9-15-2015

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Jay S. Schneider
Thomas Jefferson University

Franca Cambi
University of Pittsburgh

Stephen M. Gollomp
Lankenau Medical Center

Hiroto Kuwabara
Johns Hopkins University

James R. Brašić
Johns Hopkins School of Medicine

See next page for additional authors

HHS Public Access

Author manuscript

J Neurol Sci. Author manuscript; available in PMC 2016 September 15.

Published in final edited form as:

J Neurol Sci. 2015 September 15; 356(0): 118–123. doi:10.1016/j.jns.2015.06.028.

GM1 Ganglioside in Parkinson's Disease: Pilot Study of Effects on Dopamine Transporter Binding

Jay S. Schneider, Ph.D.[1], **Franca Cambi, M.D., Ph.D.**[4], **Stephen M. Gollomp, M.D.**[3], **Hiroto Kuwabara, M.D., Ph.D.**[5], **James R. Brašić, M.D., M.P.H.**[5], **Benjamin Leiby, Ph.D.**[2], **Stephanie Sendek, B.A.**[1], and **Dean F. Wong, M.D., Ph.D.**[6]

[1]Department of Pathology, Anatomy and Cell Biology and Parkinson's Disease Research Unit, Thomas Jefferson University, Philadelphia, PA 19107

[2]Department of Pharmacology and Experimental Therapeutics, Thomas Jefferson University, Philadelphia, PA 19107

[3]Division of Neurology, Lankenau Medical Center, Wynnewood, PA 19096

[4]Dept. of Neurology, University of Pittsburgh School of Medicine and Pittsburgh VAMC, Pittsburgh, PA 15213

[5]Division of Nuclear Medicine, Russell H. Morgan Department of Radiology and Radiological Science, Johns Hopkins School of Medicine, Baltimore MD 21287

[6]Russell H. Morgan Department of Radiology and Radiological Science, Departments of Psychiatry and Behavior Sciences and Solomon Snyder Department of Neuroscience, Johns Hopkins University School of Medicine, Baltimore MD 21287

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 minutes following injection of [^{11}C]methylphenidate. Regional values of binding potential (BP_{ND}) were analyzed for several striatal volumes of interest.

Corresponding author's name and address: Dr. J.S. Schneider, Department of Pathology, Anatomy and Cell Biology, Thomas Jefferson University, 1020 Locust Street, 521 JAH, Philadelphia, PA 19107. Phone and fax: 215-503-0370 (phone); 215-923-3808 (fax). jay.schneider@jefferson.edu.

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.

Keywords

Parkinson's disease; GM1 ganglioside; PET; dopamine transporter; caudate; putamen

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 [23]. 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 [1614171819202122].

Promising preclinical findings in animal models of PD have recently been translated to the clinic. Since previous work suggested that GM1 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 wks. followed by GM1 for 96 wks. (delayed-start (DS) group). Additional subjects who received standard-of-care (Comparison group) were followed for 96 wks. to obtain information about disease progression. At wk. 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 wk. 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 the 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 minutes 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 minutes 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 side (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].

The treatment effects in the subjects participating in the imaging sub-study were similar to those described for the entire group of subjects who participated in the main randomized delayed start trial [1]. In the initial 24 wks. of the study (Phase I), subjects who received GM1 (ES subjects) showed improvement in UPDRS motor scores compared to subjects who received placebo (DS subjects) and Comparison group subjects, whose UPDRS motor scores worsened over the same time period (Figure 1). During the next phase of the study in which all treatment subjects received GM1 (Phase II), ES subjects showed a slow progression of symptoms, and by the end of the study, "off" period UPDRS motor scores were approximately back to the level observed at study baseline (Figure 1). During this second phase of the study, DS subjects showed an initial symptomatic benefit after switching to GM1 and by the end of the study, their UPDRS motor scores were only slightly higher than those observed at the end of the placebo period. The symptom progression trajectory for the ES and DS groups was divergent at the end of the study, as in the larger study group [1], suggestive of a possible disease-modifying effect of GM1.

