS Baseline UFC &gt; 5 ULN</td>
<td>1500 mg/day</td>
<td>Increase by 250–500 mg/day</td>
<td>1500–1000 mg/day</td>
</tr>
<tr>
<td>Severe CS Baseline UFC &gt; 5 ULN</td>
<td>3000 mg/day</td>
<td>Increase by 250–500 mg/day</td>
<td>3000–5000 mg/day</td>
</tr>
</tbody>
</table>

STATUS

- The study commenced in 2015 and is ongoing.
- By April 2018, 35 patients were included; 24 women and 11 men, with a mean age of 45 years old (range: 21-73).
- A total of 32 patients had CD and 21 patients had previously undergone TSS (range: 1-3).
- Nine patients discontinued the study at the primary objective endpoint (Week 12) owing to inefficacy (n=3), mUFC >2 x ULN despite improvement by 10% (n=1), hirsutism (n=1), serious AEs (n=1; severe hypotension, cellulitis, venous thrombosis and renal insufficiency); and decision to undergo TSS despite metyrapone control (n=1).
- The mean of the mUFC values in the first 28 patients treated over 12 weeks decreased from 860 nmol/24h at baseline to 186 nmol/24h at Week 12 (Figure 3).

Acknowledgments and disclosures

B.Akcini, A.Bekker, M.Bolanowski, F.A.Hanju, E.Mezojsi, A.Tonjes, M.Boscaro and C.Scaroni have each received research grants from HRA Pharma. M.Bostnavaron, A.Jaspart, and P.Borenztein are full-time employees of HRA Pharma. L.Nieman's work in this study was supported by the intramural division of NIH. This study and poster were funded by HRA Pharma.

References