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Trial of Magnetic Resonance-Guided Putaminal Gene Therapy for Advanced Parkinson's Disease

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Abstract

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Objective.—To investigate the safety and tolerability of convection-enhanced delivery (CED) of an adeno-associated virus, serotype-2 vector carrying glial cell line-derived neurotrophic factor (AAV2-GDNF) into the bilateral putamina of PD patients.

Methods.—13 adult patients with advanced PD underwent AAV2-GDNF and gadoteridol (surrogate MRI-tracer) co-infusion (450μl/hemisphere) at escalating doses: 9×10^{10}vg (n=6); 3×10^{11}vg (n=6); 9×10^{11}vg (n=1). Intraoperative-MRI monitored infusion distribution. Patients underwent UPDRS assessment and [^{18}F]FDOPA-PET scanning pre-operatively and 6 and 18 months post-operatively.

Results.—AAV2-GDNF was tolerated without clinical or radiographic toxicity. Average putaminal coverage was 26%. UPDRS scores remained stable. 10/13 and 12/13 patients had increased [^{18}F]FDOPA Ki's at 6- and 18-months post-infusion (increase range: 5–274% and 8–130%, median: 36% and 54%), respectively. Ki differences between baseline and 6- and 18-months follow-up were statistically significant (P<0.0002).

Conclusions.—AAV2-GDNF infusion was safe and well-tolerated. Increased [^{18}F]FDOPA uptake suggests a neurotrophic effect on dopaminergic neurons.

Keywords

Convection-enhanced Delivery; GDNF; Gene Therapy; Parkinson's; Vector

Introduction

Parkinson's disease (PD) affects about 1 million people in the U.S.[1] Medications palliate PD symptoms but do not prevent neurodegeneration. The pathological PD hallmark is progressive nigral dopaminergic (DA) neuron loss. Neuroprotective agents to prevent neurodegeneration and possibly arrest the disease have been identified,[2] including glial cell line-derived neurotrophic factor (GDNF), which promoted embryonic DA neuron survival *in vitro* and in PD animal models.[3–7] Clinical trials delivering GDNF protein to the brain via ventricular or parenchymal infusion were inconclusive or negative,[8, 9] suggesting that GDNF did not selectively or effectively affect nigrostriatal neurons, respectively. A trial of AAV2-vector delivering the GDNF homolog, Neurturin, to the putamen was also negative.[10]

The U54 "PD Gene Therapy Study Group" conducted preclinical investigations of GDNF gene transfer.[11–13] The clinical trial reported here sought to increase the neurotrophic effect seen in the Neurturin trial by 1) delivering GDNF, a more potent neurotrophic factor than Neurturin,[14–16] via an AAV2-vector[17–19] 2) using intraoperative MRI to target vector to the putamen, 3) monitoring convection-enhanced delivery (CED) of vector with a surrogate MRI tracer, and 4) increasing vector infusion volume. A previous Phase 1 gene transfer clinical trial of PD patients at UCSF had similar clinical response measures and patient populations.[20] We discuss the first-in-human use of the AAV2-GDNF vector co-infused with gadoteridol via CED into the bilateral putamina of adult PD patients. The study investigated the 1) safety of the vector and delivery technique, 2) vector distribution throughout the putamina, 3) tolerability, and 4) disease course measured by UPDRS, [^{18}F]FDOPA PET, and L-DOPA equivalent dose.

Methods

Study Design

This was a Phase 1 single-center, open-label, dose escalation, safety and tolerability study of AAV2-GDNF infused via CED into the bilateral putamina of adult patients with PD. Gadoteridol (ProHance), a gadolinium contrast agent, was co-infused with AAV2-GDNF. 25 patients were enrolled (Supplementary Figure S1), with 13 patients receiving AAV2-GDNF (Supplementary Table S1), 8 failing screening, and 4 withdrawing prior to treatment. Three escalating dose levels were evaluated: 1) 9×10^{10}vg (n=6); 2) 3×10^{11}vg (n=6); 3) 9×10^{11}vg (n=1). This study was approved by the institutional review board and registered at clinicaltrials.gov (NCT01621581). All participants gave informed consent.

Outcome Measures

Primary outcome measures were the safety and tolerability of different AAV2-GDNF infusion dose levels in patients with advanced PD. Secondary outcome measures included changes in pre-synaptic dopamine activity by [^{18}F]FDOPA PET scanning, clinical rating scores (UPDRS), and total levodopa equivalent doses (TLED).

Statistical Analysis

For each outcome measure, a repeated-measures analysis of variance (RM-ANOVA) examined the effect of time on [^{18}F]FDOPA Ki values, UPDRS score, and TLED with compound symmetry as covariance structure. The Dunnett-Hsu method was used for post-hoc analysis with baseline as control.

