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DEVELOPMENT OF SOFTWARE PROGRAM FOR THE ANALYSIS OF ALZHEIMER'S DISEASE SCANS

Short title: Evaluation of PET imaging with PBR-111 in HV and AD subjects.

Final Technical Report

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Outline of Research
Primary Objective: To evaluate the cerebral distribution of PBR-111 positron emission tomography (PET) for detection/exclusion of microglial activation in patients with Alzheimer disease subjects compared to healthy volunteers.
Secondary objectives:
o- To assess the dynamic uptake and washout of 18-fluorodeoxyglucose [18F]PBR-111, a potential imaging biomarker for inflammatory changes in brain, using positron emission tomography (PET) in subjects with Alzheimer disease (AD) and healthy volunteers (HV).
o- To perform blood metabolite characterization of [18F]PBR-111 in subjects with AD and HV to determine the nature of metabolites in assessment of [18F]-PBR-111 as a PET brain imaging agent.

Name of radioactive drug substance: PBR-111 Dose(s): The applied PBR-111 radioactive dose was up to 5.0 mCi, diluted in a maximum of 10 ml of saline. The radioligand was administered as a slow intravenous bolus injection (i.e., 6 sec/ml) into a large vein (e.g., antecubital vein). Route of administration: Intravenous injection Duration of treatment: Single administration of a diagnostic agent Indication: PBR-111 positron emission tomography (PET) imaging has the potential to detect microglial activation. In the presence of PBR-111 uptake (representative of microglial activation), inflammation in the brain can be detected. Diagnosis and main criteria for inclusion: Study participants were HVs and patients diagnosed with probable AD. HVs were 18 years of age (at least four subjects 50 years of age) and had no evidence of cognitive impairment or other neurologic disease by medical history. The lack of cognitive impairment was based on a Clinical Dementia Rating (CDR) of 0. Patients with probable AD were 50 years of age and fulfilled the National Institute of Neurological and Communicative Disorders and Stroke, Alzheimer's Disease and Related Disorders Association [NINCDS-ADRDA] criteria for probable AD. The CDR score weas 1.0 and 2.0 and had a modified Hachinski of 4.

All HVs and all patients with probable AD were able to comply with all study procedures. Study design: This was a Phase 1, open-label, single-center, non-randomized single dose study to assess the kinetics, clearance and cerebral distribution of PBR-111 PET imaging in detecting microglial activation in the brain in patients with probable AD compared to HVs. All aspects related to image acquisition, processing, and visual as well as quantitative evaluation were developed, optimized, and validated (where required).

Each subject was required to visit the study center during the screening phase and on the PBR-111 PET imaging day (baseline). A telephone follow-up visit will be performed 7 days (± 3 days) after PBR-111 PET administration. At the screening visit, each subject (or caregiver in the case of AD subjects) was asked to provide written informed consent or assent. During the screening phase (maximum duration of 60 days) subject medical, neurological, and surgical history, clinical assessments, and a neuro-psychiatric evaluation were performed on all eligible subjects. Subjects were allowed to leave the center after all evaluations had been completed. During this period an MRI of the brain was performed during the screening period. If an MRI of the brain had been performed within six months of the imaging visit using the methods described in the protocol, and there had been no medically significant events in the interim, the previous MRI was used. During the PBR-111 PET imaging day, all subjects received a single intraveous injection of PBR-111 and scanning was performed over a 3.5 hour period. Each subject had a telephone follow-up 7 days (± 3 days) thereafter to assess for adverse events.

Methodology:
o- Assessments to provide clinical characterization of the AD subjects were performed.
o- After administration of PBR-111, images were generated with a state-of-the-art PET imaging. Images were assessed quantitatively for the presence of microglial activation by a nuclear physician blinded to clinical data.
o- Total radioactivity and estimation of the fraction of radioactivity associated to the unmetabolized tracer were determined. In addition, the metabolite patterns of PBR-111 were determined in venous plasma and arterial samples based on high-performance liquid chromatography (HPLC) analyses.
o- Arterial sampling was acquired in the initial two AD and two HV subjects and modeling was assessed to determine if additional arterial sampling was necessary. Type of control: The results of PET imaging with PBR-111 was compared to the clinical diagnosis.

Primary variable: Analysis included the decay-corrected time activity data to assess time to peak specific uptake, amplitude of peak, and washout rate, and metabolism of parent compound and assessment of metabolites. In addition, a ratio of early to late regional uptake was assessed as a potentially simple, albeit semi-quantitative way, to distinguish subjects with AD from HVs. Kinetic models, starting with a classic two-tissue compartmental model and non-invasive reference tissue models were evaluated.
Statistical analysis: The sample size proposed for this study was too limited to complete statistics that would lead to significant values. The a priori criteria for assessing the utility of the different radiotracers required at least a 25 percent signal difference in the standard uptake value ratio (SUVR) in the subjects with AD compared to HVs.

Completed Analysis and Results/Conclusions of the Study
A total of 5 healthy control (HC) subjects and 3 subjects with Alzheimer disease (AD) participated in the first round of imaging. Three HC subjects participated in the second round (2 injections and scans per each of the 3 subjects). All subjects underwent arterial blood sampling to assist in data analysis.
Analysis of the PET images and arterial blood metabolites indicated that [18F]PBR-111 has good initial brain penetrance and uptake with relatively fast washout and no evidence of confounding lipophilic metabolites. The dynamic images and metabolites were subjected to several analytic models. Two tissue compartment models well-characterize the data, including good fit over the first 90 minutes post-injection. There were no apparent differences in AD subjects and controls with regard to radiotracer metabolism. For the AD subjects, uptake was seen in several brain regions, but specific conclusions regarding their signal relative to HC is limited based on the small sample size.