3.2 [^{11}C]methylphenidate ([^{11}C]MP) Binding

The estimated mean fall in BP_{ND} from baseline was calculated for each VOI for each study group. In these analyses, a negative number indicates a gain in BP_{ND} and a positive number

indicates a loss of BP_{ND}. During the first 6 months of the study, there was less loss of BP_{ND} in almost all regions (except the ventral striatum) in the ES group compared to the DS group however this difference was statistically significant only in one region, the right posterior putamen (Table 2). Six months may be too short a time interval in which to observe reliable changes in the PET BP_{ND} or to observe potential disease modifying effects of GM1 therapy. However, there was either no change or a gain of BP_{ND} in 7 of the 10 VOIs analyzed in the ES group at 6 months vs. baseline while loss of BP_{ND} was measured in all VOIs in the DS group (Table 2).

The mean BP_{ND} loss from baseline to the next imaging study performed at 1 year into the second phase of the study was also analyzed. At this point, the ES subjects had been on GM1 for 18 months and the DS subjects had been on GM1 for 12 months. The Comparison subjects were also scanned at 12 months following their baseline scans. Overall, the ES subjects showed little loss of BP_{ND} after 18 months of GM1 use, compared to baseline and for each region analyzed, and showed less loss of BP_{ND} compared to the DS subjects and the Comparison group subjects (Table 3). There was less BP_{ND} loss in several striatal regions in the ES group 18 months after baseline (and after 18 months of GM1 use) than in the Comparison group over only a 12 month period (Table 3) and an apparent gain of BP_{ND} was still detected in some regions in the ES subjects. Even though the DS group generally showed less BP_{ND} loss in most striatal regions over a 12 month period of GM1 use compared to the BP_{ND} loss in the Comparison group over 12 months, these differences were not statistically significant (Table 3).

The next data analyzed were the mean BP_{ND} loss from baseline to the end of year 2 of the second phase of the study. At this point, the ES subjects had been on GM1 for 30 months and the DS subjects had been on GM1 for 24 months. The Comparison subjects were also scanned at 24 months following their baseline scans. In each region analyzed, there was less BP_{ND} loss detected in the ES subjects at this time period compared to the DS subjects and the Comparison group subjects. There was significantly less BP_{ND} loss in several striatal regions in the ES group 30 months after baseline (and after 30 months of GM1 use) than in the Comparison group over only a 24 month period (Table 4; Figure 2). In most regions, the BP_{ND} loss in the DS subjects after 24 months of GM1 use was also less than that detected in the Comparison group (Figure 2), although the difference was statistically significant only for 1 region, the right posterior caudate nucleus (Table 4).

Taking the data collected at the 6 month point of the study as a new baseline for the DS subjects (as they had been on placebo for the first 6 months of the study) we examined the BP_{ND} loss between the 6 month time point and the end of the 2 year second phase of the study. During this period, the DS subjects had used GM1 for 2 years. When analyzed this way, the DS subjects showed less loss of BP_{ND} in all regions than did the Comparison subjects over this 2 year period and the differences were statistically significant for 6 of the 10 regions analyzed (Table 5).

4. Discussion

The results of this pilot study suggest the possibility of a slowing of BP_{ND} loss in several striatal regions in GM1-treated subjects and in some cases, the data suggest an increased BP_{ND} in some striatal regions, compared to baseline. There was less loss of BP_{ND} in ES subjects versus the Comparison group, measured after 18 and 30 months of GM1 use. It is possible that these results could have been affected by subjects in the Comparison group having a slightly longer time since diagnosis compared to subjects in the ES and DS groups. However, the decline in striatal dopamine transporter binding in early-stage PD patients suggest no substantial differences in the rate of annual BP decline over the first 5 to 7 years after symptom onset [34] ND. Also, once they switched to using GM1, the DS subjects also showed less BP_{ND} loss over time than did Comparison group subjects, however, consistent with the results of larger clinical study [1], there was an advantage to being in the ES group.

