Ultra-Sound Directed Blood-Brain Barrier Opening: Proof of Concept and Evidence Against Amyloid-Beta Causation of Alzheimer's Disease

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Abstract

In a recent report in the New England Journal of Medicine, each of three patients with Alzheimer's disease had a reduction in amyloid-beta deposits in regions of brain treated with ultrasound blood-brain barrier opening after intravenous aducanumab administration. The report was a proof of concept of effectiveness of ultrasound-guided blood-brain barrier opening. However, as analyzed in this evaluation of the reported data, the patients' neuropsychiatric events during therapy and cognitive and behavioral functions afterwards were inversely proportional to their degree of amyloid-beta deposit reduction. This inverse correlation is consistent with the premise that the amyloid-beta deposits are not a primary cause of Alzheimer's disease.

Authors' Disclosure

Neither author has any known relevant financial relationship or related conflict of interest with the enterprises engaged in, reported, or analyzed with methods and data. On the contrary, both are committed to understand their spouse's dementia, one of whom died of Alzheimer's disease.

Introduction

In the first issue of the New England Journal of Medicine in 2024, a report that received world-wide attention showed the feasibility and effectiveness of ultrasound blood-brain barrier (BBB) opening in enabling intravenously-injected aducanumab to reduce amyloid-beta (Aβ) deposits in regions of brain subsequently exposed to ultrasound designed to open the BBB.[1] The participants were treated with the aducanumab-BBB method six times at monthly intervals Each was reported to have neuropsychological and behavioral benefits that were still present months up to 6 months after the treatment interval.

It was also in the first issue of the *Journal* of the year, after the *Journal* published ten articles on amyloid deposits the previous year. The report was accompanied with an editorial about its "proof of concept" and the potential of ultra-sound BBB opening in preventing and treating Alzheimer's disease when more of the brain can be exposed to the technique than was feasible in the reported patients.[2] Only three patients were reported however and, from our perspective, the clinical results were inconsistent with the amount of amyloid beta (Aβ) deposits eliminated by the procedure.

Methods

Data in the original report narrative, figures and supplemental appendix were analyzed patient by patient. As described in the report, quantification of the standardized uptake value ratio was determined with the use of cerebellar gray matter as a reference and converted to centiloids for standardized quantification of Aβ load. In each participant and at each prespecified time after baseline, the centiloid value for the entire focused ultrasound–targeted region was compared with the centiloid value of the contralateral homologous brain region that did not undergo exposure to focused ultrasound.

Neuropsychiatric, cognitive and behavioral functions during and after therapy (Supplemental Fig. S1) were derived from the supplemental appendix in the original report. As described in the original report, each participant completed the National Institutes of Health Stroke Scale daily during the first week after each combination treatment of aducanumab-BBB treatment and then weekly until the next combination treatment. A comprehensive neurologic examination was conducted by a board-certified neurologist at baseline, immediately before and immediately after each of the six monthly combination treatments, and 24 hours after each combination treatment. During the follow-up phase, neurologic examinations were conducted on days 30, 90, and 180, as well as at 12 and 18 months.

Cognitive and behavioral assessments were conducted at baseline with the Alzheimer's Disease Assessment Scale Cognitive Subscale (ADAS-Cog 11), RBANS, Mini Mental State Examination (MMSE), Geriatric Depression Scale (GDS), Neuropsychiatric Inventory (NPI) questionnaire, Alzheimer's Disease Cooperative Study–Activity of Daily Living Inventory (ADCS–ADLI), and the Columbia Suicide Severity Rating Scale (CSSRS). In the intervention phase, the ADAS-Cog 11 assessment (and RBANS, if necessary) were conducted 7 days after each combination treatment and 1 day before the next combination treatment. During the follow-up phase, participants completed the RBANS at 30, 90, and 180 days, as well as the ADAS-Cog 11, MMSE, GDS, NPI, CSSRS, and ADCS–ADLI assessments at 12 and 18 months.

