During the COVID-19 Pandemic and Beyond

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INTRODUCTION

- Achieving/maintaining effective hormone suppression is fundamental in treating central precocious puberty (CPP)
- CPP patients are vulnerable to late dosing as they cannot self-administer and require clinic/hospital visits for injections, currently exacerbated by COVID-19
- In children, the hypothalamic-pituitary-gonadal axis may rebound faster than elderly oncology patients, so hormone escapes are possible with late dosing
- The stimulatory flare from gonadotropin-releasing hormone agonists (GnRHa) increases risk of escapes with late injections
- Older duration formulations demonstrating hormone suppression through the dosing interval should be considered
- Longer duration formulations, such as 6-month formulations, may have benefits

RESULTS

- CPP Study
  - Mean age at onset of treatment was 7.5±0.1 years (Table 1)
  - LH levels of <4 IU/L were achieved by ≥85% of children at each timepoint (Figure 1)
  - All but 2 children achieved suppression of E2 <20 pg/mL (58/60; 97%) or T <28.4 ng/dL (2/2; 100%) at week 24, meeting predefined prespecified targets (Table 2)
- PCa Study
  - Patient demographics were well-balanced across subgroups (Table 3)
  - 27% of GnRHa agonists were administered later than scheduled
  - Number of late doses/year for 1, 3, 4, 6-month GnRHa formulations were 5.4, 0.8, 0.8, 0.6, respectively (Table 4)
  - 43% of testosterone values exceeded 20 ng/dL for late injections compared to only 21% for early/on-time injections (Figure 2)

OBJECTIVE

- The first study evaluated efficacy and safety of 6-month 45 mg subcutaneous leuprolide acetate for CPP
- As large numbers of CPP patients are not present in real-world databases, we present data from a second study in prostate cancer (PCa) patients treated with drugs with the same active ingredient and similar mechanism of action to determine the scope and impact of late injections on androgen deprivation therapy
- The second study in PCa patients evaluated:
  - Timeliness of Leuprolide administration
  - Subsequent rate of T breakthroughs above 20 ng/dL

METHODS

- Sixty-two children (60 girls, 2 boys) with treatment-naive CPP received 2 doses of 45 mg subcutaneous leuprolide acetate at 24-week intervals
- Calculate the percentage of children with serum luteinizing hormone (LH) <4 IU/L at 30 minutes following GnRHa stimulation at week 24
- PCa Study
  - A retrospective analysis (1/10-6/2016) of US oncology/urology clinics, multispecialty practices, small group practices and physician offices (EMR of PCa patients receiving GnRHa injections (n=85,030) was conducted to evaluate the frequency of late injections and testosterone (T) >20 ng/dL (target levels in PCa)
  - Mean late doses/year for 1, 3, 4, 6-month GnRHa doses were calculated by multiplying late dose proportion and number of doses/year
  - Late dosing was defined as occurring after days 33, 98, 129, 195, respectively

CONCLUSIONS

- A small volume of 45 mg subcutaneous leuprolide acetate administered at a 6-month interval effectively suppressed pubertal hormones
- This long-acting GnRHa preparation of leuprolide acetate is a new and effective therapy for children with CPP
- 6-month GnRHa formulations require fewer visits for treatment, which will likely be preferred by patients and clinicians, especially during a pandemic
- 6-month formulations had fewer late doses/year vs. 1, 3, 4-month formulations
- Late injections were correlated with ineffective T suppression: 10 levels were >20 ng/dL over 40% of the time
- Late dosing decreased the proportion of T >20 ng/dL compared to early/on-time dosing

IMPLICATIONS

- The 45-mg, subcutaneous formulation of leuprolide acetate is the first leuprolide acetate therapy with a polymeric gel delivery system and a small injection volume administered subcutaneously every 6 months, and represents an effective and convenient addition to existing treatment options for children with CPP
- Clinicians should ensure dosing is on time or consider using 6-month formulations that have less frequent opportunities for late dosing and demonstrate/maintain efficacy through the labelled dosing period
- This will give greater confidence of continued hormone suppression when dosed late
- Similar studies should be conducted to assess the impact late dosing of GnRHa in CPP patients