There was an improvement in “off” UPDRS motor scores in GM1-treated subjects in Phase I of the study and symptom worsening in placebo-treated subjects that mirrored the change observed in the Comparison group. We previously suggested that the symptomatic effect from GM1 in PD may relate to functional improvement in residual dopaminergic neurons, a conclusion supported by data showing enhanced dopamine synthesis in residual dopamine neurons in a mouse model of Parkinsonism following GM1 treatment [17]. In Phase II, ES subjects maintained some of the initial benefit of GM1 treatment and DS subjects showed benefit after switching to GM1 use and both treatment groups fared better than the Comparison subjects. We previously reported that such findings are suggestive of a potential disease-modifying effect of GM1. If GM1 levels are decreased in the PD brain [35, 36] then our GM1 replacement therapy may have provided a sufficient amount of GM1 to substantia nigra neurons to stabilize them and promote their survival. Although the precise mechanisms underlying the potential disease modifying effects of GM1 in PD are likely multi-factorial, as suggested by us previously [1], recent work by Hadaczek et al. [36] suggest a new potential neuroprotective role of GM1 based on its role in regulating GDNF signaling, a function necessary for maintaining the health of dopaminergic neurons. GM1 was shown to be required for assembly of the GDNF receptor and effective GDNF signaling was dependent on an adequate level of GM1 [36]. This is relevant as studies with GDNF infusion in PD patients have shown some clinical benefit as well as increases in putamenal ^{18}F-dopa uptake on PET and postmortem evidence of increased tyrosine hydroxylase immunopositive nerve fibers, suggestive of terminal sprouting, in the infused putamen [37]. The present imaging results showing less loss of BP_{ND} in GM1 treated subjects in several striatal regions versus Comparison subjects suggest improvement in imaging parameters as well as clinical status, providing further support for a potential disease modifying effect of GM1 in PD.

Preclinical studies with GM1 ganglioside in a variety of PD models, including MPTP-treated monkeys [14], have reported neuroprotective or neurorestorative effects of GM1 and increased striatal dopamine and metabolite levels in GM1-treated animals as well as a possible terminal sprouting effect in the striatum[14, 22, 38, 39]. GM1 administered to MPTP-exposed monkeys resulted in a significant increase in ^{3}H-mazindol binding to dopamine transported sites in the striatum [19]. Other studies also have reported increases in the dopamine innervation of the striatum in GM1-treated animals with nigrostriatal

lesions [16, 22]. This, however, is the first clinical imaging study to suggest that GM1 administration to PD patients might slow the loss of dopamine terminals, detected by measuring binding of [^{11}C]MP to dopamine transporter sites, and perhaps at least in some subjects in some striatal regions, even increase the number of dopamine terminals. These data are consistent with the findings from GDNF infusion studies mentioned above.

Previous studies (CALM-PD-CIT [40], REAL-PET[41]) have suggested a slowing in disease progression based on either SPECT imaging of the dopamine transporter (CALM-PD) or ^{18}F-dopa positron emission tomography (REAL-PET) in PD patients taking pramipexole or ropinirole, respectively, compared to patients taking levodopa. Although results from these imaging studies suggested that both pramipexole and ropinirole were potentially neuroprotective (i.e., both studies reported a slower loss of BP_{ND} over time in subjects with agonist treatment compared to subjects receiving L-dopa), the imaging findings were not supported by clinical observations of the subjects. Several potential reasons for the discrepancy between clinical and imaging findings in these studies have been suggested including confounding of UPDRS scores by anti-PD medications despite patient evaluations in a “defined off” state [40] and drug-related differences in dopamine transporter binding regulation [42], as the dopamine transporter is a highly regulated protein [43]. The effects of levodopa and ambient dopamine levels on dopamine transporter binding are unclear [44]. Striatal dopamine transporter levels may be up-regulated in a state of synaptic dopamine excess and down-regulated in a dopamine-deficient condition, with the latter serving to maximize the efficacy of the remaining dopamine. However, under some conditions the dopamine transporter might actually be down-regulated by a treatment that enhances dopaminergic function in the human [44]. It is unlikely that the effects observed in the current study can be substantially attributed to effects of levodopa on dopamine transporter regulation. However, it is possible that improved dopamine neurotransmission in GM1-treated subjects may have had an effect on dopamine transporter binding.