Results

Each of three patients with Alzheimer's disease had a reduction in Aβ deposits in regions of brain after the six aducanumab-BBB treatments. The adjusted mean reduction was 108, 15 and 158 centiloids for participants 1, 2 and 3, respectively (Fig.1 top panel green columns). However, their neuropsychiatric events during therapy and cognitive and behavioral functions afterwards were inversely proportional to their numerical degree of Aβ reduction (top panel). For neuropsychiatric events during the 6 months of therapy, participant 3 with the greatest two participants with the greatest Aβ reduction reported increased agitation, sleep disturbances and appetite fluctuations during the treatment interval whereas the other two participants with less Aβ reported no adverse effects (Fig.1 middle panel). During the follow-up at 1, 3 and 6 months after the treatment interval, participant 3 was also the only one to have worsening of behavioral symptoms, as judged by a care partner (NPI-Q Sx Total) and including suicidal ideation (CSSRS) (Fig.1 lower panel purple and blue columns). Cognitive function also worsened more in participant 3, especially overall neuropsychologic status (RBANS Total), activity of daily living (Alzheimer's Disease Cooperative Study – Actvitiy), and cognitive subscale (ADAS-Cog 11 assessment) (Fig.1 lower panel red, yellow and orange columns). Participant 2 had some worsening of cognitive function after the treatment interval, but at a fraction of the progression in participant 3 and participant 1 had, based on the average of the test results, no worsening (Fig.1 lower panel yellow, red orange and gray columns).

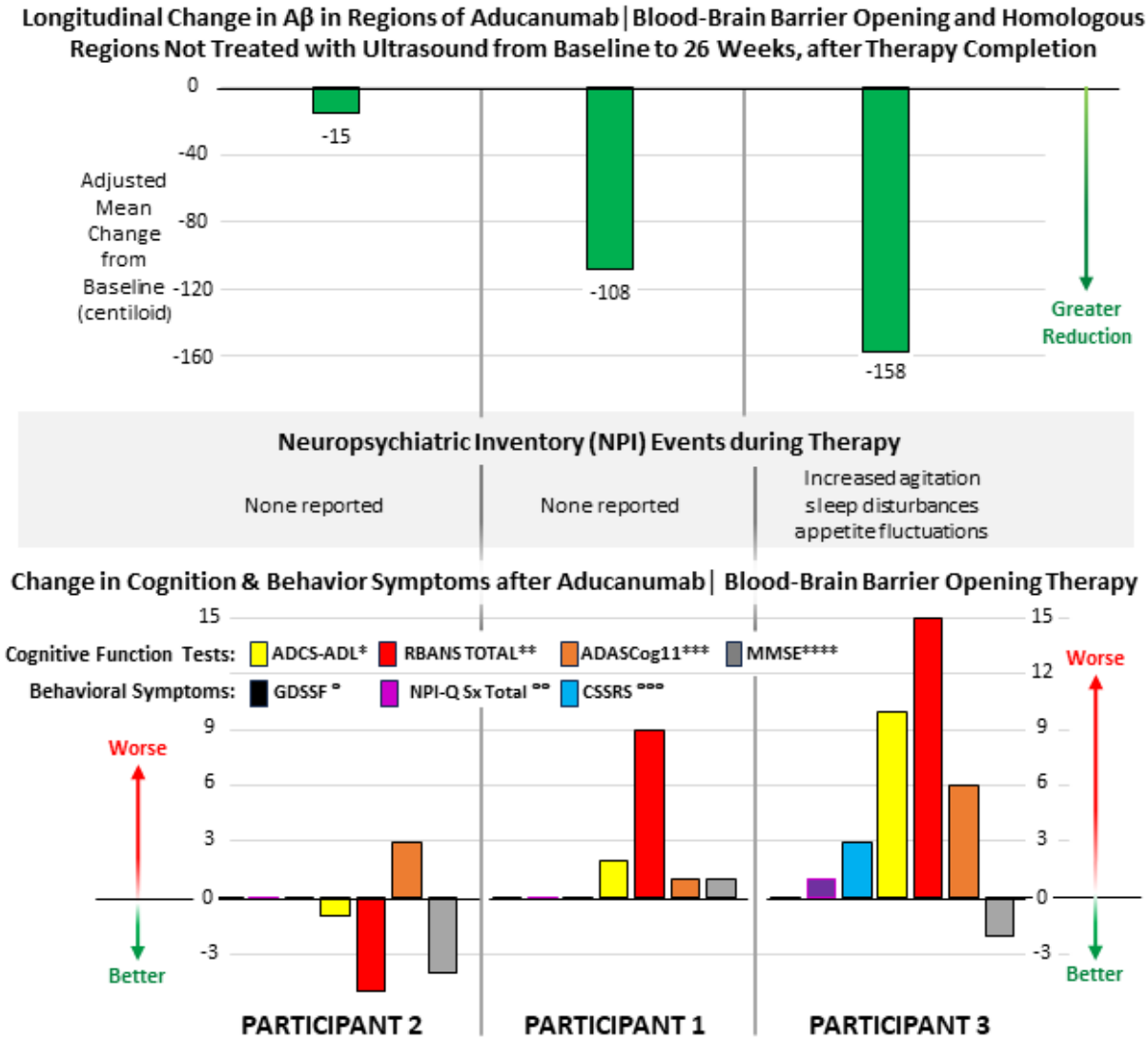

Figure 1. **Aβ Reduction after 6 Monthly Treatments with Aducanumab and Localized Ultrasound Mediated Blood-Brain Barrier Opening** (top panel) **and Change in Neuropsychiatric Events during Therapy** (middle, gray panel) **and Cognition and Behavior Symptoms 30 Days after Therapy** (bottom panel).

