Autopsy Findings in an Individual with Alzheimer's Disease who Received Long-Term Treatment with Lecanemab (BAN2401)

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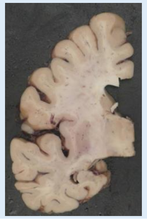
INTRODUCTION

- One strategy being explored to slow progression of Alzheimer's disease (AD) is systemic administration of monoclonal antibodies directed against Aβ species.
- PET scan using amyloid-specific ligands can be used to assess amyloid burden.
- While some amyloid-specific antibodies have not resulted in clearance of beta-amyloid by PET scan, others, such as lecanemab (BAN2401), have been shown to prominently reduce brain amyloid observed radiologically through use of PET amyloid ligands, with a phase 2 study showing correlated slower clinical decline.
- In assessing the influence of these antibodies on the progression of Alzheimer's pathophysiological changes, it would be useful to have neuropathological studies. Such data has been sparse to date.
- Autopsies of persons treated with active immunization (AN1792) have shown low levels of cortical amyloid, but the interpretation of these patients is complicated by the substantial immune reactions that occurred.
- A recent publication has shown the neuropathological findings of a patient treated with aducanumab, a different monoclonal antibody directed against fibrillar beta-amyloid.
- Here we present the first, to our knowledge, autopsy findings on an individual treated in a phase 2 trial with lecanemab.
  - Lecanemab, a humanized IgG1 monoclonal antibody, preferentially targets soluble aggregated Aβ species (protofibrils) with activity at insoluble fibrils.[1-5]
  - Treatment with 10 mg/kg IV biweekly lecanemab reduced amyloid positron emission tomography (PET) standard uptake value ratio (SUVr) and slowed clinical AD decline in an 18-month, phase 2 proof-of-concept study (Study 201 Core) in early AD with an open-label extension (OLE).[6-7]
  - Lecanemab is currently studied in phase 3 trials in early AD (CLARITY-AD) and preclinical AD (AHEAD3-45).

METHODS

- Autopsy was performed on an ~85-year old who had received lecanemab in the BAN2401 phase 2 study (NCT01767311)[6] over a (interrupted) 6-year period.
- He was enrolled in the Core study, with diagnosis of MCI after 3 years of mild memory problems, was on active treatment at 10 mg/kg q 4 weeks for 79 wk, then had 98 wk without treatment, followed by OLE study with 10 mg/kg q2 weeks for 94 wk.
- He developed behavioral symptoms, stopped treatment, and died 12 weeks later, 9 years after first symptoms.
- Family consented to brain autopsy examination.

FIGURE 1. BRAIN AUTOPSY GROSS SECTION



- Brain showed moderate atrophy (brain weight 1052 gm). No infarcts or bleeds were present.
- Tissue was sampled from multiple regions (frontal, parietal, occipital, hippocampus, brainstem), and full neuropathological evaluation was performed with histological (LH&E, Bielschowsky, thioflavine) and immunohistochemical stains for pathological proteins (tau [AT8], beta-amyloid [6E10], α-synuclein, TDP43) and astroglial and microglial responses (GFAP, CD68).

FIGURE 2. REPRESENTATIVE AXIAL AND CORONAL FLORBETAPIR PET SUVR IMAGES SHOWING PROGRESSIVE CLEARANCE OF AMYLOID OVER TIME

SUVR: Standardized uptake value ratio; CL: Centiloid unit; OLE: Open label extension; Top row: Baseline MRI; Rows 2-5: Florbetapir PET SUVR images at Baseline, weeks 55, 79 and 171 (OLE Baseline), respectively.