This study has several potential limitations. This pilot imaging sub-study as well as the overall clinical trial was conducted only at a single site. Only a small number of subjects enrolled in the larger clinical study consented to participate in the imaging study and thus there may have been some selection bias and systematic differences between the groups. However, subjects in the two treatment groups were very well matched and only mean time since diagnosis, a rather imprecise measure, was significantly different between the three study groups at baseline. The time from diagnosis to participation in this study was longer for subjects in the Comparison group compared to the subjects in the treatment groups. While this may suggest that these subjects were studied at a slightly different point in the course of their disease, time from diagnosis is an imprecise measure of disease duration. Arguing against a significant clinical difference between the groups is the finding that Comparion group subjects and DS subjects (receiving placebo) showed the same rate of symptom progression during the first 6 months of the study. Due to the small number of subjects studied and the pilot nature of the study, our analysis is mainly descriptive and exploratory. P-values are provided for group comparisons but were not adjusted for multiple testing and as such, statistical significance should be interpreted with caution. This study also utilized subjects already receiving anti-PD medications, including dopamine agonists and levodopa, and use of these medications could have influence the imaging results.

Although clinical results were obtained and imaging studies were performed during a practically defined “off” period, it is possible that long-lasting effects of these medications on dopamine neurotransmission and the dopamine transporter site may have contributed to some of the present findings. However, there was no significant difference between the groups in regard to levodopa or dopamine agonist use. An additional limitation is the choice of the PET radioligand [^{11}C]MP and its targeting of DAT. While MP is not the most selective and highest affinity ligand for DAT (in comparison with tropanes, for example [^{11}C] Win 35,428 [45], [^{123}I]CIT, [^{11}C]Altropane), it was chosen in part because its reversible kinetics did not require a radial arterial input function with radioactive plasma measurements and metabolites assessment. Also the measurement of DAT by any PET or SPECT radioligand could be modulated by endogenous dopamine or medications. Nevertheless MP is a well established radioligand for DAT measures and DAT is a well established measure for evaluating the presynaptic dopamine system in PD.

5. Conclusion

The clinical results of a previously reported delayed start trial of GM1 in PD [1], and results of a previous 5 year open extension trial of GM1 in PD [24] suggest that long term use of GM1 may result in a slower than expected progression of symptoms. The current PET imaging findings, although preliminary, provide additional data to suggest a potential disease modifying effect of GM1 on PD. These preliminary results need to be confirmed in a larger number of subjects and within the context of a larger, multi-center study.

Acknowledgements

This study was supported by NIH grants NS038681 (JS) and K24 DA000412 (DFW).

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Highlights

- PET imaging data were obtained from subjects enrolled in a trial of GM1 in PD.
- Striatal [^{11}C]methylphenidate binding potential values (BP_{ND}) were analyzed.
- GM1 use was associated with slowed symptom progression.
- Imaging results showed significant slowing of BP_{ND} loss in several striatal regions.
- Results provide additional data supporting a disease modifying effect of GM1 on PD.

