Assessing Systemic Toxicity and Therapeutic Efficacy of Atosiban and Nafarelin in a Rabbit Endometriosis Model

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Abstract

Endometriosis is a chronic, painful disease whose etiology remains unknown and affects roughly 6-10% of women. The disease occurs when endometrial cells, which normally grow inside of the uterine body form and adhere outside the uterus. Symptoms of the disease include abdominal or pelvic pain and infertility. Due to the unknown etiology of the disease, current treatment for affected women ranges from laparoscopic removal of ectopic lesions and tissues from the reproductive tract to pharmacological pain management of the symptoms. As a result, further research is necessary to determine the most effective and safe regimen to alleviate and/or prevent disease. The goal of the autologous rabbit model of surgically induced endometriosis is to mimic the disease in women, and determine the toxicity of commonly used hormone therapies such as Atosiban (an Oxytocin receptor blocking agent) and Nafarelin (a Gonadotropin releasing hormone agonist). Confirmation of endometriosis was determined by clinical signs and post mortem intra-abdominal tissue evaluation. At the designated time points and testing groups, animals were dosed with either Nafarelin or Atosiban (subcutaneously). Upon planned endpoints, blood work (CBC-Chemistry) was done on the rabbits from all groups to detect any toxicity of the treatment doses versus no treatment. Endometrial tissue was excised from all groups and histologically analyzed to determine the efficacy of the drug regimen.

Objective

To establish a model of endometriosis while evaluating the safety and efficacy of possible therapeutics of Atosiban (Oxytocin receptor blocking agent) and Nafarelin (Gonadotropin releasing hormone agonist) that may help mitigate clinical signs of endometriosis.

Materials and Methods

**Experimental Design**: 30 female, sexually mature New Zealand White rabbits ranging from 2.5 - 4.5 kg were placed into one of the following groups: Group 1, 3 High Dose Nafarelin; Group 2, 3 Low Nafarelin; Group 3, 3 High Dose Atosiban; Group 4, 3 Low Dose Atosiban; Group 5, 3 High Dose Nafarelin; Group 6, 3 Low Dose Nafarelin; Group 7, 2 High Dose Atosiban; Group 8, 2 Low Dose Atosiban; Group 9, 3 No Treatment Group 10, 3 No Treatment.

*Group 1-4 started their dose regimen 1 week prior to endometriosis induction surgery. Group 5-8 started their dose regimen 1 week post endometriosis induction surgery. Group 9 had surgery but no treatment, and group 10 had surgery and no treatment.

**Experimental Procedures**
- Endometriosis was induced under anesthesia by excising about 0.5-2.0cm from the uterine horn, exposing the endometrial mucosa, and implanting it on the ipsilateral side with a biodegradable suture (monocryl-3).0.
- Animals were either continued or started 1 week post-surgery, on a daily dose regimen of Nafarelin (High Dose = 800 µg; Low Dose = 400 µg) or Atosiban (High Dose = 800 µg; Low Dose = 400 µg).
- General health observations, body weights, gross necropsy, and histopathologic evaluations were performed through the course of the study.

**Histopathology of Endometrial Tissue**

- Figures ii, iv, vi: Hyperplasia of columnar epithelial cells along with varying degree of endometrial disruption (20-75%) along the lumen of the excited tissue. Groups 1-8 possessed ectopic cystic lesions on the serosal surface with adhesions and synchia discovered microscopically within the abdominal cavity. Focal areas of inflammation (neutrophils) were seen, but no compromise of glandular tissue appreciated.
- Figures i: Group 1-2 (Low Mag)
- Figures iii: Group 3-4 (Low Mag)
- Figures iv: Group 5-8 (Low Mag)

**Figure (vii):** Group 7-8 (High Mag)
**Figure (viii):** Group 9-10 (High Mag)

Groups 9-10 displayed no significant histopathological difference in endometrium with no evidence of disruption or hyperplasia of columnar epithelium cells or glandular tissue.

**Serum Chemistry/ Hematologic Analysis**

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<th>Procedures</th>
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<td>Creatinine</td>
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**Conclusions**

As a known induced ovulator, rabbits have been historically used in the field of comparative medicine for studying reproductive disorders. As our study indicated, the formation of endometrial foci in rabbits has proven to be effective as a pre-clinical model for evaluating pharmacological therapies for endometriosis. Although prior research and clinical trials have utilized Atosiban and Nafarelin for treatment of clinical signs of this disease, the utilization of these drugs in prevention of disease onset is yet to be determined. In terms of toxicity and excretion, the drug dosages utilized did not result in clinical abnormalities.

Histopathology confirmed the presence of ectopic uterine tissue adhered to the serosal surface of reproductive tissue and gastrointestinal tissue (except for groups 9 & 10). Further evidence is required to establish the long term prophylactic benefits of such drugs by determining optimal frequency and dosages while minimizing systemic and local toxicity.

**Acknowledgements**

The authors of this project would like to acknowledge-reveal biosciences for providing tissue processing and histopathologic services.

**References**