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Diffusion Magnetic Resonance Imaging Detects Progression in Parkinson's Disease: A Placebo-Controlled Trial of Rasagiline

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Abstract

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Supporting Data

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Background: Rasagiline has received attention as a potential disease-modifying therapy for Parkinson's disease (PD). Whether rasagiline is disease modifying remains in question.

Objective: The main objective of this study was to determine whether rasagiline has disease-modifying effects in PD over 1 year. Secondarily we evaluated two diffusion magnetic resonance imaging pulse sequences to determine the best sequence to measure disease progression.

Methods: This prospective, randomized, double-blind, placebo-controlled trial assessed the effects of rasagiline administered at 1 mg/day over 12 months in early-stage PD. The primary outcome was 1-year change in free-water accumulation in posterior substantia nigra (pSN) measured using two diffusion magnetic resonance imaging pulse sequences, one with a repetition time (TR) of 2500 ms (short TR; n = 90) and one with a TR of 6400 ms (long TR; n = 75). Secondary clinical outcomes also were assessed.

Results: Absolute change in pSN free-water accumulation was not significantly different between groups (short TR: $P = 0.346$; long TR: $P = 0.228$). No significant differences were found in any secondary clinical outcomes between groups. Long TR, but not short TR, data show pSN free-water increased significantly over 1 year ($P = 0.025$). Movement Disorder Society Unified Parkinson's Disease Rating Scale testing of motor function, Part III increased significantly over 1 year ($P = 0.009$), and baseline free-water in the pSN correlated with the 1-year change in Movement Disorder Society Unified Parkinson's Disease Rating Scale testing of motor function, Part III ($P = 0.004$) and 1-year change in bradykinesia score ($P = 0.044$).

Conclusions: We found no evidence that 1 mg/day rasagiline has a disease-modifying effect in PD over 1 year. We found pSN free-water increased over 1 year, and baseline free-water relates to clinical motor progression, demonstrating the importance of diffusion imaging parameters for detecting and predicting PD progression.

Keywords

Parkinson's; rasagiline; MAO-B; diffusion imaging; progression

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In Parkinson's disease (PD), a major unmet medical need is a disease-modifying therapy to slow neurodegeneration and to improve long-term clinical outcomes. Numerous therapies and substantial investments have been made by both government and industry to develop a disease-modifying therapy for PD.[1–6] Large sample sizes are needed to power these studies, resulting in recruitment challenges, difficulties in retention, and skyrocketing costs that have delayed the development of disease-modifying therapies for PD. A medication that has received considerable focus for potential disease modification is rasagiline. Rasagiline is a second-generation, selective irreversible inhibitor of monoamine oxidase type B (MAO-B) currently approved for the treatment of PD motor symptoms. This agent has the advantage of lacking the amphetamine metabolites seen in first-generation MAO-B inhibitors, which may attenuate potential neuroprotection.[7]

The neuroprotective potential of MAO-B inhibitor administration has been tested in preclinical rodent models of PD, and this class of medication has been shown to counteract cell loss in the substantia nigra (SN) after striatal injection of 6-hydroxydopamine.[8] In addition, MAO-Bs have been shown to exert a significant neuroprotective effect

against lactacystin-induced nigrostriatal degeneration.[9] In a primate model of parkinsonism, both MAO-Bs selegiline and rasagiline were able to attenuate toxicity from 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine.[10]

Rasagiline also has been studied in a randomized trial for a potential neuroprotective role, resulting in continuing controversy regarding whether it has disease-modifying qualities at the 1 mg, but not the 2 mg dose.[4] In humans, the Attenuation of Disease Progression with Azilect Given Once-daily (ADAGIO) trial tested 1 mg, 2 mg, and placebo doses in early-stage PD.[4] Using a delayed-start paradigm, the study showed evidence that 1 mg/day met all study outcomes for a disease-modifying therapy. However, the failure of the 2 mg/day dosage to meet outcomes resulted in significant controversy in the field and significant skepticism from the U.S. Food and Drug Administration panel, which rejected the labeling of rasagiline as disease modifying. The ADAGIO trial applied a delayed-start paradigm and chose the Unified Parkinson's Disease Rating Scale (UPDRS) for the primary outcome variable given the absence of an objective disease progression biomarker. The field was left with an unanswered question: if viable biomarkers of nigrostriatal progression were to exist, would we have been able to detect that 1 mg of rasagiline used in early PD slows nigrostriatal degeneration?

