Prostate Volume in Sexually Immature and Mature Dogs as Measured by MRI

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Introduction: Magnetic Resonance Imaging (MRI) techniques have the capability of providing non-invasive and repeatable means of assessing molecular, biochemical, physiological, and anatomical information in laboratory animals and humans with high spatial resolution and high soft-tissue contrast. One area in which MRI may contribute to drug development is augmenting traditional histopathology and complementing histopathological evaluations. Among other factors, the addition of longitudinal monitoring has the potential to minimize statistical variability incurring from inter-subject comparisons. Carefully conducted imaging experiments with validation from traditional methods are needed for eventual acceptance of imaging biomarkers by regulatory agencies. In-vivo MRI allows for longitudinal monitoring of effects of a compound over a range of dosing regimens and when desired, during a recovery period. MRI also provides a 3D view of the whole organ/tissue under investigation, potentially reducing sampling bias. In-vivo prostate volume is an important marker for pre-surgical planning (MRI volume compared with pathology), beneficial therapeutic effects, or adverse effects. A study was undertaken to evaluate MRI as a non-invasive marker of prostate volume in sexually immature dogs and sexually mature dogs, as well as prostate volume change over 4 weeks.

Methods: All procedures performed on these animals were in accordance with established guidelines and were reviewed and approved by the Institutional Animal Care and Use Committee (IACUC). The study began with four groups of 6 male dogs/group: IM 1 (Sexually Immature Dogs, 29-31 weeks of age at study start orally administered 5 mL/kg of 20% Vitamin E TPGS (d-Alpha-Tocopheryl Polyoethylene Glycol-1000 Succinate) daily), MA 1 (Sexually Mature Dogs, 69-76 weeks of age at study start orally administered 5 mL/kg of 20% Vitamin E TPGS) daily, IM 2 (Sexually Immature Dogs), and MA 2 (Sexually Mature Dogs). Data for groups IM 2 and MA 2, which are part of another evaluation, are included in baseline calculations but are not in the longitudinal results. Necropsy was performed after 4 weeks of dosing on 3 animals each of IM 1 and MA 1, and the remaining 3 animals per group originally designated for final necropsy were removed from the study due to satisfactory interim results. In-Vivo MRI: MRI scanning was carried out during baseline and at 4 weeks during the dosing period. The dogs were anesthetized and ventilated on medical grade air and 2.0% isofluorane gas anesthesia and imaged using a Siemens 3T Trio using the following parameters: 2D multi-slice TSE sequence, 4cm surface coil, TR/TE = 4500/34ms, ~0.5x0.5x1.5 resolution, ~24 slices, with fat saturation for better contrast around the perimeter of the organ. The volumes were calculated semi-manually in axial sections with the prostate outlined in each contiguous slice as Region of Interest (ROI) and the prostatic urethra removed from the ROI. Prostate volumes were calculated by slice summation using images of sufficient number of slices to span the organ. Histopathology of the prostate at end of study, including organ weight, was compared with MRI findings in an attempt to validate volume measurement results. Results are reported below.

Results and Discussion: With excellent capabilities to visualize the prostate (Figure 1), the protocol allowed for a prostate volume coefficient of variation of 0.82% on a single animal scanned three times. This was used to power the study estimating significance to be shown when volume changes exceed 2.3% in a given animal. The MRI findings, based on calculated prostate volumes for animals during the dosing period, were compared for variability, volume change, and ultimately to ex-vivo prostate weight at necropsy. Mean and standard error of the mean (SEM) for baseline prostate volumes were 1.10 ± 0.13cm³ (n = 12, IM 1 and IM 2) and 9.36 ± 0.77 cm³ (n = 12, MA 1 and MA 2). There was a significant increase in prostate volume in immature versus mature animals of 69.42 ± 27.87% IM 1 and -14.00 ± 7.21% MA 1, p = 0.016. Results of the 6 animals taken at necropsy are shown in Figure 1, a correlation plot of calculated in-vivo prostate volumes versus absolute prostate weights from sexually immature and mature dogs.

Conclusions: There was a significant amount of age-related prostate volume change in 4 weeks. The longitudinal variability indicates that age and study duration are important factors if prostate volume is an endpoint of interest. The comparison to ex-vivo absolute prostate weights at necropsy shows a high correlation (R² = 0.916). This demonstrates that Magnetic Resonance Imaging may be used to accurately monitor prostate volume, and therefore weight. With continued validation, future studies might include the addition of MR Spectroscopy or diffusion to better characterize the prostate for drug discovery. The non-invasive nature of the technique could also aid in the reduction in number of animals required for a study and improve power through longitudinal studies.