Updates on Adrenal Disease: GnRH AGONISTS AND GnRH VACCINE STUDIES

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Ferret Adrenal Cortical Disease (ACD)

- Common (60-70%) in 2-5 year old ferrets
- Females ≥ Males
- Left adrenal tumor ≥ right tumor frequency
- Clinical signs are due to sex hormones
- Signs: Alopecia, swollen vulva, 30% pruritic, behavior changes, others.
- Dx: Clinical signs, sex hormones, palpate, ultrasound, exploratory surgery.
- Tx: Adrenalectomy, Lupron, Deslorelin, GnRH vaccination, melatonin
Normal Sex Hormones in Castrated Ferrets

- Estradiol < 180 pmol/L
- 17 OH Progesterone < 0.8 nmol/L
- Androstenedione < 15 nmol/L
- Dehydroepiandrosterone < 0.03 µmol/L
Limiting LH stimulation of the adrenal is the best way to medically treat ACD

- There is a lag-time between the rise of sex hormones and clinical signs.
- The time between the rise of LH and the stimulation of adrenal hyperplasia or tumor growth is immediate.
- Long-term continuous LH suppression with minimal stimulation of adrenal LH receptors is probably the best way to medically assure minimal tumor growth.
ACD ENDOCRINOLOGY

Hypothalamus

GnRH

Central Nervous System

GnRH Vaccination

Anterior Pituitary

FSH LH

GnRH Agonist

Lupron, Deslorelin, Triptorelin

Adrenal Gland

Sex Hormones
Concerns for Medical Management of ACD

• Various drugs and variable efficacy
• GnRH agonist is the primary Tx
• Risks: Tumor growth and necrosis, metastasis, limited other organ diagnostics and treatments, regular treatment is necessary, variable hormone control
• Tumor control questionable
• Benefits: non-invasive, few side effects, can be used for diagnostics, stabilize ferret before Sx, effective Tx for non-surgical patients,
• Cost: depends on drug used and frequency given
Clinical use of GnRH Agonist (Lupron and Deslorelin)

- < 7 days to lower hormone concentrations below pathologic concentrations
- Repeat injection or implant at the time of clinical relapse or at regular intervals.
- 4.7 mg Des implant < 5% develop large tumors
- Monitor adrenal size on a regular schedule
  - Ultrasound or Palpation
- Some ferrets are not responsive
- Some ferrets require higher doses
New Medical Treatment and Prevention of ACD

- Deslorelin: SC implant (available in US 2012)
  - 4.7 mg ~19 mo. duration (8-26 mo)
  - 9.4 mg --- duration ~ 2.5 years

- GnRH vaccination: 500 µg SC once or twice in 3 years, may give life long protection against ACD

- Deslorelin injectable 90 day release formulation by Wildlife Pharmaceutical
Survival Times for Medical management of ACD (Lupron and Deslorelin) verses Surgery

Survival times are similar or the same!

Des implant or Lupron: AVG= 6.0 years, MEDIAN= 6.2 years

All GnRH Agonists: AVG= 6.1 years, MEDIAN= 6.1 years

Surgery: AVG= 6.0 years, MEDIAN= 6.2 years
Medical management of ACD Deslorelin verses Surgery

<table>
<thead>
<tr>
<th>Modality</th>
<th>Surgery (Lennox)</th>
<th>Deslorelin (Wagner)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to relapse</td>
<td>0-38</td>
<td>3-30</td>
</tr>
<tr>
<td>(months)</td>
<td>Range</td>
<td></td>
</tr>
<tr>
<td>Average</td>
<td>13.55</td>
<td>16.48</td>
</tr>
<tr>
<td>n=31</td>
<td></td>
<td>n=35</td>
</tr>
<tr>
<td>Time to death</td>
<td>17.82</td>
<td>AVG= 25.2</td>
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<tr>
<td>after treatment</td>
<td></td>
<td>MEDIAN= 23.0</td>
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<tr>
<td>(months)</td>
<td>n=11</td>
<td>n=34</td>
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</tbody>
</table>

2011 Symposium International Ferret Congress
GnRH vaccination for ACD treatment or prevention studies: Ferret dose 500 µg IM or SC once or twice in 3 years or once only.
GnRH Vaccination for ACD

- GnRH is a small peptide hormone secreted from the hypothalamus in the brain and controls release of FSH and LH from the pituitary.
- Antibody to GnRH interferes with its biological action and reduces secretion of FSH and LH.
- GnRH vaccination is effective in both sexes.
- Slower clinical response than GnRH agonists
GonaCon™ Untreated