Since the publication of the ADAGIO study, considerable progress has been made in developing and validating biomarkers of PD progression. Using commercially available magnetic resonance imaging (MRI) technology, we applied an imaging algorithm referred to as free-water imaging.[11] Our data demonstrated that the posterior substantia nigra (pSN) free-water increased over 1 year in an early PD cohort, but not in a control group, suggesting for the first time that the SN degeneration could be monitored longitudinally with a diffusion MRI technique.[12] The same study showed that the baseline free-water in the pSN was related to the 1-year change in bradykinesia score. We then applied this technique to the Parkinson's Progression Markers Initiative cohort and found that free-water in the pSN increased over 1, 2, and 4 years, providing validation that this marker was observed in separate cohorts and across multiple sites and scanners.[13] Further, Burciu and colleagues[13] found that the change in free-water within the pSN over 1 year predicted the 4-year change in Hoehn and Yahr scale. Finally, the progression of free-water in the SN of patients with PD has been replicated by other groups.[14]

Most studies that have shown increased free-water within pSN in PD have used a longer repetition time (TR) to avoid aliasing T1 effects,[11,12] whereas some studies using multiband technology tend to use a much shorter TR.[15] However, recent work suggests that shorter TRs may result in movement artifacts related to spin-history effects, caused by the reduced time interval between successive excitations.[15] In this study, we also tested the secondary hypothesis that the type of diffusion sequence is a critical factor for detecting the progression of free-water in the SN. We designed this study to evaluate two different pulse sequences, one with a short TR of 2500 ms (short TR) and one with a longer TR of 6400 ms (long TR). We thus aimed to determine the most practical and efficient sequence to measure disease progression.

Using this technique, we aimed to inform the controversy in the field as to whether 1 mg/day of rasagiline in early PD slows down the progression of free-water diffusion in the pSN. In addition, we measured secondary clinical outcomes and adverse events, and assessed the relationship between free-water in the pSN and progression of motor symptoms.

Patients and Methods

Trial Design and Participants

This prospective, randomized, double-blind, placebo-controlled trial was conducted between January 2017 and October 2020. Participants with early-stage (<5 years of diagnosis) PD, confirmed by a movement disorders specialist using the UK PD Brain Bank diagnostic criteria,[16] were self-referred or recruited from University of Florida (UF) Health or University of Buffalo. All study-related evaluations occurred at UF Health. We targeted early-stage PD because this is the period when MAO-B inhibitors have shown the most promise. Participants were eligible if they were 40 to 77 years of age, had Hoehn and Yahr stage ≤2 *on* medication, and had never taken rasagiline. Participants were ineligible if they had a prior history of stroke or brain tumor, had an implanted electrical device (cardiac pacemaker or neurostimulator) or aneurysm clip, or were pregnant or nursing. Participants were followed for 1 year or until they withdrew from the study. The trial protocol was approved by the institutional review board, and all participants provided written informed consent.

Trial Procedures

Participants who met all eligibility criteria performed baseline testing, which included diffusion MRI and secondary motor and cognitive testing (see Supporting Information Methods in Appendix 1). All testing was performed in the *off* state, after overnight withdrawal from antiparkinsonian medication. After baseline testing, participants were assigned to either the active drug arm (receiving 1 mg/day of rasagiline) or placebo arm using the Pocock-Simon covariate adaptive randomization procedure generated by the statistician.[17] The statistician randomly assigned the first participant. The new participant was assigned to the underrepresented group with probability 2/3 if there was an imbalance and with equal probability otherwise. At each time of randomization, the underrepresented group was determined by the sum of four imbalance indices (difference in number of participants assigned to the drug and placebo groups in the category) corresponding to the four covariates: age (<60, 61–69, or ≥70 years); sex (male/female); baseline Movement Disorder Society Unified Parkinson's Disease Rating Scale testing of motor function, Part III (MDS-UPDRS-motor, Part III) score (mild: <25; moderate: ≥25); and SN free-water (mild: <0.22; moderate: ≥0.22). After each randomization, the pharmacist received a four-digit sequence to retrieve prelabeled medication/placebo bottles. All personnel remained blinded apart from the statistician. During the 1-year trial, phone calls were made to each participant every 3 months to monitor adverse events and maintain participant communication. Finally, the entire baseline assessment procedure was repeated at 12 months for the 1-year follow-up testing. Current medications and any adverse events were recorded at each visit. Participants' PD and non-PD medications could be adjusted during the trial as indicated by their treating physicians.

