P34. Age affects clinical outcome in Alzheimer's disease trials

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Abstract

Background/Objectives

The effect of age as a moderator of treatment outcome was examined in an exploratory study of deep brain stimulation targeting the fornix (DBS-f) region in participants with mild probable Alzheimer's disease (AD).

Methods

Forty-two participants were implanted with DBS electrodes and randomized to double-blind DBS-f stimulation ("on") or sham DBS-f ("off") for 12 months.

Results

The intervention was safe and well tolerated. However, the selected clinical measures did not differentiate between the "on" and "off" groups in the intent to treat (ITT) population. There was a significant age by time interaction with the Alzheimer's Disease Assessment Scale; ADAS-cog-13 (p= 0.028). Six of the 12 enrolled participants <65 years old (50%) markedly declined on the ADAS-cog-13 versus only 6.7% of the 30 participants ≥ 65 years old regardless of treatment assignment (p = 0.005).
While not significant, post-hoc analyses favored DBS-f "off" versus "on" over 12 months in the <65 age group but favored DBS-f "on" versus "off" in the ≥65 age group on all clinical metrics. On the integrated Alzheimer's Disease rating scale (iADRS), the effect size contrasting DBS-f "on" versus "off" changed from +0.2 (favoring "off") in the <65 group to -0.52 (favoring "on") in the ≥65 age group.

Conclusion

The findings highlight issues with subject selection in clinical trials for AD. Faster disease progression in the younger AD participants related to different AD sub-types may have influenced the results. Biomarker confirmation of AD diagnoses and genotyping to differentiate AD subtypes is important for future clinical trials.

Introduction

- Age of onset can be a confounding factor in clinical trials of probable Alzheimer's disease (AD): younger, early onset AD participants have a more rapid cognitive decline than later onset participants.
- In a recent study, we found that age affected clinical outcome in study participants with probable mild AD treated using deep brain stimulation targeting the fornix (DBS-f) as the experimental condition [1].
- In this post-hoc analysis, we report results from two secondary outcome measures, the ADCS-Activities of Daily Living scale (ADCS-ADL-23) and the integrated Alzheimer's Disease Rating Scale (iADRS). The iADRS is a composite of the ADAS-cog-13 and instrumental items of the ADCS-ADL (iADL) scores.

Methods

- Data comes from the phase II *ADvance study: A Twelve Month Double-blind Randomized Controlled Feasibility Study to Evaluate the Safety, Efficacy and Tolerability of Deep Brain Stimulation of the Fornix (DBS-f) in Participants with Mild Probable AD* sponsored by Functional Neuromodulation, Ltd.
- All eligible participants provided informed consent and signed an IRB approved consent form. Eligible participants were men or women living at home, ages 45 to 80 years (inclusive) with a CDR global rating of 0.5 or 1.0, and an ADAS-cog-11 score of 12-24 (inclusive) with a score ≥ 4 on ADAS-cog item 1 (immediate recall) at the screening and baseline visits.
- The protocol did not require ApoE or CSF biomarkers.
- The study was designed as a 12-month assessment period with a double-blind 1:1 randomization to DBS-f "on" (stimulation) or "off" (sham treatment) that followed implantation [1].