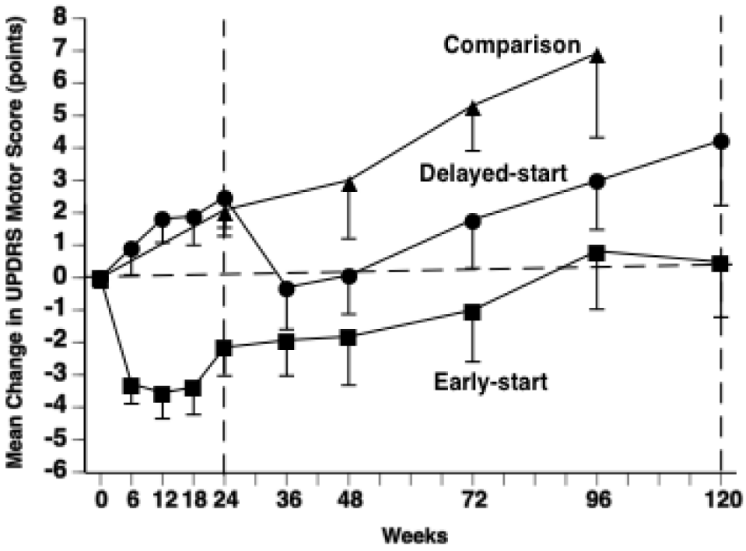

Figure 1.

Changes in Unified Parkinson's Disease Rating Scale (UPDRS) Motor Subsection Scores for the subset of subjects participating in the imaging study. The mean (±SEM) change from baseline (observed scores) in Early-start (N = 15) and Delayed-start (N = 14) sub-study subjects and in the standard-of-care Comparison group (N = 11), assessed in the practically defined "off" condition. The dashed vertical line at week 24 indicates the end of study Phase I. The dashed vertical line at week 120 indicates the end of study Phase II. The horizontal dashed line indicates baseline level. An increase of score indicates symptom worsening; a decrease in score indicates symptom improvement.

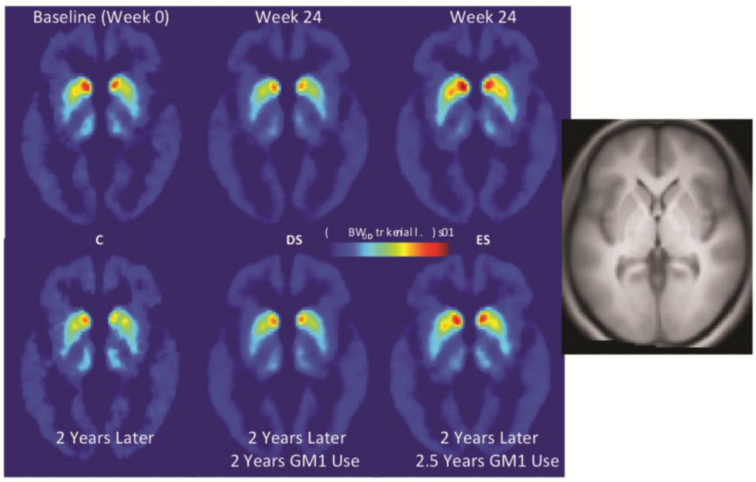

Figure 2.

Averaged striatal binding potential images at baseline (Week 0 for the Comparison group (C) subjects (N = 11)) [left panel] and at the transition point in the delayed start study (Week 24 for Delayed-start (DS: N = 14) [middle panel] and Early-start (ES: N = 15) [right panel] groups) (top row) and averaged images obtained 2 years later at the end of the second phase of study during which all treatment subjects used GM1 ganglioside. Images show less loss of BP_{ND} over time in ES subjects and DS subjects versus Comparison group subjects. The far right panel demonstrates the averaged images of the MRIs of all participants.

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/d)	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.

Table 2

Estimated Mean BP_{ND} Loss (95% CI) From Baseline to End of Study Phase I (6 Months).

Region	Early Start (N=15)	Delayed Start (N=14)	p
LtaCN	−0.04 (−0.14, 0.07)	0.07 (−0.02, 0.16)	0.11
LtaPu	−0.01 (−0.08, 0.07)	0.06 (−0.01, 0.12)	0.19
LtpCN	0.02 (−0.09, 0.14)	0.08 (−0.02, 0.18)	0.44
LtpPu	0.00 (−0.04, 0.04)	0.02 (−0.02, 0.06)	0.53
LtvS	−0.04 (−0.15, 0.08)	0.04 (−0.06, 0.14)	0.35
RtaCN	−0.01 (−0.09, 0.07)	0.09 (0.02, 0.16)	0.09
RtaPu	−0.01 (−0.05, 0.03)	0.04 (−0.00, 0.07)	0.08
RtpCN	0.01 (−0.08, 0.11)	0.07 (−0.01, 0.15)	0.38
RtpPu	−0.01 (−0.06, 0.05)	0.07 (0.02, 0.11)	0.04
RtvS	0.07 (−0.02, 0.15)	0.01 (−0.07, 0.09)	0.35