Power Calculation

The goal was to enroll a total of 96 subjects with approximately equal allocation to the rasagiline and placebo groups. Our previous cross-sectional study was used as pilot data to power this study.[18] We assumed that the mean difference in the primary outcome between the rasagiline and placebo groups would be 90% of those observed in our pilot data; in other words, the placebo group would have 10% the benefit of rasagiline over the control. Supporting Information Table 1 in Appendix 1 presents results on statistical power for the primary intent-to-treat efficacy analyses, with the use of two-sample *t* test on the change of free-water accumulation in the SN. Notably, the pilot data were collected on a different scanner using a different sequence than the one used for this study, resulting in slightly higher free-water values. Assuming a loss-to-follow-up rate of 15%, a total sample size of 96 yielded 80% power to detect the difference when the primary test is conducted at two-sided type I error of 0.025.

Statistical Analysis

Demographic and clinical variables were compared at baseline between the rasagiline and placebo groups using the two-sample *t* test for continuous variables and the chi-square test for categorical variables.

The primary outcome was the group difference in the change in diffusion MRI from baseline to 1-year follow-up. The outcome variables included free-water accumulation in the pSN from two different diffusion scans (short TR and long TR; see Supporting Information Methods in Appendix 1). We calculated free-water maps for each participant before applying nonlinear transformations to warp the free-water maps to a template in standard Montreal Neurological Institute (MNI) space. We then used a pSN region of interest obtained from a validated atlas of regions in MNI space to extract mean free-water values from each participant's free-water map in MNI space (see Supporting Information Methods in Appendix 1).[19] Intent-to-treat analysis was performed to compare the rasagiline and placebo groups using general linear regression, adjusting for participant's sex, baseline age, baseline MDS-UPDRS-motor, Part III score, and baseline outcome values. All covariates were centered at the mean. For the intent-to-treat analyses, the missing primary outcome was predicted by a fitted regression model using demographic and baseline clinical variables that characterize differences between "completers" and "noncompleters." In addition, sensitivity analyses were performed by comparing analysis results based on the earlier imputation method with those from a "complete-case" analysis and searching for a tipping point that reverses the study conclusion. All primary outcome tests were two-sided, using an a priori selected *P* value <0.025.

In addition, linear regressions were conducted to compare the group differences on the clinical and motor secondary endpoints (see Supporting Information Methods in Appendix 1), adjusting for age, sex, and corresponding baseline secondary endpoint. Pearson correlations were conducted between pSN free-water and clinical motor progression (MDS-UPDRS-motor, Part III score; bradykinesia total score from MDS-UPDRS-motor, Part III). All secondary tests, including the pSN free-water progression effect, were two-sided, using a

P value <0.05. All statistics were performed using the R statistical analysis package (Version 4.0.2, https://www.r-project.org).

Results

Participant Baseline Characteristics

There were 96 participants recruited for this study, and 90 participants were included in the final primary analyses. One participant was excluded because of a prior stroke. Three participants withdrew from the imaging because of anxiety. Two other participants were excluded because of space restrictions in the MRI and were not randomized. Of the 90 participants, 11 participants did not return to complete the 1-year follow-up visit (Fig. 1).

Descriptive statistics for the baseline demographic variables, clinical variables, and primary outcome variables are presented in Table 1. The baseline free-water measurements for the short TR and long TR scans were not significantly different between the rasagiline and placebo groups ($P = 0.841$ and $P = 0.284$, respectively). All five secondary endpoints were not significantly different between the rasagiline and placebo groups at the baseline visit.

