Brain volume change following anti-amyloid β immunotherapy for Alzheimer's disease: amyloid-removal-related pseudo-atrophy

Christopher R S Belder, Delphine Boche, James A R Nicoll, Zane Jaunmuktane, Henrik Zetterberg, Jonathan M Schott, Frederik Barkhof, Nick C Fox

Progressive cerebral volume loss on MRI is a hallmark of Alzheimer's disease and has been widely used as an outcome measure in clinical trials, with the prediction that disease-modifying treatments would slow loss. However, in trials of anti-amyloid immunotherapy, the participants who received treatment had excess volume loss. Explanations for this observation range from reduction of amyloid β plaque burden and related inflammatory changes through to treatment-induced toxicity. The excess volume changes are characteristic of only those immunotherapies that achieve amyloid β lowering; are compatible with plaque removal; and evidence to date does not suggest an association with harmful effects. Based on the current evidence, we suggest that these changes can be described as amyloid-removal-related pseudo-atrophy. Better understanding of the causes and consequences of these changes is important to enable informed decisions about treatments. Patient-level analyses of data from the trials are urgently needed, along with longitudinal follow-up and neuroimaging data, to determine the long-term trajectory of these volume changes and their clinical correlates. Post-mortem examination of cerebral tissue from treated patients and evaluation of potential correlation with antemortem neuroimaging findings are key priorities.

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See **Comment** page 957

Dementia Research Centre (C R S Belder MBBS, Prof J M Schott MD FRCP, Prof N C Fox MD) **and Department of Clinical and Movement Neurosciences, Queen Square Brain Bank for Neurological Disorders** (Z Jaunmuktane FRCPath), **UCL Queen Square Institute of Neurology, University College London, London, UK; UK Dementia Research Institute at UCL, University College London, London, UK** (C R S Belder, Prof H Zetterberg MD PhD, Prof N C Fox); **Adelaide Medical School, The University of Adelaide, Adelaide, SA, Australia** (C R S Belder); **Clinical Neurosciences, Clinical and Experimental Sciences, Faculty of Medicine, University of Southampton, Southampton, UK** (Prof D Boche PhD, Prof J A R Nicoll FRCPath); **Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, the Sahlgrenska Academy at the University of Gothenburg, Mölndal, Sweden** (Prof H Zetterberg); **Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, Mölndal, Sweden** (Prof H Zetterberg); **Department of Neurodegenerative Disease, UCL Queen Square Institute of Neurology, University College London, London, UK** (Prof H Zetterberg); **Hong Kong Center for Neurodegenerative Diseases, Clear Water Bay, Hong Kong Special Administrative Region, China** (Prof H Zetterberg); **Wisconsin Alzheimer's Disease Research Center, University of Wisconsin School of Medicine and Public Health, University of Wisconsin-Madison, Madison, WI, USA** (Prof H Zetterberg); **Department of Radiology and Nuclear Medicine, Amsterdam UMC, Vrije Universiteit,**

Introduction

Progressive cerebral volume loss, often referred to as atrophy, is a characteristic and diagnostic feature of Alzheimer's disease and an accepted biomarker of neurodegeneration.[1] The measurement of global and regional brain volume changes, by serial MRIs, has been widely used as an outcome in trials of disease-modifying drugs, with the presumption that treatment would, in time, slow neurodegeneration and lead to a reduction in rates of brain volume loss (panel 1).[7,8]

However, in the first trial of immunisation against amyloid β, using the agent AN1792, excess volume loss was observed in patients on the active drug, an observation considered paradoxical at the time.[10] A similar outcome was seen subsequently in several other immunotherapies directed at amyloid β,[11] including in the phase 3 trials of gantenerumab, lecanemab, and donanemab.[9,12,13] The cause of this paradoxical volume loss is not well understood, but has led to concerns that it might represent accelerated neurodegeneration and so lead to deleterious long term outcomes.[11,14] Other explanations include that the excess volume loss is due to the removal of amyloid β plaques, a reduction in plaque-associated inflammatory changes, or alterations in CSF dynamics.[15]

One of the difficulties in disentangling causation is that therapies that are effective in removing amyloid β from the brain also cause the potentially serious side-effect of amyloid-related imaging abnormalities with oedema and effusions (ARIA-E) or microhaemorrhages (ARIA-H),[16] which in turn might influence brain volume. Given that some of these anti-amyloid treatments are now in clinical use and others are in or entering clinical trials, it is vital to understand whether these volume changes are a signal of harm, efficacy, or neither. In this Personal View, we examine the potential explanations, their plausibility and fit with available data, and propose priority areas for further evaluation.

