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Impact of belief in neuroprotection on therapeutic intervention in Parkinson disease

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Abstract

We explored the hypotheses that an investigator's belief in a putative neuroprotective agent might influence the timing of symptomatic intervention and the assessment of signs and symptoms of Parkinson patients with the Unified Parkinson Disease Rating Scale (UPDRS). These hypotheses were tested with Cox and general linear modeling, using data from a previously published double-blind placebo-controlled futility trial of coenzyme Q₁₀ and GPI-1485. We found the investigators' level of confidence in these agents had no effect on the time to symptomatic therapy or on the change in UPDRS during 12 months of treatment.

Keywords

Parkinson disease; bias; clinical trial; Unified Parkinson Disease Rating Scale

Introduction

The strong tendency for an investigator's or patient's beliefs to influence the perceived response to a treatment is well known. Consequently, patients are commonly randomized to active agent or placebo, and the patients and investigators are blinded to the treatment.

In studies of putative neuroprotective agents, patients are typically randomized to the active agent or placebo and then assessed periodically for changes in their clinical condition.

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Author roles: Rodger Elble and Stephanie Shaftman wrote the first draft. Rodger Elble, Stephanie Shaftman, Oksana Suchowersky, and William Weiner designed and executed the study. All authors reviewed and critiqued the final draft. Stephanie Shaftman, Peng Huang and Barbara Tilley performed the statistical analyses. The NET-PD investigators performed the original clinical trial, from which the data in this study were derived.

Investigators often have the option of starting an established treatment if a patient becomes sufficiently symptomatic. The time to therapy should be greater in patients receiving an effective neuroprotective drug. This study design has been used extensively in Parkinson disease (PD) since the DATATOP study of selegiline.¹

The NINDS NET-PD investigators recently examined coenzyme Q₁₀ (CoQ₁₀, a putative neuroprotective agent) and the neuroimmunophilin-ligand compound GPI-1485 (a drug purported to promote neuronal repair and regeneration) in a randomized, double-blind, placebo-controlled, calibrated futility trial of 213 untreated patients with early PD.² At the beginning and end of this trial, investigators were asked to rate their confidence in these two drugs as neuroprotectants. In this report, we examine whether the investigators' level of confidence in CoQ₁₀ and GPI-1485 at baseline influenced the time to symptomatic therapy and the change in the Unified Parkinson Disease Rating Scale (UPDRS) and whether the investigators' level of confidence changed over time.

Methods

The details and outcome of the original clinical trial have been reported elsewhere.² Briefly, 213 patients, age 30 and over, with mild untreated Parkinson disease, not requiring treatment, were randomized 1:1:1 to receive one of the following three treatment options for 12 months: 1) 2400 mg of CoQ₁₀ and placebo for GPI-1485, 2) placebo for CoQ₁₀ and 4000 mg of GPI-1485, or 3) placebo for CoQ₁₀ and placebo for GPI-1485. Participants were re-evaluated with the UPDRS and other clinical scales at 1, 3, 6, 9, and 12 months ($\pm$ 6 days) after the baseline visit.

The primary, pre-specified outcome measure was the change in the total UPDRS score from baseline to the time at which there was sufficient disability to warrant symptomatic therapy for PD or from baseline to the end of the 12 month treatment period if the patient did not require symptomatic therapy. The decision to begin symptomatic therapy was a clinical decision, made by the investigator at each site. This decision was based on a patient's impairment in ambulation, activities of daily living, and occupational status. The site investigators (N=48) were trained on this endpoint using case vignettes.

In the original study, a futility study design³ was used to assess CoQ₁₀ and GPI-1485 against a predetermined change in UPDRS that is regarded as clinically meaningful. Thus, the mean change in total UPDRS for each treatment group was compared to a 30% reduction in a historically derived change in total UPDRS that was based on the placebo arm of the Deprenyl and Tocopherol Antioxidant Therapy of Parkinsonism trial.⁴ A placebo arm was included in the original futility study to verify and update the historical control assumptions used in sample size estimation.

The investigators' confidence in CoQ₁₀ and GPI-1485 was assessed at the beginning and end of the study using an 11-point rating scale in which confidence in each agent was estimated to be 0, 10, 20, ..., 100%. For each study drug, investigators were asked "What is your level of confidence that the study drug is an effective neuroprotectant for PD? The investigators were also asked (Yes/No) if their perceptions were based on 1) pre-clinical data, 2) clinical information, 3) steering committee recommendation, and 4) "nothing better to try".

We examined two post hoc hypotheses; hypothesis 1: investigator's baseline belief influences the time to symptomatic therapy and hypothesis 2: investigator's baseline belief influences the change from baseline in the UPDRS. We also assessed change in beliefs over time. The original study was placebo-controlled and double-blind, and the two active drugs had no perceptible symptomatic effect.² Consequently, the data from the three treatment

arms were pooled in our statistical analyses. However, treatment group was included as a covariate.

All statistical analyses were performed with SAS/STAT.5 Hypothesis 1 was tested statistically by modeling the time to symptomatic therapy (outcome measure) using a Cox model (SAS PHREG procedure) with duration of disease, baseline UPDRS score, age at baseline and treatment group as covariates and using confidence in CoQ10 and confidence in GPI-1485 as independent variables. Hypothesis 2 was tested by constructing a general linear model using change in total UPDRS from baseline to the 12 month visit as the outcome, age, duration of disease, and treatment group as covariates, and confidence in CoQ10 and confidence in GPI-1485 as independent variables. We used Wilcoxon signed rank tests to test the null hypothesis that change from baseline to the end of the trial in investigator confidence equal zero, separately for CoQ10 and GPI-1485. Baseline data on the covariates were previously published in the report on the trial.²

Results

The effect of investigator confidence in CoQ10 and GPI-1485 is shown in Table 1. After adjusting for patient age, duration of disease, baseline UPDRS score, and treatment group, neither investigator confidence in CoQ10 nor GPI-1485 were associated with time-to-symptomatic therapy. The effect of investigator confidence on UPDRS change from baseline is also shown in Table 1. After adjusting for age, duration of disease, and treatment group, neither CoQ10 confidence nor GPI-1485 was associated with change in total UPDRS from baseline.