Primary Outcomes

The results from linear regressions on primary endpoints are presented in Table 2. The absolute change in free-water accumulation in the SN was not significantly different between the two groups (estimated mean difference of 0.0015 and –0.0015 based on short TR and long TR scans, $P = 0.346$ and $P = 0.228$, respectively). Complete-case analyses yielded qualitatively the same results. No tipping point that reversed the study conclusion was found. The Cohen's D effect sizes of the between-group difference ranged between 0.2 and 0.3 from various models.

Secondary Outcomes

Results from the long TR scan data show that the free-water measurements increased significantly from baseline to follow-up (Table 2). No progression effects were found for the short TR scan (Table 2). When restricting the analysis to participants with complete-case long TR scans (n = 67), we did not find significant change over time in the free-water measurements derived from the short TR scans (Supporting Information Table 2 in Appendix 1).

Follow-up and absolute change values for demographic, clinical, and primary outcome variables are presented in Supporting Information Table 3 in Appendix 1. The absolute change in the five secondary endpoints (Parkinson's Disease Questionnaire [PDQ-39], Montreal Cognitive Assessment [MoCA], Hamilton Rating Scale for Depression, Hamilton Anxiety Rating Scale, and MDS-UPDRS-motor, Part III score) was not significantly different between the two groups after adjusting baseline covariates; however, a progression effect was seen for the MDS-UPDRS-motor, Part III score ($P = 0.009$) (Table 3).

Correlation analyses demonstrated significant positive relationships between long TR baseline free-water values in the pSN and the 1-year change in MDS-UPDRS-motor, Part III total score ($r = 0.326$; $P = 0.004$), as well as the 1-year change in bradykinesia score ($r =$

0.233; $P = 0.044$). No significant correlations were found between the 1-year change in long TR free-water values and the 1-year change in MDS-UPDRS-motor, Part III total score ($r = –0.006$; $P = 0.957$) or the 1-year change in bradykinesia score ($r = –0.127$; $P = 0.278$).

Additional Secondary Analyses

This study design assumes progression of free-water within the pSN of the placebo group. Therefore, to confirm the presence of pSN free-water progression, we conducted additional linear regressions on the primary endpoints for the placebo group only. Results from the long TR scan show that the free-water measurements increased significantly from baseline to follow-up ($P = 0.004$). No progression effects were found for the short TR scan ($P = 0.677$). This indicates progression of pSN free-water accumulation in the placebo group, justifying the comparison of the placebo and rasagiline groups when using the long TR scan.

To assess confounding effects that may occur because of participants taking and/or adjusting other medications, we conducted linear regressions on the primary endpoints adjusting for either levodopa-equivalent daily dose (LEDD) or the change in LEDD, as well as sex, baseline age, baseline MDS-UPDRS-motor, Part III score, and baseline outcome values. The absolute change in free-water accumulation in the SN was not significantly different between the two groups when adjusting for LEDD ($P = 0.390$ and $P = 0.222$ based on short TR and long TR scans) or the change in LEDD ($P = 0.349$ and $P = 0.233$ based on short TR and long TR scans). Complete-case analyses yielded qualitatively the same results. This indicates any additional medications the participants were taking or changes to medications did not affect the outcomes of the study.

Adverse Events

One participant withdrew because of headaches, one withdrew as a result of hair loss, one withdrew because of fatigue, one withdrew because of dizziness, two withdrew as a result of fatigue and light-headedness, and one withdrew because of edema. Any additional adverse events were determined to be either due to PD symptoms or due to other medications not related to the study. All adverse events are reported in Table 4. In addition, another participant required surgery to implant a cardiac pacemaker and completed their follow-up testing at 8 rather than 12 months.

Additional Reasons for Study Withdrawal

One participant withdrew to begin taking rasagiline outside the study supervised by their personal health care provider. Two participants elected to undergo deep brain stimulation surgery and were withdrawn from the study. Finally, one participant withdrew because of medical complications unrelated to the study.