* ADCS–ADL: Alzheimer's Disease Cooperative Study–Activity of Daily Living Inventory

** RBANS: Repeatable Battery for the Assessment of Neuropsychological Status Line Orientation Test Overall Scales Score

*** ADAS-Cog 11: Alzheimer's Disease Assessment Scale Cognitive Subscale

**** MMSE: Mini Mental State Examination

° GDSSF: Geriatric Depression Scale – Short Form

°° NPI-Q Sx Total: Neuropsychiatric Inventory – Questionnaire (total number of symptoms, completed by care partner)

°°° CSSRS: Columbia Suicide Severity Rating Scale (CSSRS, assessing recent or current suicidal ideation or attempt) at both the initial and follow-up stages of the study

Data Source: Rezai AR, et al.[1]

Discussion

The inverse correlation of clinical changes during and after therapy with the numerical degree of Aβ reduction is consistent with the premise that the Aβ deposits are not a primary cause of Alzheimer's disease, as discussed by others.[3-10] The major limitation of this assessment is the very limited number of patients (three) upon which it is based. The original report and conclusions of effectiveness were based on the same patients, however. Another limitation is that only a portion of the brain underwent BBB opening. As mentioned in the accompanying editorial, ultrasound-opening of a larger volume of brain would, in a disease like Alzheimer's, expected to be more effective.[2]

As to the BBB technique itself, a concern is that the mircobubbles injected intravenously that are required to enable the ultrasound waves to open the BBB may have clinical toxicities that are yet to be fully recognized such as microhemorrhage, overt hemorrhage from vascular rupture, ischemia from vascular constriction, cerebral edema, inflammation from protein extravasation, and/or a potentially direct cellular injury from heat or mechanical forces.[11]

Nonetheless, focused-ultrasound BBB opening is a promising technique to deliver effective therapeutic moieties, as promoted in the editorial that accompanied the original report.[2] Which ones to deliver via it for the treatment of Alzheimer's disease, however, merit better understanding of the disease's etiology, pathogenesis, and pathophysiology.

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Supplemental Table S1

Analysis of Patient Data based on *Table S3a - Baseline and 30-day follow-up Cognitive Scores for Participants 1, 2, and 3*

Source: Rezai AR et al.[1]

	Score Range	Clinically Meaningful Change		Participant 2	1	3
Cognitive Scores						
ADCS-ADL*	0 - 78		Baseline	71	73	61
			Follow-Up Phase 30 days	70	75	71
			Change ˅	-1	2	10
RBANS TOTAL**	40 - 160	>11	Baseline	76	83	76
			Follow-Up Phase 30 days	81	74	61
			Change ^	-5	9	15
ADASCog11***	0 - 70	>4	Baseline	7	13	5
			Follow-Up Phase 30 days	10	14	11
			Change ˅	3	1	6
MMSE****	0 - 30	><4	Baseline	28	25	27
			Follow-Up Phase 30 days	24	26	25
			Change ˅	-4	1	-2
Behavioral Symptom Scores^						
GDSSF°	0-15		Baseline	1	1	4
			Follow-Up Phase 30 days	1	1	5
			Change ˅	-0.04	-0.04	1
NPI-Q Sx Total°°	0-12		Baseline	3	2	4
			Follow-Up Phase 30 days	3	2	7
			Change ˅	-0.04	-0.04	3
CSSRS°°°	0-24		Baseline	0	0	0
			Follow-Up Phase 30 days	-0.04	-0.04	-0.04
			Change ˅	-0.04	-0.04	-0.04

˅ Higher scores indicate more behavioral symptoms; the greater the change, the worse the behav

^ Higher scores indicate better cognition; the greater the change, the worse the cognition

* ADCS-ADL: Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale

** RBANS: Repeatable Battery for the Assessment of Neuropsychological Status Overall Scaled Sc

*** ADAS-Cog11: Alzheimer's Disease Assessment Scale Cognitive Subscale

**** MMSE: Mini-Me Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale

° GDSSF: Geriatric Depression Scale – Short Form

°° NPI-Q Sx Total: Neuropsychiatric Inventory – Questionnaire (total number of symptoms, completed by care partner)

°°° CSSRS: Columbia Suicide Severity Rating Scale (assessing recent or current suicidal ideation or attempt) at both the initial and follow-up stages of the study

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