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GM1 ganglioside in Parkinson's disease: Pilot study of effects on dopamine transporter binding

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ABSTRACT

Objective: GM1 ganglioside has been suggested as a treatment for Parkinson's disease (PD), potentially having symptomatic and disease modifying effects. The current pilot imaging study was performed to examine effects of GM1 on dopamine transporter binding, as a surrogate measure of disease progression, studied longitudinally.
Methods: Positron emission tomography (PET) imaging data were obtained from a subset of subjects enrolled in a delayed start clinical trial of GM1 in PD [1]: 15 Early-start (ES) subjects, 14 Delayed-start (DS) subjects, and 11 Comparison (standard-of-care) subjects. Treatment subjects were studied over a 2.5 year period while Comparison subjects were studied over 2 years. Dynamic PET scans were performed over 90 min following injection of [^{11}C]methylphenidate. Regional values of binding potential (BP_{ND}) were analyzed for several striatal volumes of interest.
Results: Clinical results for this subset of subjects were similar to those previously reported for the larger study group. ES subjects showed early symptomatic improvement and slow symptom progression over the study period. DS and Comparison subjects were initially on the same symptom progression trajectory but diverged once DS subjects received GM1 treatment.
Imaging results showed significant slowing of BP_{ND} loss in several striatal regions in GM1-treated subjects and in some cases, an increased BP_{ND} in some striatal regions was detected after GM1 use.
Interpretation: Results of this pilot imaging study provide additional data to suggest a potential disease modifying effect of GM1 on PD. These results need to be confirmed in a larger number of subjects.

1. Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by loss of dopamine-producing neurons in the substantia nigra pars compacta, loss of forebrain dopamine (primarily in the caudate nucleus and putamen), and a progressive worsening of clinical symptoms. Although improvement for many of the motor symptoms of the disease can be obtained with available pharmacotherapies, functional ability continues to deteriorate over time. Therefore, the development of disease modifying therapies is an area of intense interest.

GM1 ganglioside, a major constituent of neuronal plasma membranes, is associated with specialized signaling domains called lipid rafts [2,3]. GM1 modulates various cell activities during development and plays important roles during adulthood in supporting neuronal function and survival [4]. GM1 is highly expressed in the adult brain [4] where it modulates Ca^{2+} homeostasis [5] and signal transduction, may promote lysosomal integrity [6] and influence mitochondrial function [7,8]. In a variety of preclinical studies, administration of GM1 following different types of lesions resulted in significant biochemical and behavioral recovery [9–15], with results particularly impressive in animal models of PD [16,14,17–22].

Promising preclinical findings in animal models of PD have recently been translated to the clinic. Since previous work suggested that GM1

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might have both symptomatic and disease modifying effects on PD [23,24], a randomized, controlled, delayed start trial of GM1 in PD patients was conducted [1]. Subjects with mild/moderate PD were randomly assigned to receive GM1 for 120 weeks (early-start (ES) group) or placebo for 24 weeks followed by GM1 for 96 weeks (delayed-start (DS) group). Additional subjects who received standard-of-care (Comparison group) were followed for 96 weeks to obtain information about disease progression. At week 24, the ES group had significant improvement in the primary outcome measure (i.e., change in Unified Parkinson's Disease Rating Scale (UPDRS) motor score). The DS group (as well as the standard-of-care Comparison group) showed a worsening of scores during the same period. The ES group also showed a sustained benefit out to week 120 and their UPDRS scores remained below those recorded at study baseline [1]. Subjects in both treatment groups fared better than the Comparison group subjects. As part of this study, a subset of subjects who consented to undertake imaging studies were examined longitudinally with positron emission tomography (PET) after intravenous (IV) bolus injection of [^{11}C]methylphenidate ([^{11}C]MP), which binds to and is used as a measure for the concentration of the dopamine transporter (DAT). The decline of the binding potential (BP_{ND}) of [^{11}C]MP in the striatum of PD patients has been shown to be inversely correlated with UPDRS scores and severity of motor disability [25] and has been suggested as a marker of disease progression [25]. The purpose of this imaging study was to evaluate potential effects of GM1 treatment on the integrity of striatal dopamine terminals.

2. Subjects and methods

This study (ClinicalTrials.gov NCT00037830) was approved by the Division of Human Subjects Protection at Thomas Jefferson University and by the Western IRB (Johns Hopkins University). Written informed consent was obtained from all subjects prior to study. Subjects enrolled in the main delayed start clinical trial (results reported previously [1]) were men or women between 39 and 85 years of age with a diagnosis of idiopathic PD consistent with the UK PD Society brain bank PD diagnostic criteria. Details of inclusion/exclusion criteria were discussed previously [1] and Comparison group subjects were recruited according to the same criteria.