Cerebral volume loss due to anti-amyloid β immunotherapy

Immunotherapies designed to remove amyloid β from the brain and so to slow the progression of Alzheimer's disease have been a major focus of therapeutic development over the past 25 years. These efforts started with the study of AN1792 for active immunisation against the full-length Aβ1-42 peptide, but the phase 2 trial of this drug was stopped after 18 (6%) of 300 patients on active treatment developed meningoencephalitis.[17] Despite early termination, excess brain volume reduction and ventricular enlargement were seen in these participants, compared with those receiving placebo, over around 11 months of follow up.[10] Both volume reduction and ventricular enlargement correlated with antibody titres. However, individuals in the highest titre group did better cognitively than those on placebo, despite having the greatest brain volume reductions; this group also had a disproportionately greater ventricular volume increase relative to brain loss—a deviation from the balance of brain to ventricular volume changes usually seen in people with Alzheimer's disease (panel 1).[7,10]

Excess brain volume reduction has been observed in many, but not all, subsequent anti-amyloid β immunotherapy trials, dependent largely on the ability of the drug to remove amyloid β. Notably, despite influencing plasma and CSF concentrations of amyloid β, solanezumab and crenezumab neither achieved amyloid reduction in the brain, assessed by use of amyloid PET, nor were these treatments associated with excess volume changes.[18–21]

Bapineuzumab was the first anti-amyloid β antibody tested in a phase 3 trial. *APOE* ε4 carriers and

Amsterdam, Netherlands (Prof F Barkhof MD)**; Queen Square Institute of Neurology and Centre for Medical Image Computing, University College London, London, UK** (Prof F Barkhof)

Correspondence to: Prof Nick C Fox, Dementia Research Centre, UCL Queen Square Institute of Neurology, University College London, London WC1N 3BG, UK
n.fox@ucl.ac.uk

Panel 1: The natural history of cerebral volume loss in Alzheimer's disease

Cerebral volume loss in patients with Alzheimer's disease is closely associated with cognitive impairment, both temporally and spatially, according to findings from studies of the natural history of the disease.[2] Typical amnestic Alzheimer's disease has a characteristic pattern of atrophy, thought to relate to tau pathology and neuronal loss, with disproportionate hippocampal atrophy; over time, atrophy becomes generalised and rates increase as individuals become symptomatic.[2–6] For example, in cognitively healthy individuals aged 70–80 years, whole-brain atrophy rates are on average around 0·5% per year, increasing to 1% per year in those with mild cognitive impairment and to 1·5% per year in individuals with mild Alzheimer's disease dementia.[7] For the hippocampus, the rates are 1% per year in cognitively healthy controls, 2·6% per year in those with mild cognitive impairment, and 4·4% per year in individuals with Alzheimer's disease; ventricular volumes increase by 1·4 mL/year in cognitively healthy controls, 2·8 mL/year in those with mild cognitive impairment, and 4·5 mL/year in individuals with Alzheimer's disease.[7] These differences in atrophy rates between Alzheimer's disease and healthy ageing, the precision with which they can be measured, and their association with cognitive decline, led to the widespread adoption of atrophy rates as outcome measures in Alzheimer's disease trials.[8] These rates hold for the cohorts of people with early Alzheimer's disease included in current anti-amyloid immunotherapy trials. For example, in the placebo groups of the GRADUATE trials of gantenerumab, there was an annual brain volume loss of 1·2%, cortical grey matter loss of 1·5%, and hippocampal volume loss of 4%.[9]

non-carriers were enrolled in separate phase 3 trials, with different maximal doses of the drug,[22] all of which were relatively low compared with the doses administered in more recent studies. Within each of the trials, relative to placebo, those on treatment showed small or equivocal changes in amyloid burden, accompanied by significant increases in ventricular enlargement, and small (1–2 mL) but not statistically significant increases in brain volume loss.[23] The group of *APOE* ε4 non-carriers who received 1 mg/kg bapineuzumab (the highest dose) had greater brain and hippocampal volume declines and ventricular enlargement than pooled carriers and non-carriers on placebo.[23]

