123-I Ioflupane SPECT Measures of Parkinson Disease Progression in the Parkinson Progression Marker Initiative (PPMI) Trial

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ABSTRACT

Original abstract, additional data in poster

Objective: The objective of this study is to report initial quantitative 123-I Ioflupane SPECT one year disease progression data in the PPMI PD cohort.
Background: The Parkinson's Progression marker initiative (PPMI) is a multicenter, international, longitudinal study evaluating clinical, biochemical, and imaging measures of Parkinson's disease (PD) progression.
Methods: In this on-going study, baseline and one year follow-up123-I Ioflupane SPECT scans from 22 imaging centers include 117 Parkinson's subjects. Data were centrally reconstructed, attenuation corrected, and analyzed with a standardized volume of interest template for extraction of regional count densities in the left and right caudate and putamen. Striatal binding ratios (SBR) were calculated using the occipital lobe reference region. Mean percent changes in striatal composite, ipsilateral putamen, and contralateral putamen SBRs were calculated.
Results: PD subjects at baseline had a mean age of 61.1 y and an average disease duration of 8.5 ± 8.2 months. Total UPDRS score was 34.0 ± 12.9 at baseline and 41.1 ± 16.0 at one year follow up. Mean average SBR change encompassing left and right caudate and putamen was -13.3% ± 16.0% (p< 0.0001). Ipsilateral and contralateral striatum showed 13.0% ± 16.5% and 13.5% ± 16.7% change, respectively. No significant differences were noted between ipsilateral and contralateral striatum.
Conclusions: Quantitative DAT 123-I Ioflupane SPECT imaging data acquired at baseline and one year follow-up in PD demonstrate reductions in striatal ratios for both mean striatum and ipsilateral and contralateral putamen. Symmetric rates of striatal signal loss are noted in this preliminary data.

INTRODUCTION

- **PPMI is an observational multi-center study to assess progression of clinical features, imaging and biologic biomarkers in Parkinson's patients and healthy controls**
- **PPMI is a five-year natural history study of *de novo* idiopathic PD patients and healthy controls**
- **Subjects are assessed at baseline and every 3-6 months thereafter**
  - **Clinical assessments: motor, neuropsychiatric and cognitive**
  - **Imaging assessment (dopamine transporter imaging, MRI)**
  - **Biologics collected: blood, CSF, urine and DNA**
- **Clinical, imaging and biological data and samples collected under standardized protocols and analyzed, stored at core facilities, and made available to the investigator community**
- **Screening dopamine transporter imaging is required to be abnormal in all PD subjects and normal in controls**
- **Biological samples will be used for verification of promising biomarkers.**

Study synopsis

Study population	400 de novo PD subjects (newly diagnosed and unmedicated) 200 age- and gender-matched healthy controls Subjects will be followed for a minimum of 3 years and a maximum of 5 years
Assessments/ Clinical data collection	• Motor assessments • Neuropsychiatric/cognitive testing • Olfaction • DaTSCAN imaging, structural MRI,DTI
Biologic collection/ Verification studies	• DNA collected at baseline • Blood collected at each visit; CSF collected at 6mo and then annually • Samples aliquoted and stored in central biorepository • Lead biologic candidates to be tested: alpha-synuclein, DJ-1, urate
PD treatment	• De novo for 6 months • Can participate in clinical trials after 12 months

METHODS

123-I Ioflupane SPECT Imaging Processing

In this ongoing study, 117 PD subjects were imaged at baseline and 1 Year follow-up with 123-I Ioflupane SPECT

Mean striatal binding ratios determined as follows:

- **Central SPECT Core lab performed reconstruction from raw projection data, including attenuation correction based on phantoms acquired during the site visit**
- **Spatial normalization of image performed for consistent orientation**
- **Apply standard volume of interest template on caudate, putamen, occipital regions**
- **Extract count densities and calculate Striatal Binding Ratios (SBR) = (striatal region)/(occipital) -1 from 4 h post-injection 123-I Ioflupane image**

Percent change from baseline SBR calculated for follow-up images.

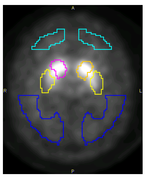


Fig 1 Axial SPECT 123-I Ioflupane image is spatially normalized to the MNI template and standardized volumes of interest placed on left and right caudate and putamen. A cortical region (occipital) serves as a tissue reference region for calculation of striatal binding ratio (SBR) defined as striatal count density divided by occipital count density minus 1.