Discussion

This study showed that diffusion measures of free-water in the SN provide a viable marker of disease progression and predict disease progression when using a long TR. We used this technique to inform on the still highly controversial subject as to whether 1 mg of rasagiline delays PD progression. Results from this randomized, double-blind, placebo-controlled trial,

which used diffusion imaging, do not support the hypothesis that 1 mg/day of rasagiline has a disease-modifying effect in PD. No differences were found in the 1-year change in free-water accumulation in the pSN between the rasagiline and placebo groups. In addition, no differences were found in the 1-year change in any of the five secondary measures (PDQ-39, MoCA, Hamilton Rating Scale for Depression, Hamilton Anxiety Rating Scale, and MDS-UPDRS-motor, Part III score) between the two groups. Taken together, these results suggest that 1 mg/day of rasagiline does not have disease-modifying qualities in early PD over 12 months. We did observe differences between the short TR and long TR diffusion MRI data, with only the long TR data showing that free-water measurements increased significantly from baseline to follow-up. Also, free-water in the pSN at baseline predicted the 1-year change in MDS-UPDRS-motor, Part III and 1-year change in bradykinesia scores. This finding is significant because it demonstrates that the type of diffusion sequence used is critical for detecting the progression of free-water in the SN.

The initial motor PD symptoms occur as a result of the loss of dopaminergic neurons in the SN, suggesting that this area may be useful for tracking disease progression. Recently, a primate model of PD has been used to show that diffusion MRI measures of the nigrostriatal tract relate to nigral cell counts, suggesting diffusion measures may represent a noninvasive marker of nigrostriatal injury.[20] Diffusion MRI measures of free-water also have been shown to increase in instances of other neurodegenerative disorders and in neuroinflammation.[21] Furthermore, we have shown that free-water in the pSN increases in individuals with PD over a 1-, 2-, and 4-year period across different sites and different scanners, and that the 1- and 2-year change in free-water predicts long-term progression on the Hoehn and Yahr stage scale.[13]

Using free-water accumulation within the SN as a primary outcome in this clinical trial, we found no difference in the 1-year change in free-water accumulation between the rasagiline and placebo groups. Prior evidence from retrospective data suggested that taking rasagiline at 1 mg/day may have disease-modifying benefits.[18] We found no differences in the 1-year change in any of the five secondary measures (PDQ-39, MoCA, Hamilton Rating Scale for Depression, Hamilton Anxiety Rating Scale, and MDS-UPDRS-motor, Part III score) between the two groups. In contrast, the results of the ADAGIO trial indicate that 1 mg/day of rasagiline met all study outcomes for a disease-modifying therapy.[4] The primary outcome measure in the ADAGIO trial was the UPDRS total score. Likewise, the TEMPO study also showed better UPDRS total scores, as well as UPDRS motor subscores, in the group receiving rasagiline compared with the placebo group.[2] However, the randomized longitudinal ADAGIO trial did not find significant long-term improvement in motor symptoms from rasagiline at a 2 mg/day dosage.[4] Furthermore, given that we found no difference in free-water accumulation in the pSN, or any of the secondary measures, our data do not support that 1 mg/day of rasagiline possesses disease-modifying qualities over 12 months in early PD.

Although we found no differences between the rasagiline and placebo groups, it is possible that this was due to the slightly greater disease duration of our participants compared with prior studies. The average disease duration of participants in the ADAGIO trial was 4.5 months,[4] while disease duration in the TEMPO study was 1 year.[2] In this study,

the average disease duration was slightly greater, at 1.75 years, which could suggest that rasagiline may confer only a disease-modifying effect in the earliest stages of PD (ie, <1.75 years). However, other studies have suggested that rasagiline also improves symptoms in participants with later-stage PD.[3,22] Furthermore, given that free-water diffusion appears to be an effective marker of disease progression, and that we found no group differences with this marker in this placebo-controlled trial, it seems more likely that 1 mg/day of rasagiline does not have a disease-modifying effect in a 12-month study design, even in early-stage PD. In addition, it should be acknowledged that the sample size of this study was small relative to the ADAGIO trial, which could have affected our ability to detect differences, particularly in the secondary outcomes, such as the MDS-UPDRS-motor, Part III score. Because participants could adjust other PD medications during the trial, such a design could reduce the ability to detect symptomatic benefit from rasagiline based on MDS-UPDRS-motor, Part III scores.[23] In addition, this was a single-center study with a relatively homogenous participant group with respect to age, disease severity, and geographic location, potentially affecting our results from the global population means. Finally, it is possible that other regions show free-water progression; however, the focus of this clinical trial was on the pSN. Future studies should explore whether long TR diffusion measures in other brain regions are relevant to PD progression.