LtaCN – left anterior caudate nucleus; LtaPu = left anterior putamen; LtpCN = left posterior caudate nucleus; LtpPu = left posterior putamen; LtvS = left ventral striatum; RtaCN = right anterior caudate nucleus; RtaPu = right anterior putamen; RtpCN = right posterior caudate nucleus; RtpPu = right posterior putamen; RtvS = right ventral striatum. A negative number indicates gain in BP_{ND}.

Table 3

Estimated Mean BP_{ND} Loss (95% CI) From Baseline to End of First 12 Months of Study Phase II for Early-Start and Delayed Start Groups.

Region	Early-Start (ES) (GM1 used for 18 mos)	Delayed-Start (DS) (GM1 used for 12 mos)	Comparison (C) (12 mos from Bx)	p, ES vs. C	p, DS vs. C
LtaCN	−0.01 (−0.11, 0.09)	0.10 (0.01, 0.19)	0.15 (0.04, 0.25)	0.030	0.194
LtaPu	0.06 (−0.01, 0.13)	0.10 (0.03, 0.17)	0.09 (0.01, 0.16)	0.564	0.645
LtpCN	0.01 (−0.11, 0.12)	0.06 (−0.05, 0.16)	0.08 (−0.04, 0.20)	0.391	0.581
LtpPu	0.02 (−0.02, 0.06)	0.04 (−0.00, 0.08)	0.05 (0.00, 0.09)	0.396	0.415
LtvS	−0.02 (−0.13, 0.09)	0.03 (−0.07, 0.13)	0.05 (−0.07, 0.16)	0.428	0.695
RtaCN	0.01 (−0.07, 0.08)	0.13 (0.05, 0.20)	0.10 (0.02, 0.19)	0.086	0.670
RtaPu	−0.01 (−0.05, 0.03)	0.05 (0.02, 0.09)	0.05 (0.01, 0.09)	0.049	0.560
RtpCN	0.01 (−0.08, 0.10)	0.09 (0.01, 0.18)	0.18 (0.08, 0.27)	0.016	0.046
RtpPu	0.01 (−0.05, 0.06)	0.06 (0.02, 0.11)	0.12 (0.07, 0.18)	0.002	0.013
RtvS	0.04 (−0.04, 0.13)	0.09 (0.01, 0.17)	0.06 (−0.03, 0.15)	0.799	0.982

LtaCN – left anterior caudate nucleus; LtaPu = left anterior putamen; LtpCN = left posterior caudate nucleus; LtpPu = left posterior putamen; LtvS = left ventral striatum; RtaCN = right anterior caudate nucleus; RtaPu = right anterior putamen; RtpCN = right posterior caudate nucleus; RtpPu = right posterior putamen; RtvS = right ventral striatum. A negative number indicates gain in BP_{ND}. Bx = Baseline (start of study). Early-Start (N =15); Delayed-Start (N =14); Comparison (N =11). P-values were calculated for comparing change over 18 months in the DS and ES arms vs the extrapolated change over 18 months in the comparison group (1.5 x change from Bx to 12 months).

Table 4

Estimated Mean BP_{ND} Loss (95% CI) From Baseline to End of Study Phase II for Early-Start and Delayed Start Groups.