Results

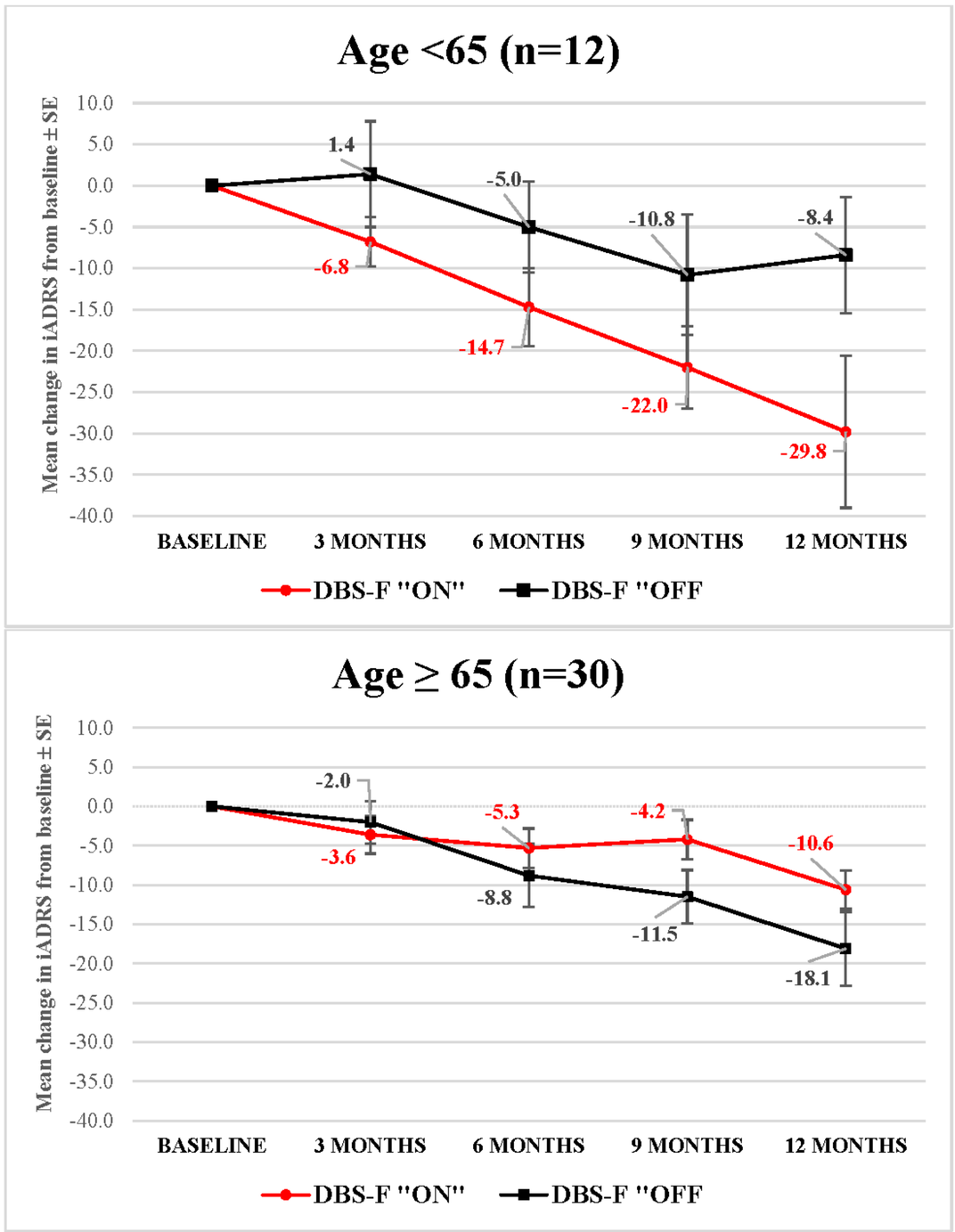
- In this study, 12 participants were <65 years of age (28.6% of the study population).
- The exploratory clinical outcomes (ADAS-cog-13 and CDR-SB) did not differentiate between the DBS-f "on" and "off" groups after 12 months of double-blind treatment.
- A post-hoc multivariate regression analysis of the ITT population revealed a significant time by age interaction with ADAS-cog-13 outcomes (beta= -0.41; SE 0.18; p= 0.028):
  - The 12 participants < 65 years old had greater cognitive decline and decreased glucose metabolism over 12 months regardless of treatment assignment than the 30 older participants.
- As shown in Table 1, the DBS-f "on" group did substantially better than the DBS-f "off" group in the ≥65 age cohort over 12 months.
- The mean iADRS change score difference between the DBS-f "on" and "off" groups increased from 0.4 in the ITT population to 21.4 points favoring DBS-f "off" group in the <65 age cohort (ES= 1.41).
- However, the mean iADRS change score increased to a 9.3-point difference favoring the DBS-f "on" group versus the DBS-f "off" group in the ≥65 age cohort.
  - The effect size (ES) for the iADRS improved from +0.02 in the ITT population to -0.52 favoring DBS-f "on" in the ≥65 age cohort.
- Figure 1 compares the trajectories of the mean iADRS scores in the two age cohorts.
- As shown in Table 2, 4 of the 6 younger participants who had ≥20-point score change (worsening) on the ADAS-cog-13 were randomly assigned to the DBS-f "on" group and 2 were assigned to the "off" group.

Reference

1. Lozano et al.. 2016. A Phase II Study of Fornix Deep Brain Stimulation in Mild Alzheimer's Disease. J Alzheimers Dis 54: 777-787.

Figure 1

Change in iADRS from baseline to month 12 in ADvance 1 study



NOTE: iADRS is the integrated Alzheimer's disease rating scale; negative mean change scores indicate worsening from baseline.