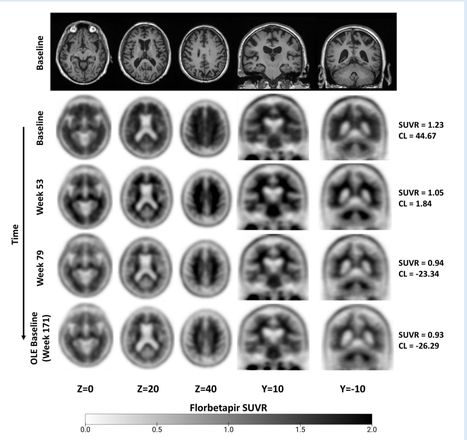


FIGURE 3. CLINICAL, BIOMARKER, AND IMAGING DATA

Line plots of clinical scales (A) and biomarkers (B) during the course of the core phase, during which the patient received lecanemab 10 mg/kg IV biweekly for 79 weeks, separated by a gap period of 92 weeks without lecanemab treatment. The clinical scales assessed included MMSE, CDR-SB, ADAS-cog and ADCOMS. Biomarkers assessed included amyloid PET, plasma Aβ42/40 ratio (C2N assay), plasma p-tau181, and volumetric MRI.

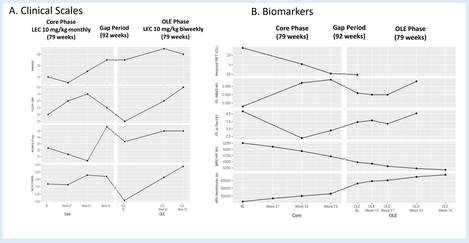


TABLE 1. NEUROPATHOLOGICAL FINDINGS

- Principal findings were the low levels of beta-amyloid: there was near-absence of diffuse amyloid, and only sparse, and infrequent focal presence of neuritic plaques.

Topographic Distribution of Alzheimer's Findings

Brain Regions	Beta-Amyloid Plaques	Phospho-Tau	Bielschowsky
Superior Frontal Cortex (BA8, BA9)	+	+	++
Posterior Frontal Cortex (BA4)	±	+	-
Parietal Cortex (BA1, BA3, BA5, BA40)	-	+	-
Calcarine Cortex (BA17, BA18 & BA31)	++	++	++
Hippocampal Formation with LGB and CN tail	++	+++	+++
CAP (Caudate, Putamen, Accumbens)	-	+	-
GP and Putamen with Claustrum	-	n/a	n/a
Thalamus (level of anterior nucleus)	-	n/a	n/a
Midbrain	-	+	n/a
Upper Pons (level of locus coeruleus)	n/a		n/a
Cerebellum (with dentate nucleus)	±	n/a	n/a
Subthalamic Nucleus with Anterior Thalamus	n/a	+	n/a

± extremely rare; + mild; ++ moderate; +++ severe; Note that for Beta-amyloid plaques and for Phospho-tau findings (neurofibrillary tangles and threads), semiquantitative scoring is based on average distribution pattern throughout the rated region; for Bielschowsky staining, scoring is based on the maximum density of neuritic plaques within the region.

FIGURE 4. LECANEMAB TREATED (SUPERIOR FRONTAL CORTEX BA8,9)

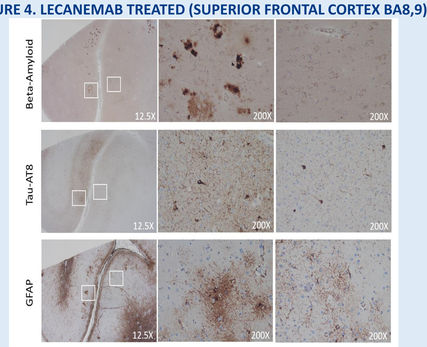


FIGURE 5. ALZHEIMER'S DISEASE COMPARISON CASE (SUPERIOR FRONTAL CORTEX BA8,9)

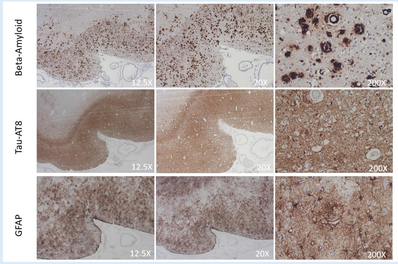


FIGURE 6. HIPPOCAMPAL FORMATION

- Amyloid plaques were infrequent – but some were present in CA4
- Tau staining is present in hippocampal formation – as is glial GFAP staining