Results

Adverse Events

AAV2-GDNF infusion was well-tolerated by all subjects. Six serious adverse events (SAEs) occurred but were not attributable to study drug and resolved (Supplementary Table S2). The 423 non-serious adverse events included minimal elevations of CSF IgG, glucose and protein without clinical sequelae. No study drug or infusion-related brain injuries occurred.

AAV2-GDNF MRI Distribution

Gadoteridol distribution on T1-weighted intraoperative MR-imaging is shown in Figure 1A. The volume of distribution was $2.63\text{cm}^3 \pm 1.09\text{cm}^3$ (mean±SD; range: 0.82–4.36cm^3). The volume of distribution to infusion ratio (Vd:Vi) was 2.93±1.21. The putaminal coverage of infused fluid (AAV2-GDNF) was $995\text{mm}^3 \pm 376\text{mm}^3$ (mean±SD; range: 315–1881mm^3), approximately 26% of the putaminal volume.

PET Scanning

[^{18}F]FDOPA Ki values increased from baseline in bilateral putaminal injection sites in 10/13 patients at the 6-month timepoint (percent increased Ki range: 5–274%, median: 36%) (Figure 1B–C). In the remaining three patients, 2 had slight increases in [^{18}F]FDOPA Ki values on one side and slight decreases on the other while the final patient had unchanged

[^{18}F]FDOPA Ki values in the right putamen and slightly decreased Ki values (-13%) in the left.

At the 18-month postoperative PET scan timepoint, 12/13 patients showed increased [^{18}F]FDOPA Ki values bilaterally compared to baseline (increase range: 8–130%, median: 54%). In the other patient, [^{18}F]FDOPA Ki values increased 29% in the right putamen, but decreased 16% contralaterally. The two different AAV2-GDNF dose cohorts were not significantly different in their [^{18}F]FDOPA putaminal Ki percentage change from baseline at the 18-month timepoint (right putamen: $P = 0.69$; left putamen: $P = 0.58$) (Table 1).

Ki values differed significantly between baseline and the 6- and 18-month follow-up scans bilaterally (RM-one-way ANOVA, $P = 0.0001$ (right); $P = 0.0002$ (left)). Post hoc analysis showed significant increases between baseline and 6-months bilaterally ($P = 0.006$ (right); and $P = 0.016$ (left)), and between baseline and 18-months bilaterally ($P = 0.0002$ (right); $P = 0.0003$ (left)) (Figure 1D–E).

Lumbar Puncture: CSF and Serum Samples

Clinical laboratory analysis of CSF and serum samples revealed no clinically significant abnormalities. 3/13 (#6, 13, 21) and 2/13 (#6, 13) patients had increased serum anti-AAV2 antibody titers at 6- and 18-months post-infusion, respectively. 1/13 patients (#6) had an increased CSF anti-AAV2 antibody titer at each of the 6- and 18-months post-infusion timepoints (same patient). Increased serum anti-GDNF antibody titers were seen in 3 patients (#12, 13, 16) 6-months, and 3 (#10, 12, 15) 18-months post-infusion. Increased CSF anti-GDNF antibody titers were seen in 3 patients (#1, 10, 15) 6-months, and 4 (#6, 10, 15, 16) 18-months post-infusion. Serum and CSF anti-AAV2 and-GDNF antibody titer increases were clinically silent and unrelated to [^{18}F]FDOPA Ki values.

UPDRS Assessments

UPDRS assessment scores varied between visits but generally remained stable over the study. Specifically, there were no statistically significant differences between dose cohorts in UPDRS Part 1, 3 “On” or “Off”, or 4 scores across any timepoints (Table 1). UPDRS Part 2 “On” and “Off” scores also remained stable throughout the study for all dose cohorts, except for significant difference in Part 2 “Off” scores between baseline and 1 month post-infusion ($P = 0.0252$).

Total Levodopa Equivalent Dose

Differences in TLED change between AAV2-GDNF dose cohorts were not statistically significant from baseline 18-months post-infusion ($P = 0.99$) (Table 1). However, there was a statistically significant increase in TLED between the first and second dose levels from baseline to 48-months post-infusion ($P = 0.0433$).

Discussion

This Phase 1 clinical trial included 13 adult patients with advanced PD who received bilateral AAV2-GDNF CED to their putamina. AAV2-GDNF delivery to the human brain using CED was safe and well-tolerated, with no SAEs attributable to AAV2-GDNF infusion.