Table 1

Outcome score changes from baseline to 12 months stratified by age cohorts

	ITT population		Participants ≥ 65 years old		Participants < 65 years old	
	DBS-f "off"	DBS-f "on"	DBS-f "off"	DBS-f "on"	DBS-f "off"	DBS-f "on"
Enrolled (n)	21	21	15	15	6	6
ADAS-cog-13						
Mean change ± SD	8.0 ± 1.9	8.0 ± 2.2	7.8 ± 2.1	3.7 ± 1.5	8.3 ± 4.5	18.7 ± 4.1
Difference ± SD		0.0 ± 2.9		4.1 ± 2.6		-10.3 ± 6.1
p		ns		0.12		0.12
Cohen's d (ES)		**0.00**		**0.58**		**-0.97**
CDR-SB						
Mean change ± SD	2.4 ± 0.4	2.7 ± 0.7	3.5 ± 0.9	2.1 ± 0.5	0.5 ± 0.3	3.4 ± 0.8
Difference ± SD		-0.3 ± 0.8		1.4 ± 1.0		-2.9 ± 0.8
p		ns		0.17		0.006
Cohen's d (ES)		**0.09**		**0.52**		**-2.16**
CDR-Global						
Mean change ± SD	0.4 ± 0.1	0.4 ± 0.1	0.5 ± 0.1	0.4 ± 0.1	0.1 ± 0.1	0.6 ± 0.2
Difference ± SD		0.0 ± 0.1		0.1 ± 0.2		-0.5 ± 0.2
p		ns		0.38		0.02
Cohen's d (ES)		**-0.11**		**0.32**		**-1.63**
ADCS-ADL-23						
Mean change ± SD	-9.8 ± 2.9	-9.5 ± 1.5	-12.0 ± 3.6	- 7.9 ± 1.8	-3.2 ± 3.1	-13.3 ± 2.3
Difference ± SD		0.3 ± 3.2		4.1 ± 4.0		10.1 ± 3.8
p		ns		0.32		0.02
Cohen's d (ES)		**-0.03**		**-0.37**		**1.63**
iADRS						
Mean change ± SD	-15.7 ± 4.0	- 16.1 ± 3.0	-17.3 ± 5.9	- 8.0 ± 2.4	-8.4 ± 7.0	-29.8 ± 6.0
Difference ± SD		0.4 ± 5.0		9.3 ± 6.4		-21.4 ± 9.2
p		ns		0.16		0.04
Cohen's d (ES)		**0.02**		**-0.52**		**1.41**

NOTE: Positive mean change scores indicate worsening for the ADAS-cog-13, CDR-SB, and CDR-Global scores, whereas negative mean change scores indicate worsening for the ADCS-ADL-23 and the iADRS.
A positive mean difference between the assigned treatment groups indicates that the DBS-f "on" group had less decline than the "off" group over 12 months on that metric, whereas a negative mean difference between the groups indicates that the DBS "on" group has had more decline than the "off" group.
Students' t tests were used to calculate the p value.
Positive Cohen's d (effect size) favors DBS-f "on" group for ADAS-cog-13, CDR-SB, and CDR-Global; negative effect size favors DBS-f "on" group for ADCS-ADL-23 and iADRS.

Summary and Conclusions

- In the cohort ≥65 years old, all of the clinical metrics and glucose metabolism measures favored DBS-f "on" treatment over the DBS-f "off" sham treatment after 12 months
- The ES favored DBS-f "on" versus "off" in the age cohort ≥65 years old and improved on all clinical metrics relative to the ITT population (Table 1).
- Conversely, the younger participants <65 years old in the DBS-f "on" group did significantly worse than the "off" group on the CDR measures, ADCS-ADL-23 and iADRS.
- The findings reinforce the importance of heterogeneity within AD and suggest that more restricted age limits, genotyping, and CSF biomarkers need to be part of the eligibility criteria for future AD trials.

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Table 2

Trajectory of ADAS-cog-13 and CDR-SB scores in AD participants <65 years old

Patient	1 on	2 on	3 on	4 on	5 on	6 on	7 off	8 off	9 off	10 off	11 off	12 off
age	51	57	58	59	61	64	48	52	57	58	59	62
sex	m	f	f	f	m	f	m	f	f	f	m	m
ADAS-cog-13 scores												
Baseline	24	34	27	28	25	30	29	27	30	20	20	30
1 month	44	38	32	28	26	35	15	35	29	22	18	38
3 months	35	44	30	29	25	39	14	41	27	12	15	37
6 months	43	54	37	27	28	42	26	44	36	21	15	35
9 months	49	49	43	27	26	52	32	47	42	26	16	39
12 months	55	54	51	36	30	54	25	47	50	27	15	42
△ baseline-12 months	**31**	**20**	**24**	**8**	**5**	**24**	**-4**	**20**	**20**	**7**	**-5**	**12**
CDR-SB scores												
Baseline	3.5	6.5	5	3	5	7	4.5	4.5	4.5	1.5	3	4
3 months	5	4.5	5	4	4.5	9	4	4.5	8	1	2.5	4
6 months	5.5	6.5	5	5	5.5	11	4.5	6	4	0.5	1	4.5
9 months	8	9	5	5	5.5	10	4.5	7	6	2	2.5	5
12 months	9	9		6	5.5	12	5	6	4.5	2	2.5	5
△ baseline-12 months	**5.5**	**2.5**	**0.0 ***	**3.0**	**0.5**	**5.0**	**0.5**	**1.5**	**0.0**	**0.5**	**-0.5**	**1.0**

NOTE: The designation of "on" indicates that the patient was assigned to DBS-f stimulation treatment whereas "off" indicates that the patient was assigned to sham treatment after the surgical implant
△ baseline-12 months reflects score change from baseline to 12 months where positive scores reflect cognitive and/or functional worsening
*Last observation carried forward from CDR-SB assessment at 9 months

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