The results of this study also demonstrated a longitudinal change for the long TR diffusion MRI data, whereas no longitudinal change was observed for the short TR diffusion MRI data. Specifically, the long TR data demonstrated a significant increase in free-water accumulation in the pSN, whereas the short TR data did not show this progression effect. Ofori et al.[12] were the first to report a progressive increase in free-water in the pSN, and the TR used in that study was 7748 ms. Andersson et al.[15] recently demonstrated that shorter TRs, like those used in multiband acquisitions, can result in movement artifacts related to spin-history effects. These spin-history effects are caused by the reduced time interval between successive excitation of the same spins and likely explain the differences we see in our short TR and long TR data. More importantly, this demonstrates the importance of selecting specific diffusion sequences and emphasizes that long TR sequences are critical for detecting free-water increases in PD SN progression.

Our correlation analyses indicated that baseline, but not longitudinal, free-water measures from the long TR scan are associated with the longitudinal change in both MDS-UPDRS-motor, Part III total and bradykinesia scores. Ofori et al.[12] previously reported a correlation between baseline free-water values and longitudinal change in bradykinesia score. These results provide evidence that baseline diffusion MRI measures are a clinically useful marker for predicting disease progression.

In conclusion, we found no evidence that 1 mg/day of rasagiline has a disease-modifying effect in PD. However, we did find that free-water increased in the SN over 1 year, adding to the growing literature suggesting free-water changes within the SN represent a viable marker of PD progression.[24] Furthermore, we demonstrate the significance of the diffusion imaging parameters and the importance of using long TR scans to assess free-water increases in PD SN progression.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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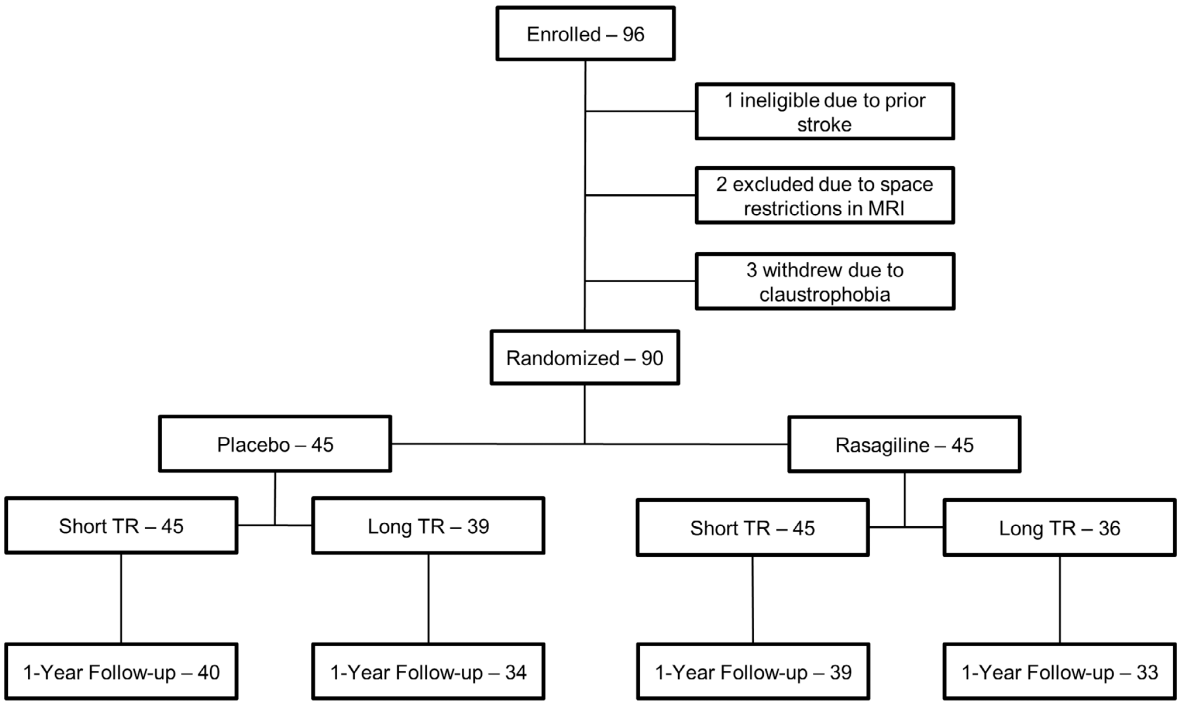