Region	Early-Start (ES) (GM1 used for 30 mos)	Delayed-Start (DS) (GM1 used for 24 mos)	Comparison (C) (24 mos from Bx)	p, ES vs. C	p, DS vs. C
LtaCN	0.06 (−0.04, 0.16)	0.16 (0.07, 0.26)	0.30 (0.16, 0.43)	0.002	0.035
LtaPu	0.09 (0.02, 0.16)	0.14 (0.07, 0.21)	0.18 (0.09, 0.28)	0.055	0.199
LtpCN	0.11 (−0.01, 0.22)	0.11 (0.00, 0.22)	0.21 (0.06, 0.36)	0.150	0.162
LtpPu	0.04 (−0.00, 0.08)	0.06 (0.02, 0.11)	0.07 (0.01, 0.12)	0.318	0.654
LtvS	0.00 (−0.11, 0.11)	0.10 (−0.01, 0.21)	0.17 (0.02, 0.31)	0.058	0.312
RtaCN	0.10 (0.02, 0.18)	0.16 (0.08, 0.24)	0.21 (0.11, 0.31)	0.032	0.173
RtaPu	0.02 (−0.02, 0.06)	0.06 (0.02, 0.10)	0.07 (0.02, 0.12)	0.093	0.553
RtpCN	0.11 (0.02, 0.21)	0.13 (0.05, 0.22)	0.29 (0.17, 0.41)	0.007	0.012
RtpPu	0.07 (0.02, 0.12)	0.13 (0.08, 0.18)	0.17 (0.10, 0.24)	0.005	0.099
RtvS	0.13 (0.04, 0.22)	0.15 (0.07, 0.23)	0.15 (0.04, 0.26)	0.500	0.669

LtaCN – left anterior caudate nucleus; LtaPu = left anterior putamen; LtpCN = left posterior caudate nucleus; LtpPu = left posterior putamen; LtvS = left ventral striatum; RtaCN = right anterior caudate nucleus; RtaPu = right anterior putamen; RtpCN = right posterior caudate nucleus; RtpPu = right posterior putamen; RtvS = right ventral striatum. A negative number indicates gain in BP_{ND}. Bx = Baseline (start of study). Early-Start (N =15); Delayed-Start (N =14); Comparison (N =11). P-values were calculated for comparing change over 30 months in the DS and ES arms vs the extrapolated change over 30 months in the comparison group (1.25 x change from Bx to 24 months).

Table 5

Estimated Mean BP_{ND} Loss (95% CI) From End of Study Phase I (6 Months) to the End of Study Phase II.

Region	Delayed Start: GM1 for 24 months (Phase II start/end difference)	Comparison 0 −24 months difference	p-value for DS vs. C
LtaCN	0.09 (0.00, 0.18)	0.30 (0.16, 0.43)	0.012
LtaPu	0.08 (0.02, 0.14)	0.18 (0.09, 0.28)	0.080
LtpCN	0.03 (−0.07, 0.13)	0.21 (0.06, 0.36)	0.049
LtpPu	0.04 (0.01, 0.08)	0.07 (0.01, 0.12)	0.520
LtvS	0.06 (−0.04, 0.16)	0.17 (0.02, 0.31)	0.250
RtaCN	0.07 (0.00, 0.14)	0.21 (0.11, 0.31)	0.033
RtaPu	0.03 (−0.01, 0.06)	0.07 (0.02, 0.12)	0.210
RtpCN	0.07 (−0.01, 0.15)	0.29 (0.17, 0.41)	0.003
RtpPu	0.06 (0.02, 0.11)	0.17 (0.10, 0.24)	0.012
RtvS	0.14 (0.06, 0.22)	0.15 (0.04, 0.26)	0.900

LtaCN – left anterior caudate nucleus; LtaPu = left anterior putamen; LtpCN = left posterior caudate nucleus; LtpPu = left posterior putamen; LtvS = left ventral striatum; RtaCN = right anterior caudate nucleus; RtaPu = right anterior putamen; RtpCN = right posterior caudate nucleus; RtpPu = right posterior putamen; RtvS = right ventral striatum. A negative number indicates gain in BP_{ND}. Delayed-Start (N =14); Comparison (N =11)