PET imaging data were obtained from a subset of subjects enrolled in the main delayed start clinical trial [1]: 15 subjects from the ES group, 14 subjects from the DS group, and 11 subjects from the Comparison group. Treatment groups were scanned at baseline, at study week 24 and at approximately one and two years after that. The Comparison group was scanned at baseline and approximately one and two years later. Thermoplastic face masks were constructed and individually fitted to each subject's face for immobilization and positioning for each MRI and PET scan as described by us previously [26]. A transmission scan of 10 min duration was obtained using rotating germanium-68 rods before injection of the radiotracer. Subjects were scanned while in a practically defined "off" period as described previously [1]. Dynamic PET scans were performed over 90 min in a 3D mode with a GE Advance PET scanner following an IV bolus injection of 740 megabecquerels (MBq) [20 millicuries (20 mCi)] [^{11}C]MP. Three series of structural MRIs of the brain without contrast were performed [27] on a GE 1.5 T Signa MRI scanner. PET images were reconstructed using the back projection algorithm with a ramp filter using the software provided by the manufacturer correcting for attenuation, scatter, and dead-time. The radioactivity was corrected for physical decay to the injection time. The final spatial resolution of the PET images was estimated to be 5.5 and 6.1 mm full width at half maximum (FWHM) in the radial and tangential directions, respectively, at 10 cm radius from the center of the field-of-view [28]. Volumes of interest (VOIs) were defined on structural MRIs for the caudate nucleus (CN), putamen (PU), and cerebellum (Cb; both hemispheres excluding white matter and the vermis) by an experienced, blinded rater (HK) according to methods previously reported [29]. VOIs were divided into associative striatum (anterior putamen, aPu, and anterior and posterior caudate nucleus, aCN and pCN), motor striatum (posterior putamen, pPu), and limbic or ventral striatum (vS) on left and right sides (a total of 10 VOIs) [30]. VOIs were transferred from MRI to PET space according to MRI-to-PET co-registration parameters (the co-registration module of the statistical parametric mapping (SPM) software; [31], available at http://www.fil.ion.ucl.ac.uk/spm/') to obtain time-activity curves (TACs). Regional values of BP_{NDs} [32] were obtained by the multilinear reference tissue method with 2 parameters (MRTM2) using the cerebellum as the reference region [33] without applying any manipulations to TACs.

Mixed effects linear regression (SAS v9.4, SAS Institute, Cary, NC) was used to simultaneously model BP_{NDs} for all 10 VOIs. Fixed effects were included for Group (ES, DS, Comparison group), Time (0, 6, 12, 18, 24, and 30 months), and Region and all possible interactions. An unstructured direct product covariance structure was assumed to model correlation among the 10 VOIs measured at the same time and among the repeated measurements across time. Within the mixed effects model, changes in BP_{NDs} were estimated and groups were compared with respect to change in BP_{NDs} using appropriate linear contrasts. Estimated mean BP_{ND} loss over time was calculated along with 95% confidence limits. The analysis was intended to be exploratory and descriptive considering the small number of subjects studied and P-values are provided for group comparisons without adjustments for multiple comparisons.

3. Results

3.1. Subject characteristics

The baseline characteristics of the imaging sub-study subjects are shown in Table 1. There were no significant group differences in most variables with the exception of time since diagnosis, in which ES and DS subjects differed from the Comparison subjects (Table 1). The baseline characteristics of the subjects participating in this imaging sub-study were comparable to the entire group of subjects who participated in the main randomized delayed start trial [1].

Table 1
Subject demographics and baseline characteristics.

	Early-start (n = 15)	Delayed-start (n = 14)	Comparison (n = 11)	P value[1]
Age (years)	60.0 (8.9)	59.9 (9.4)	59.0 (12.8)	0.9652
Sex: n (%)				
Male	11 (73.3)	9 (64.3)	10 (90.9)	0.3158
Female	4 (26.7)	5 (35.7)	1 (9.1)	
Mean time since diagnosis (years)	1.8 (1.1)	2.4 (2.0)	5.0 (3.9)	0.0055
Median, range (years)	1.5, 0.5–3.9	1.5, 0.4–6.1	3.8, 1.5–13.2	
MMSE score	29.0 (1.0)	28.6 (1.3)	29.5 (0.9)	0.1483
BDI-II score	4.7 (2.8)	5.4 (3.3)	3.8 (2.9)	0.4758
Total UPDRS score (Off)	29.3 (8.3)	28.7 (10.3)	36.7 (10.8)	0.1493
UPDRS motor score (Off)	19.3 (6.9)	20.6 (6.4)	24.3 (6.7)	0.0760
UPDRS ADL score (Off)	8.4 (3.2)	9.1 (4.1)	10.6 (4.5)	0.3770
UPDRS mentation score (Off)	0.6 (1.3)	0.6 (0.8)	0.8 (1.1)	0.8136
Medication usage				
Levodopa (# of subjects (percent))	10 (66.7)	10 (71.4)	8 (72.7)	0.1681
Dopamine agonist* (# of subjects (percent))	10 (66.7)	9 (64.3)	9 (81.8)	0.8093
Selegiline (# of subjects (percent))	5 (33.3)	5 (35.7)	4 (36.4)	0.4686
Levodopa equivalent dose (mg/day)	300.8 (183.4)	420.3 (274.3)	544.1 (239.0)	0.0611

Data presented as mean ± SD, unless otherwise noted. Levodopa equivalent dose calculations exclude 1 Comparison group subject who was unmedicated at baseline.

* Dopamine agonists included pramipexole, ropinirole, pergolide and bromocriptine.

[1] P value was from one-way ANOVA for continuous variables and Kruskal–Wallis test for categorical variables for testing the differences between Early-start, Delayed-start and Comparison groups.

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