FIG. 1.

Participant enrollment and randomization. Of the 90 participants randomized, 11 did not return for follow-up visit.

TABLE 1

Baseline group demographics and all primary and secondary variables

	Placebo	Rasagiline	*P* value
Number of subjects	45	45	
Sex, n (%)			0.652
Female	13 (28.89)	16 (35.56)	
Male	32 (71.11)	29 (64.44)	
Age at baseline, y	63.44 ± 8.48	65.02 ± 7.77	0.360
Disease duration, mo	24.11 ± 19.86	18.00 ± 15.34	0.106
Days between baseline and follow-up	373.08 ± 9.77	378.46 + 22.38	0.173
Levodopa-equivalent daily dose	421.36 ± 324.21	304.82 ± 228.74	0.125
MDS-UPDRS-motor, Part III score	32.76 ± 12.42	29.62 ± 10.87	0.206
PDQ-39 score	25.93 ± 20.36	18.28 ± 18.84	0.071
MoCA score	25.82 ± 2.77	26.64 ± 2.17	0.120
Hamilton Rating Scale for Depression score	7.02 ± 6.02	5.09 ± 4.38	0.085
Hamilton Anxiety Rating Scale score	10.69 ± 7.94	8.53 ± 8.04	0.210
Long TR free-water in the pSN	0.1491 ± 0.03	0.1565 ± 0.03	0.284
Short TR free-water in the pSN	0.1514 ± 0.03	0.1502 ± 0.03	0.841

Data are mean ± standard deviation unless otherwise indicated.

MDS-UPDRS-motor, Part III, Movement Disorder Society Unified Parkinson's Disease Rating Scale testing of motor function, Part III; PDQ-39, Parkinson's Disease Questionnaire; MoCA, Montreal Cognitive Assessment; TR, repetition time; pSN, posterior substantia nigra.

TABLE 2

Linear regressions for the absolute change in free-water accumulation in the pSN from the intent-to-treat and complete-case analyses

	Estimate	95% CI	*P* value	Estimate	95% CI	*P* value
	Short TR absolute change in free-water (n = 90)			Long TR absolute change in free-water (n = 75)		
Intent-to-treat analysis						
Intercept	0.0015	–0.0018, 0.0049	0.367	**0.0029**	**0.0004, 0.0054**	**0.025**
Sex	–0.0013	–0.0048, 0.0022	0.450	–0.0021	–0.0047, 0.0005	0.119
Age at baseline	–0.0002	–0.0006, 0.0001	0.219	0.0002	–0.0002, 0.0005	0.305
MDS-UPDRS-motor, Part III at baseline	–0.0001	–0.0004, 0.0001	0.318	0.0001	–0.0001, 0.0004	0.193
Free-water in the pSN at baseline	–0.1075	–0.2276, 0.0126	0.079	–0.0713	–0.1617, 0.019	0.120
Group (rasagiline vs. placebo)	0.0015	–0.0017, 0.0047	0.346	–0.0015	–0.0039, 0.001	0.228
	Short TR absolute change in free-water (n = 79)			Long TR absolute change in free-water (n = 67)		
Complete-case analysis						
Intercept	0.0016	–0.0023, 0.0054	0.418	**0.0029**	**0.0001, 0.0058**	**0.041**
Sex	–0.0013	–0.0053, 0.0027	0.513	–0.0021	–0.0051, 0.0009	0.160
Age at baseline	–0.0003	–0.0007, 0.0002	0.267	0.0002	–0.0002, 0.0006	0.346
MDS-UPDRS-motor, Part III at baseline	–0.0001	–0.0004, 0.0002	0.361	0.0001	–0.0001, 0.0004	0.223
Free-water in the pSN at baseline	–0.1055	–0.2419, 0.0308	0.127	–0.0694	–0.1683, 0.0296	0.166
Group (rasagiline vs. placebo)	0.0018	–0.0019, 0.0055	0.343	–0.0017	–0.0045, 0.0011	0.227