The box plots in Figure 1 illustrate the change in confidence in CoQ10 and GPI-1485 over the course of the study. We could not detect a difference between baseline and final visit for either agent ($p>0.05$) using a Wilcoxon signed rank test. The mean (SD) for level of confidence (0–100%) in CoQ10 at start and end of study were 41.7 (17.8) and 42.0 (19.0), and the mean (SD) for confidence in GPI-1485 at baseline and end-of-study were 35.2 (18.8) and 34.6 (20.3). Thus, confidence levels in CoQ10 and GPI-1485 were similar. These analyses were conducted on the 46 of 48 investigators who completed both confidence assessments.

The bases for investigator confidence at the start of study were similar for CoQ10 and GPI-1485. An investigator could choose more than one reason. For CoQ10, the percentage of investigators deriving confidence from preclinical data was 73.3%, clinical information 95.5%, Steering Committee recommendations 20.5%, and “nothing better to try” 15.9%. For GPI-1485, these percentages were preclinical data 88.6%, clinical information 50%, steering committee recommendations 29.6% and “nothing better to try” 20.0%. Thus, the investigators’ confidence stemmed mostly from pre-clinical and clinical data.

Discussion

Investigator bias is a well-known confounder in clinical research. Consequently, our published clinical futility trial of CoQ10 and GPI-1485 was double-blinded and placebo-controlled.² Nevertheless, we were interested in knowing whether the investigators’ level of confidence in these agents affected UPDRS scoring and time to symptomatic therapy. Investigators with greater confidence might influence or assess their patients in such a way that the UPDRS changed more slowly and the time-to-symptomatic therapy was delayed. We found no evidence of either behavior. We know of no other study of this type in Parkinson disease.

The data in this study came from a published futility study² that included a placebo arm. Thus, the original study was double-blind and placebo-controlled, and the futility method of hypothesis testing in the original study should have no effect on the results reported in this report.

We suspect that our results would have been different if our clinical trial had not been double-blind and placebo-controlled. Because placebo associated improvement is substantial in treatment trials for Parkinson disease,⁶ the investigators had difficulty separating the placebo effect from a treatment effect. Nevertheless, it is reassuring to know that investigator confidence had no appreciable effect on UPDRS scoring and timing of symptomatic therapy. It is important to note that the investigators' confidence in the two drugs did not significantly change over time suggesting that clinical equipoise was maintained throughout the study.

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References

1. Parkinson Study Group. DATATOP: a multicenter controlled clinical trial in early Parkinson's disease. *Arch Neurol*. 1989; 46(10):1052–1060. [PubMed: 2508608]
2. NINDS NET-PD Investigators. A randomized clinical trial of coenzyme Q10 and GPI-1485 in early Parkinson disease. *Neurology*. 2007; 68(1):20–28. [PubMed: 17200487]
3. Tilley BC, Palesch YY, Kieburtz K, et al. Optimizing the ongoing search for new treatments for Parkinson disease: using futility designs. *Neurology*. 2006; 66(5):628–633. [PubMed: 16534099]
4. Parkinson Study Group. Effect of deprenyl on the progression of disability in early Parkinson's disease. *N Engl J Med*. 1989; 321(20):1364–1371. [PubMed: 2509910]
5. SAS/STAT® User's Guide, Version 8. Cary, NC: SAS Institute Inc; 1999.
6. Diederich NJ, Goetz CG. The placebo treatments in neurosciences: New insights from clinical and neuroimaging studies. *Neurology*. 2008; 71(9):677–684. [PubMed: 18725593]

Appendix

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Figure 1. Box plots of investigator confidence at the beginning of the study and the change from baseline for CoQ₁₀ and GPI-1485. The median (thick horizontal bars), 25th and 75th percentiles (box) and range (whiskers) are shown.

Table 1

Models to evaluate effect of confidence levels in CoQ10 and GPI-1485 on two outcomes (N=185)

Model 1: time to symptomatic therapy = duration of disease at baseline + change in UPDRS + age at baseline + treatment + confidence in CoQ10 + confidence in GPI-1485				
Variable	Parameter Estimate	Standard Error	Hazard Ratio	p value
Duration of disease (months)	−0.007	0.01	0.99	0.50
Baseline UPDRS	0.06	0.01	1.06	<0.0001
Age at baseline	−0.02	0.01	0.98	0.03
CoQ₁₀ confidence	0.06	0.07	1.06	0.40
GPI-1485 confidence	−0.02	0.02	0.98	0.40
Treatment	0.12	0.13	1.13	0.36
Model 2: UPDRS total change from baseline = duration of disease at baseline + age at baseline + treatment + confidence in CoQ10 + confidence in GPI-1485				
Variable	Parameter Estimate	Standard Error	t-value	p value
Duration of disease (months)	0.03	0.06	0.52	0.60
Age at baseline	0.05	0.06	0.90	0.37
CoQ₁₀ confidence	0.22	0.35	0.64	0.52
GPI-1485 confidence	−0.12	0.09	1.28	0.20
Treatment	0.19	0.73	0.27	0.79