REFERENCES

2. Shore ND, et al., Prostate Cancer Prostata Dis 2013
4. Klein KG, et al., The Journal of Clinical Endocrinology & Metabolism 2020

ACKNOWLEDGMENTS

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Table 1: CPP Study Baseline Demographics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Safety (N=62)</th>
<th>ITT (N=62)</th>
<th>Protocol (N=56)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>Median (IQR)</td>
<td>12 years (10-14)</td>
<td>12 years (10-14)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td>Female (%)</td>
<td>98 (60/62)</td>
<td>98 (60/62)</td>
</tr>
<tr>
<td><strong>White</strong></td>
<td>White (%)</td>
<td>63 (134/205)</td>
<td>61 (132/205)</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td>Asian (%)</td>
<td>0 (0/62)</td>
<td>0 (0/62)</td>
</tr>
<tr>
<td><strong>Number of Late Doses/Year</strong></td>
<td>Median (IQR)</td>
<td>5.4 (3.3-8.4)</td>
<td>0.8 (0.5-1.4)</td>
</tr>
</tbody>
</table>

Table 2: CPP Study Proportion of Children Achieving Serum Hormone Suppression (ITT Population) (N=62)

<table>
<thead>
<tr>
<th>Week</th>
<th>LH &lt;4 IU/L</th>
<th>FSH &lt;2.5 IU/L</th>
<th>Estradiol &lt;73.4 pg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>73.3%</td>
<td>74.4%</td>
<td>74.4%</td>
</tr>
<tr>
<td>24</td>
<td>74.4%</td>
<td>75.0%</td>
<td>75.0%</td>
</tr>
<tr>
<td>36</td>
<td>74.4%</td>
<td>75.0%</td>
<td>75.0%</td>
</tr>
<tr>
<td>48</td>
<td>74.4%</td>
<td>75.0%</td>
<td>75.0%</td>
</tr>
</tbody>
</table>

Table 3: PCa Study Patient Demographics – Age and Race (n=22,845)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Age (Mean)</th>
<th>Sex (% Male)</th>
<th>White (%)</th>
<th>Asian (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>Mean (SD)</td>
<td>Median (IQR)</td>
<td>Mean (SD)</td>
<td>Median (IQR)</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td>Median (IQR)</td>
<td>72.5 (5-83)</td>
<td>65.0 (5-83)</td>
<td>37.5 (5-83)</td>
</tr>
<tr>
<td><strong>Asian</strong></td>
<td>Median (IQR)</td>
<td>1.6 (1-2.3)</td>
<td>1.6 (1-2.3)</td>
<td>1.6 (1-2.3)</td>
</tr>
</tbody>
</table>

Table 4: PCa Study Illustration of Expected Number of Late Injections per Year by Formulation

<table>
<thead>
<tr>
<th>Formulation</th>
<th>1-Month</th>
<th>2-Month</th>
<th>3-Month</th>
<th>4-Month</th>
<th>5-Month</th>
</tr>
</thead>
<tbody>
<tr>
<td>FSH Levels &lt;2.5 IU/L</td>
<td>15.2%</td>
<td>10.2%</td>
<td>7.2%</td>
<td>5.2%</td>
<td>3.2%</td>
</tr>
<tr>
<td>Estradiol Levels &lt;73.4 pg/mL</td>
<td>15.2%</td>
<td>10.2%</td>
<td>7.2%</td>
<td>5.2%</td>
<td>3.2%</td>
</tr>
<tr>
<td>Testosterone Levels &lt;20 ng/dL</td>
<td>15.2%</td>
<td>10.2%</td>
<td>7.2%</td>
<td>5.2%</td>
<td>3.2%</td>
</tr>
</tbody>
</table>

Figure 1. CPP Study Mean (±SE) Peak LH Level and Proportion of Children Who Achieved Peak LH <4 IU/L (ITT Population)

- GnRHa Stimulation
- Target Level (<4 IU/L)
- Actual Peak LH

Figure 2. CPP Study Proportion of T Tests >20 ng/dL After Early/On-Time1 and Late1 Injections

- Early/On-Time1 (n=480) and Late1 Injections (n=804)
- Percent of T Tests >20 ng/dL After Early/On-Time1 Injections
- Pooled: 21%
- Late1 Injections
- Pooled: 43%
- 32% 36%