Hypothalamus

Hypothalamo-pituitary portal vessels

Anterior pituitary gland cell

TWO-WAY DIFFUSION

Venous outflow to heart

GnRH

LH and FSH

After Vander et al. 1998

GonaCon™ Treated

Hypothalamus

Hypothalamo-pituitary portal vessels

Anterior pituitary gland cell

NO DIFFUSION:
GnRH - antibody complexes are too large to diffuse

Venous outflow to heart

GnRH

GnRH - specific antibodies

GnRH - antibody complex

LH and FSH

After Vander et al. 1998
### 9 Ferrets GnRH Vaccination for ACD Tx Study: 500 ug IM

*(Wagner, Miller and Finkler unpublished data)*

<table>
<thead>
<tr>
<th>Response</th>
<th>Response</th>
<th>GnRH titer @ 2 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 mo Post</td>
<td>&gt; 2 mo</td>
<td></td>
</tr>
<tr>
<td>100%</td>
<td>100%</td>
<td>128,000</td>
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<tr>
<td>80%</td>
<td>90%</td>
<td>32,000</td>
</tr>
<tr>
<td>100%</td>
<td>100%</td>
<td>128,000</td>
</tr>
<tr>
<td>100%</td>
<td>100%</td>
<td>128,000</td>
</tr>
<tr>
<td>80%</td>
<td>100%</td>
<td>32,000</td>
</tr>
<tr>
<td>20%</td>
<td>80%</td>
<td>8,000</td>
</tr>
<tr>
<td>40%</td>
<td>60%</td>
<td>slow tail growth</td>
</tr>
<tr>
<td>100%</td>
<td>100%</td>
<td>128,000</td>
</tr>
<tr>
<td>0%</td>
<td>0%</td>
<td>ND to 1 (ND=non-detectable)</td>
</tr>
</tbody>
</table>

32,000 is effective
ACD Treatment Study with GnRH vaccine

- 50 ferrets with ACD, 25 given vaccine SC and 25 given IM
- IM caused some large vaccine granulomas but most ferrets did well
- Favorable response with 80-100% resolution of clinical signs
- 6 ferrets had only a partial or no response
- Clinical response was not as good as GnRH agonists
ACD GnRH Vaccine Prevention Study

- 125 normal ferrets vaccinated at 1-3 years of age
- Vaccinated either twice in 3 years or once
- 11 of 125 (9%) ferrets have developed ACD over all age groups
- Comparison group: Most ferrets develop ACD between 3-5 years of age. 60-70% develop ACD before death.
- 30-40% of comparison group never develop ACD
- Serum for GnRH titers at time 0, 1-3 mo. post vaccination and then at signs of ACD
% of ACD by age in CONTROL GROUP:
118 ferrets Carlson data 2011, 120 ferrets AFA data 2010
and 100 ferrets AFA data 2009
GnRH Vaccine ACD Prevention Study

- 125 active ferrets on study 6/11
  Avg age = 4.0

- 11 ferrets developed ACD on study
  Avg age = 5.0

- 35 ferrets finished study
  Avg age = 6.2

- Many ferrets lost to follow-up
Preliminary Data (125 vaccinated): ACD Prevention Study with GnRH vaccine.
GnRH Vaccine ACD Prevention Study

- Vaccinated ferrets that developed ACD had mild clinical signs and often did not develop severe alopecia.
- Some of these ACD ferrets maintained high GnRH titers but developed adrenal signs.
- Vaccinated ferrets responded well to GnRH agonists.
- 11 of the ferrets that developed ACD on study averaged 5 years of age. Non-vaccinated ferrets average age of ACD onset is 3.5 years of age.
ACD Prevention and Treatment Studies with GnRH vaccine

- Treatment studies are completed
- 125 ferrets are enrolled in prevention study
- The vaccine looks promising as a prevention vaccine and has some utility as a treatment modality.
- Best medical treatment for ACD still seems to be Deslorelin implants or Lupron.
- ACD prevention will be the ultimate goal for practitioners
Wildlife Pharmaceutical Inc.
10 mg Deslorelin SR

• Clinical trials using a 90 day slow release polygalactin deslorelin injectable for ferret ACD treatment.

• This formulation is designed to produce therapeutic blood concentrations of deslorelin for up to 90 days.

• Preliminary results show variable control of ACD but similar to 1 month Lupron Depot.

• Drug release profile may be the problem.

• 0-6 month ACD control duration, N=50
Future ACD Treatments

- Improved surgical techniques, nothing really new
- Improved GnRH analog delivery
- LH-RH antagonists
- Improved use of hormone blocker and receptor drugs, new drugs, questionable efficacy
- Anti-neoplasia drugs---Palladia has eliminated ACD signs in some ferrets!
- Anti-angiogenesis approach, doesn’t seem to work
- GnRH immunization, shows promise
- LH – Receptor immunization, needs work
- Genetics: breeding or genetic manipulation