GDNF was the first identified neurotrophic factor related to basic fibroblast growth factor. Neurturin, persephin and artemin were subsequently identified.[3] GDNF isolated from the B49 cell line promoted survival of embryonic DA neurons *in vitro*.[21, 22] GDNF protein delivery methods had tolerability and safety problems in preliminary GDNF clinical trials, prompting interest in viral vectors delivering GDNF for PD treatment.[17–19, 23] Our study used an AAV2 vector encoding GDNF. Whone et al. recently reported a blinded clinical study of CED delivering intraputaminal GDNF protein versus placebo in PD patients.[24, 25] GDNF infusion was safe and well-tolerated. Furthermore, the group receiving GDNF had increased putaminal [^{18}F]FDOPA uptake on PET, as in our study, suggesting neurotrophic effect on putaminal DA neurons. However, clinical benefit was not different between GDNF and placebo treated groups. CED into the putamen in PD patients was safe in both studies. Future trials with increased infusion volumes and doses of AAV2-GDNF or GDNF may demonstrate clinical benefit.

Our study evaluated escalating AAV2-GDNF dose levels, starting at an anticipated minimally effective dose of 9×10^{10}vg, that was expected to produce somewhat less than 1ng of GDNF/mg of putaminal protein. Slow enrollment and interim analysis of limited putaminal infusion coverage prompted premature enrollment closure prior to completing the proposed 3rd or 4th dose cohorts. Clinical evaluation showed safety at the dose levels studied.

In this study, co-infused gadoteridol allowed tracking of the AAV2-GDNF infusion within the putamina during T1-weighted MR-imaging. The Vd/Vi ratio of gadoteridol was consistent with previous related studies.[26] The volumetric distribution of infusate covered about 26% of the putaminal volume and did not significantly differ between dose cohorts. Limited coverage was due, in part, to the infused fluid distributing around the cannula, whose trajectories were perpendicular to, rather than aligned with the long axis of each putamen. A follow-up clinical trial is planned using larger infusion volumes and a posterior surgical approach along the putamen's long axis to increase coverage sffuciently to affect the relevant motor circuitry of the post-commissural putamen.[11]

Evidence for GDNF expression within putaminal infusion sites was provided by the enhanced [^{18}F]FDOPA PET uptake. [^{18}F]FDOPA Ki values were significantly increased above baseline values at the 6- and 18-month timepoints. Increases in [^{18}F]FDOPA uptake have been associated with upregulated pre-synaptic dopamine activity, potentially due to restoration or sprouting of nigrostriatal dopaminergic terminal fibers in nonclinical studies.[15] In certain patients, Ki values at the 6- and 18-month timepoints reached putaminal values reported in control patients of earlier trials.[27] The wide range of Ki percentage increase at the 18-month timepoint corresponded to the wide range of patient baseline Ki values. Also,

the large Ki increase variability in our study may have arisen from incomplete and variable coverage of the putaminal target and variable extra-putaminal leakage of infusate.

No significant PD medication changes or LED were made during the study. Two patients, however, did reduce their daily LED, while most (8 patients) had increased daily LEDs, as expected with normal PD progression. UPDRS scores remained stable throughout the study. No clinical or statistically significant changes in UPDRS scores were observed between dose cohorts. The AAV2-GDNF, a placebo effect, and/or close medical monitoring could have resulted in the medication changes or clinical improvements noted in specific participants.

Higher doses of AAV2-GDNF in the originally proposed 3rd and 4th cohorts and greater (>50%) putaminal coverage would be expected to provide higher putaminal levels of GDNF. The proposed higher doses of AAV2-GDNF were expected to approach GDNF levels produced in nonclinical studies,[14,15] which demonstrated significant restoration of dopamine activity and motor function in parkinsonian animals.