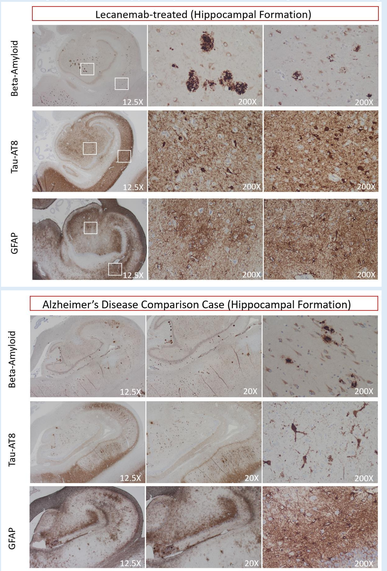


FIGURE 7. AMYLOID PLAQUES IN LECANEMAB TREATED ARE LESS HOMOGENEOUS & LESS DENSE

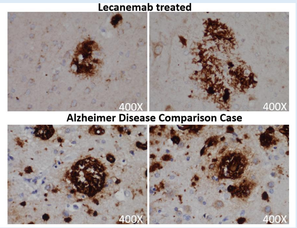
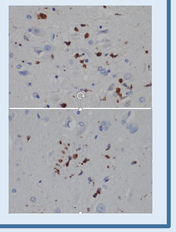


FIGURE 8. CD68 STAINING FOR MICROGLIA IS PRESENT IN LECANEMAB TREATED



SUMMARY OF NEUROPATHOGICAL FINDINGS

- Diffuse amyloid plaques were nearly absent in this patient with AD for 9 years
- Neuritic plaques were present in neocortex and allocortex, but overall quite sparse, despite a few areas of more clustered plaques
- Neurofibrillary threads were present throughout all cortical regions
- Neurofibrillary tangles were widely present, but were not in high densities
- Modest focal amyloid angiopathy was present
- Mild granulovacuolar degeneration was present
- CD68 staining for microglia was present around amyloid material
- Minor TDP43 cytoplasmic staining only in amygdala and entorhinal cortex (not shown)
- Lewy bodies (synuclein positive) were present only in the amygdala (not shown)

AD NEUROPATHOLOGIC STAGING IN THIS CASE

- Amyloid Thal Phase 2 (A1) (beta-amyloid in neocortex and somewhat in allocortex)
- Braak Neurofibrillary degeneration stage VI (B3) (extends through neocortex)
- CERAD Neocortical neuritic plaque Stage B (C2) (moderate)

Overall ADNC Alzheimer Disease Neuropathologic Score: **A1 B3 C2**

CONCLUSIONS

- The neuropathological findings in this case with a 9-year history of Alzheimer's symptoms are most notable for a marked paucity of diffuse plaques, and a variable but overall very low burden of neuritic plaques. Those plaques that were present had a "moth-eaten" appearance. There was also a lack of marked amyloid angiopathy.
- Neurofibrillary pathology is present, but more prominently threads than tangles. Whether amyloid clearance slows cerebral tau accumulation will be assessed antemortem using tau PET scan longitudinal studies in the phase 3 CLARITY AD study.
- The presence of topographically extensive neurofibrillary pathology in the setting of near absence of diffuse amyloid and only scattered neuritic amyloid is very uncommon in typical AD: in the NACC neuropathology dataset, only 2% of brains with extensive neurofibrillary degeneration (Braak B2 or B3) show low Thal stages of A0 or A1.
- The neuropathological findings are consistent with the florbetapir PET scans which show marked reduction of tracer uptake following lecanemab treatment.
- Increased plasma Aβ42/40 ratio antemortem after lecanemab treatment, is consistent with the sparse plaque burden found upon this brain autopsy.
- Plasma p-tau, reduced during the Core treatment with lecanemab, but then with increase during gap and OLE phases, may correlate with tangles observed on autopsy.
- Overall, the results of the neuropathological examination support lecanemab-induced removal of fibrillar cerebral amyloid - both diffuse and neuritic.

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