RESULTS

Table 1. Baseline demographic data

Variable	Enrolled Subjects: PD Subjects (N =422) N (%)	Healthy Controls (N =195) N (%)	SWEDD Subjects (N = 63) N (%)	p-value (PD vs. HC)	p-value (PD vs. SWEDD)
Gender				0.79	0.58
Male	276 (65%)	125 (64%)	39 (62%)		
Female	146 (35%)	70 (36%)	24 (38%)		
Missing	0 (0%)	0 (0%)	0 (0%)		
Age				0.53	0.22
<56 Years	114 (27%)	55 (28%)	22 (35%)		
56-65 Years	135 (32%)	69 (35%)	14 (22%)		
>65 Years	173 (41%)	71 (36%)	27 (43%)		
Missing	0 (0%)	0 (0%)	0 (0%)		
Age				0.27	0.59
Mean	61.7	60.7	60.9		
(Min, Max)	(33, 85)	(31, 84)	(38, 79)		
Missing	0	0	0		
Education				0.55	0.03
<13 Years	77 (18%)	29 (15%)	18 (29%)		
13-23 Years	341 (81%)	165 (85%)	43 (68%)		
>23 Years	4 (1%)	1 (1%)	2 (3%)		
Missing	0 (0%)	0 (0%)	0 (0%)		
Ethnicity				0.76	0.64
Hispanic/Latino	9 (2%)	3 (2%)	2 (3%)		
Not Hispanic/Latino	413 (98%)	192 (98%)	61 (97%)		
Missing	0 (0%)	0 (0%)	0 (0%)		
Race				0.87	1.00
White	389 (92%)	181 (93%)	59 (94%)		
Black/African-American	6 (1%)	9 (5%)	1 (2%)		
Asian	8 (2%)	1 (1%)	1 (2%)		
Other	16 (4%)	4 (2%)	1 (2%)		
Missing	3 (1%)	0 (0%)	1 (2%)		

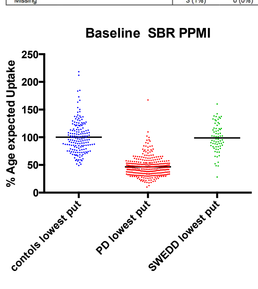


Fig 2 Lowest putamen SBR (age corrected) for PD (n= 378), controls (n=182), and subjects recruited as PD but without evidence of dopaminergic deficit (SWEDD n=48). PD SBRs are on average 50% of controls, whilst SWEDD SBRs are similar to healthy controls.

Table 2. Baseline mean SBR parameters in PD and controls

Variable	Enrolled Subjects: PD Subjects (N =378)	Healthy Controls (N =182)	p-value (PD vs. HC)
Lowest Caudate	1.21	1.89	<0.001
Lowest Putamen	0.57	1.27	<0.001
Mean Caudate	1.32	1.94	<0.001
Mean Putamen	0.65	1.33	<0.001
Mean Striatum	0.98	1.63	<0.001
Ipsilateral Caudate	1.41	1.89	<0.001
Ipsilateral Putamen	0.73	1.27	<0.001
Contralateral Caudate	1.22	1.99	<0.001
Contralateral Putamen	0.58	1.40	<0.001
Caudate Asymmetry Index	15.96	5.27	<0.001
Putamen Asymmetry Index	26.48	10.20	<0.001
Striatum Asymmetry Index	36.86	8.72	<0.001
Ipsilateral CDR	2.05	1.56	<0.001
Contralateral CDR	2.23	1.47	<0.001

Fig 3. Mean SBR signal loss is 6.2% per Decade in Healthy Volunteers

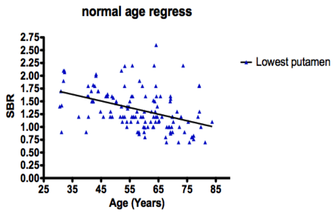
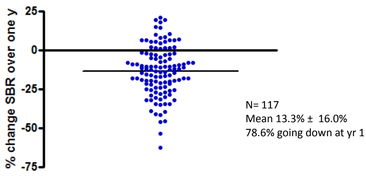


Fig 4. Mean SBR signal loss between baseline and Year 1 DAT imaging in PD subjects (n=117) is 13.3 %



DISCUSSION

In the ongoing PPMI cohort:

- Baseline DAT SPECT suggests *de novo* PD subjects have average SBR reduction about 50% of age matched controls
- Normal aging is associated with about 6% signal loss per decade (0.6%/y) based on cross-sectional data
- First longitudinal data in 117 PD subject suggests SBR reductions over one year is 13.3%, approximately 20 times the rate of signal loss seen in normal aging
- This rate of change is Identical to % signal loss in the PROUD study with DatScan mean change was –15·5% for early (n=57) and –14·2% for delayed (n=58) pramipexole cohorts over 15 months and roughly twice the rate of signal change per annum in the PRECEPT cohort with 123-I β-CIT SPECT.
- Similar to other biomarkers, there is significant between subject variability in %SBR reduction over one year, consistent with both prior PD longitudinal imaging and clinical course.
- Correlation of signal loss with medication status, clinical features and other biomarkers are pending.

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