The safety and tolerability of AAV2-GDNF administered via CED into the human brain in our study supports additional clinical investigations providing improved putaminal coverage and use of higher AAV2-GDNF doses.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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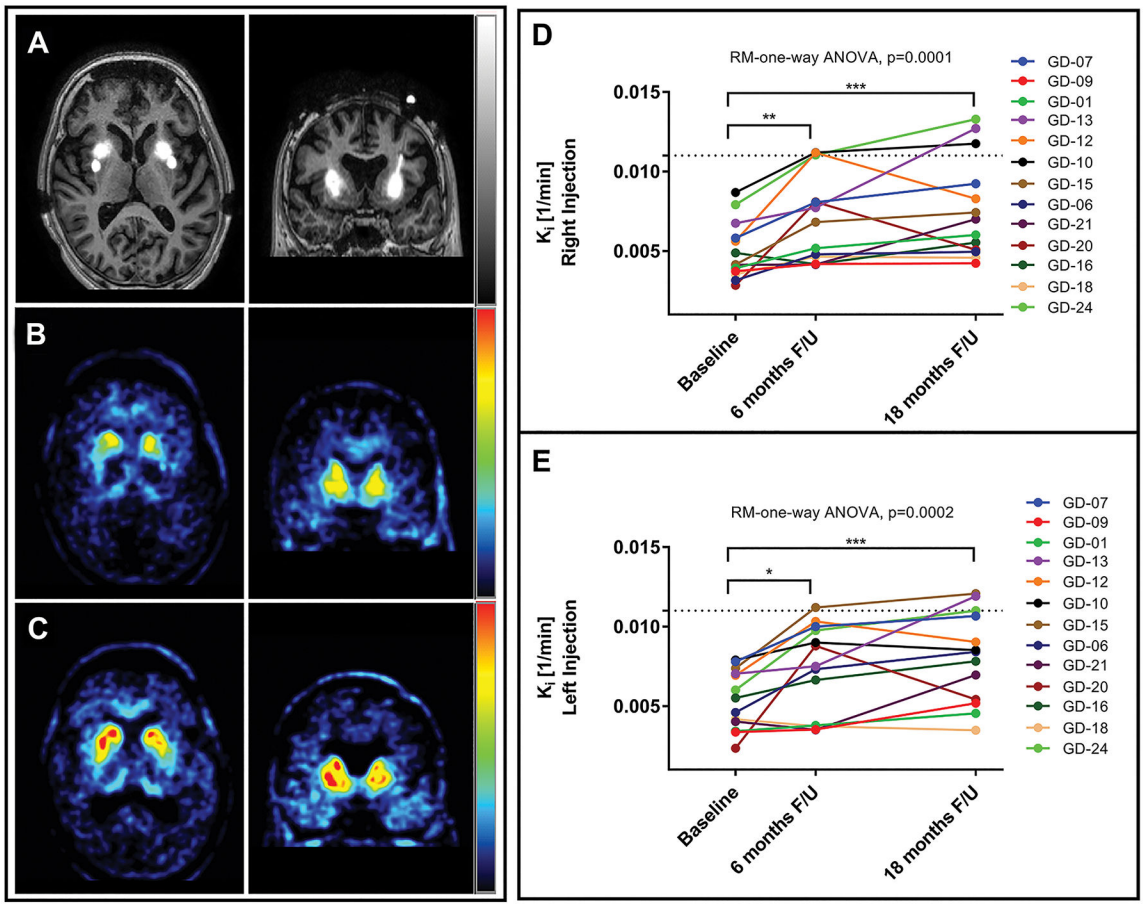

Figure 1. Gadoteridol Distribution, Parametric Ki Maps, and Longitudinal Ki Changes.

T1-weighted post-contrast MR-images show gadoteridol distribution in the axial and coronal planes following infusion into the anterior (pre-commissural) and posterior (post-commissural) putamina bilaterally (A). [^{18}F-FDOPA] Ki parametric maps in axial and coronal planes from one patient at baseline (B) and 18 months after surgery (C) showing increased Ki at follow-up. Graphical changes of Ki values corresponding to the right (D) and left (E) injection distributions for all subjects. Dashed lines reflect reported putaminal Ki values for healthy controls.[27]

TABLE 1.

Change from Baseline in Secondary Outcome Measures 18 Months after Treatment: [^{18}F]FDOPA Uptake, UPDRS Scores, & Total Levodopa Equivalent Doses.

Endpoint	Dose 1 (n=6)	Dose 2 (n=6)	Dose 3 (n=1)	*P*
[^{18}F]FDOPA Uptake[a]				
Right Putamen	0.5 (0.13 to 0.88)	0.63 (0.16 to 0.79)	N/A	0.696
Left Putamen	0.35 (0.08 to 0.69)	0.56 (−0.16 to 1.30)	N/A	0.586
UPDRS Part III (Off)	2.60 (−37.5 to 50)	−7.10 (−44.7 to 50)	N/A	0.754
UPDRS Part III (On)	−9.55 (−45.7 to 36.8)	7.5 (−61.4 to 42.9)	N/A	0.697
UPDRS Part I	−22.5 (−50 to 0)	−16.7 (−100 to 100)	N/A	0.936
UPDRS Part II (Off)	2.26 (−45.5 to 28.6)	−10.7 (−33.3 to 26.7)	N/A	0.586
UPDRS Part II (On)	50 (−30 to 85.7)	−5.45 (−50 to 62.5)	N/A	0.298
UPDRS Part IV	0 (−66.7 to 44.4)	−16.7 (−42.9 to 28.6)	N/A	0.423
TLED	100 (−101.3 to 273)	−119.5 (−400 to 667.5)	N/A	0.999

Data are median (range) and the *P*-value comparing dose-related effects was calculated using a Wilcoxon test.

[*] Dose cohort 3 was excluded from this analysis because the cohort included only 1 patient.

[a] percentage change