Safety and Feasibility Trial of Dapagliflozin in Early Alzheimer's Disease

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Introduction

There is growing interest in targeting the metabolic manifestations of Alzheimer's Disease (AD) as a therapeutic strategy. Dapagliflozin, a sodium-glucose cotransporter 2 inhibitor (SGLT2i) used to treat type 2 diabetes mellitus (T2DM), has systemic metabolic effects (i.e., insulin sensitivity and weight loss) and metabolomic data suggest potential mitochondrial effects. Additionally, epidemiological studies suggest SGLT2i may reduce the long-term risk of dementia in T2DM patients.

Methods

We conducted a 12-week exploratory study investigating safety, tolerability, and metabolic effects of dapagliflozin on the brain and systemically in individuals with an AD clinical syndrome or MCI due to AD.

We randomized 48 participants to dapagliflozin (10 mg) vs. placebo (2:1 ratio) and performed brain magnetic resonance spectroscopy (MRS), oral glucose tolerance testing, brain fluorodeoxyglucose (FDG) PET, dual X-ray absorptiometry (body composition), and cognitive testing at baseline and 12 weeks.

Sample

Data are presented on n=46 participants with follow-up data. The participants had a mean age of 71.2 years (8.0SD), BMI 28.3 kg/m^2 (4.4SD), mean MMSE of 20.2 (5.5SD), were predominantly male (65%, n=30), and largely without T2DM (91.3%; n=42).

	Dapagliflozin n=30	Placebo n=16	P-value
Age (years) mean (sd)	71.9 (8.1)	69.5 (8.2)	0.34
Sex, female n (%)	12 (43%)	3 (20%)	0.13
Education (yrs) median (sd)	16.5 (14, 18)	14 (12, 17)	0.07
MMSE median (IQR)	20.5 (17.5, 24.5)	21.0 (11.0, 25.0)	0.49
APOE4 e4 carriers n (%)	19 (68%)	12 (80%)	0.49
Body Mass Index	27.0 (24.9, 30.6)	28.0 (24.8, 30.9)	0.83
Diabetes, n (%)	12 (43%)	4 (27%)	0.30

RESULTS

Safety and Tolerability

Dapagliflozin was safe and well-tolerated. Participants took 99% of their doses with no treatment-related withdrawals. The dapagliflozin group had more total adverse events (AEs; n=41) vs the placebo group (n=18) but only 4 AEs (2 in each group) were considered possibly or probably related to study drug (dysuria and frequency with dapagliflozin; dysuria and diarrhea with placebo) and these were mild and resolved.

NAA and Glutathione Measures

There was no change in the pre-specified primary outcome of MRS-determined N-acetylaspartate-to-creatine ratio (NAA/Cr; p=0.60), considered a proxy measure of mitochondrial mass. We observed a trend to increased NAA concentrations (p=0.06) that correlated with changes in urinary NAA (r=0.32, p=0.04). We also observed an increase in brain glutathione (GSH), a major brain antioxidant that represents cerebral antioxidant defences and is lower in AD (p<0.05).

	Timepoint	Dapagliflozin N=30	Placebo N=16	P-value
NAA/Cr	Baseline	1.5 (0.1)	1.4 (0.1)	0.60
	Week 12	1.5 (0.1)	1.4 (0.1)	
Total NAA	Baseline	361.5 (29.7)	355.9 (40.1)	0.06
	Week 12	365.2 (27.9)	347.6 (26.7)	
Urinary NAA	Baseline	5996 (5272)	5941 (4748)	0.22
	Week 12	7326 (3648)	6138 (3987)	
Plasma NAA	Baseline	53.3 (24.9)	53.3 (17.4)	0.90
	Week 12	61 (17.1)	59.9 (33.5)	
GSH 6x6	Baseline	1.14 (0.11)	1.06 (0.10)	0.047
	Week 12	1.20 (0.10)	1.10 (0.09)	

FDG-PET

There were no differences across treatment and placebo groups in FDG PET globally and regionally (hippocampal, anterior cingulate, precuneus, and posterior cingulate regions).

Systemic Metabolic Measures

We observed treatment-related reductions in hemoglobin A1c (adjusted mean difference -0.18, p=0.02), 2-hr Glucose Area Under the Curve (-2109.0 mg min/dL, p=0.03), and body composition (total mass –1.73kg, p=0.012; fat mass -0.95kg, p=0.05; and lean mass -0.85kg, p=0.01). There were no treatment-related effects on fasting levels of beta-hydroxybutyrate, glucose, insulin, and cholesterol (total, LDL, and HDL).

Cognition

The treatment group improved in executive function (Stroop Interference) compared to the placebo group (mean difference +4.1 points, p=0.03) with no change in ADAS-Cog, Trailmaking A, Trailmaking B, delayed Logical Memory, and MMSE.

	Timepoint	Dapagliflozin	Placebo	P-value
ADAS-Cog Total	Baseline	32.1 (9.6)	30.5 (14.5)	0.85
	Week 12	33.0 (11.8)	29.5 (14.5)	
MMSE	Baseline	20.9 (4.2)	18.9 (7.3)	0.06
	Week 12	19.3 (5.2)	19.3 (8.1)	
Stroop Interference	Baseline	15.8 (9.9)	20.1 (10.9)	0.03
	Week 12	17.8 (11.9)	17.4 (10.5)	
Trailmaking A	Baseline	67.5 (44.4)	46.2 (34.0)	0.55
	Week 12	71.4 (41.3)	55.5 (44.3)	
Trailmaking B	Baseline	220.4 (99.6)	169.6 (91.8)	0.75
	Week 12	258.7 (199.9)	190.1 (96.3)	
Immediate Logical Memory	Baseline	2.3 (2.7)	3.9 (3.5)	0.79
	Week 12	2.7 (3.8)	4.4 (3.9)	
Delayed Logical Memory	Baseline	1.0 (1.8)	2.6 (3.8)	0.42
	Week 12	1.1 (2.5)	3.3 (4.6)	

Conclusions

These exploratory findings suggest dapagliflozin may influence cognition and cerebral metabolism, as suggested by epidemiological studies.

- Dapagliflozin was safe and well-tolerated in a largely non-diabetic population with early AD and MCI
- Dapagliflozin did not increase brain NAA/Cr, the pilot study's pre-specified primary outcome.
- Dapagliflozin therapy was associated with
  - Systemic metabolic effects (glucose disposal, body weight)
  - Improvement in executive function
  - Increases in MRS measures of brain GSH and NAA concentrations.

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