All variables are centered at the mean, and significant values are shown in bold.

pSN, posterior substantia nigra; CI, confidence interval; MDS-UPDRS-motor, Part III, Movement Disorder Society Unified Parkinson's Disease Rating Scale testing of motor function, Part III; TR, repetition time.

TABLE 3

Linear regressions for the absolute change in clinical variables from the intent-to-treat analyses

	Estimate	95% CI	*P* value
MDS-UPDRS-motor, Part III (n = 90)			
Intercept	**2.42**	**0.6124, 4.2275**	**0.009**
Sex	0.7647	−1.0596, 2.5891	0.407
Age at baseline	0.0593	−0.1511, 0.2697	0.577
Centered baseline score	**−0.3902**	**−0.5371, −0.2433**	**<0.001**
Assignment group (rasagiline vs. placebo)	−0.096	−1.8094, 1.6174	0.912
PDQ-39 (n = 87)			
Intercept	1.5355	−0.4522, 3.5233	0.128
Sex	0.81	−1.1988, 2.8188	0.425
Age at baseline	−0.1222	−0.3691, 0.1247	0.328
Centered baseline score	−0.0489	−0.1567, 0.0589	0.370
Assignment group (rasagiline vs. placebo)	−0.2983	−2.208, 1.6114	0.757
MoCA (n = 90)			
Intercept	0.1615	−0.2236, 0.5467	0.407
Sex	−0.1087	−0.5001, 0.2827	0.582
Age at baseline	−0.0397	−0.0856, 0.0063	0.090
Centered baseline score	**−0.3303**	**−0.4825, −0.1781**	**<0.001**
Assignment group (rasagiline vs. placebo)	0.171	−0.1969, 0.5388	0.358
Hamilton Rating Scale for Depression (n = 90)			
Intercept	−0.2423	−0.9791, 0.4945	0.515
Sex	0.0958	−0.6454, 0.8371	0.798
Age at baseline	−0.0364	−0.126, 0.0531	0.421
Centered baseline score	**−0.3088**	**−0.447, −0.1706**	**<0.001**
Assignment group (rasagiline vs. placebo)	0.6033	−0.0996, 1.3062	0.092
Hamilton Anxiety Rating Scale (n = 88)			
Intercept	0.3749	−0.9183, 1.6682	0.566
Sex	0.4906	−0.8143, 1.7954	0.457
Age at baseline	0.0024	−0.1528, 0.1577	0.975

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	Estimate	95% CI	*P* value
Centered baseline score	**−0.2433**	**−0.402, −0.0846**	**0.003**
Assignment group (rasagiline vs. placebo)	0.4605	−0.7739, 1.695	0.460

All variables are centered at the mean, and significant values are shown in bold.

CI, confidence interval; MDS-UPDRS-motor, Part III, Movement Disorder Society Unified Parkinson's Disease Rating Scale testing of motor function, Part III; PDQ-39, Parkinson's Disease Questionnaire; MoCA, Montreal Cognitive Assessment.

TABLE 4

Summary of adverse events

Relation to the study	Placebo	Rasagiline
Definitely not related		
Orthostatic hypotension		1
Weight loss		1
Hypersexuality		1
Headaches		1
Falls	1	1
Hair loss		1
Vomiting	1	
Joint pain/stiffness	1	1
Vertigo/dizziness	1	
Congestion	1	
Edema	1	
Fatigue	2	1
Light-headed	1	2
Increased resting tremor		1
Possibly related		
Dizziness and light-headed		1
Definitely related	0	0
Total	9	12