In the ENGAGE and EMERGE phase 3 trials[24] of aducanumab, both of which showed pronounced amyloid removal (54–62 centiloids [CL] from a baseline of 76–77 CL in high-dose groups), a dose-dependent increase in ventricular volume was seen in all active treatment groups compared with placebo, with an excess of around 2·6 mL at 78 weeks in the high-dose groups. No significant differences in brain or hippocampal volumes were observed.[24]

In the GRADUATE I and II phase 3 trials[9] of gantenerumab, treatment was evaluated up to 116 weeks. In GRADUATE I, the participants who received gantenerumab had greater brain volume reduction (3·0% of baseline *vs* 2·7% in the placebo group; an excess of 0·32% or 4·2 mL), with proportionally greater reduction in cortical volumes (0·64% of baseline, 3·3 mL excess change in volume).[9] A 5·1 mL greater expansion in ventricular volume compared with placebo was also observed. Similar changes were seen in GRADUATE II. Gantenerumab did not show any statistically significant clinical benefit in its primary endpoint, although there was robust amyloid removal (56–66 CL reduction relative to placebo from a baseline of 94–96 CL).[9]

The phase 3 studies of lecanemab[12] and donanemab[13] were both positive, achieving their primary outcomes as well as showing robust amyloid removal. Lecanemab treatment showed a significantly greater reduction in amyloid burden over 18 months compared with placebo. The MRI outcomes were not initially published,[12] but were presented at the Clinical Trials on Alzheimer's Disease conference in 2022.[25] At a dose of lecanemab of 10 mg/kg fortnightly, after 79 weeks, there was greater brain volume reduction compared with placebo (21·8 mL *vs* 17·7 mL; a difference of 4·1 mL, equivalent to 0·4% of baseline brain volume).[12,25] There was also a greater increase in ventricular volume (1·8 mL excess increase in patients treated with lecanemab compared with placebo). However, hippocampal volume decreased 0·02 mL (0·3% of baseline) less in the treated group compared with the placebo group.

In the donanemab phase 3 trial,[13] participants were stratified by baseline tau-PET and a prespecified analysis examined those with low to medium levels of tau deposition as well as the full study cohort. A similar pattern to that observed in the trials of lecanemab was seen, with donanemab-treated patients showing a large reduction in amyloid burden (a mean of 87 CL, from 103 CL to 16 CL) accompanied by excess brain volume reduction (27·5 mL *vs* 20·8 mL; 6·7 mL difference, equivalent to around 0·7% of baseline) and excess ventricular enlargement (3 mL).[13] As with lecanemab, there was less hippocampal volume loss in treated patients compared with patients in the placebo group (0·20 mL over 76 weeks *vs* 0·22 mL with placebo; p<0·01 in the full study population), although in the participants with low to medium tau levels, the difference from placebo in hippocampal volume loss was not statistically significant. Imaging outcome measures for the phase 2 trial of donanemab (reported on ClinicalTrials.gov, NCT03367403) show that the excess whole brain and ventricular volume changes observed in study participants were a similar pattern to those observed in the phase 3 trial, with the additional reporting of cortical volume changes, which showed proportionally greater excess loss than in whole brain.

In summary, trials of anti-amyloid monoclonal antibodies with successful amyloid removal have consistently

	Dose	Duration (imaging final timepoint)	Excess whole brain volume change (% of baseline volume)	Excess cortical volume change (% of baseline)	Excess ventricular volume change	Excess hippocampal volume change	Baseline amyloid PET	Amyloid PET at final timepoint	ARIA-E incidence (%)
Solanezumab (EXPEDITION3; n=2129)[20,21]	400 mg every 4 weeks	80 weeks	−0·9 mL (0·09% less loss than placebo)	Not reported	−0·2 mL (less increase than placebo)	−0·01mL (less loss than placebo)	Not reported	No observed difference	No increase
Crenezumab (CREAD; n=813)[18]*	60 mg/kg every 4 weeks	105 weeks	No observed difference	Not reported	−0·55 mL (less increase than placebo)	−0·02 mL (less loss than placebo)	72 CL†	No observed difference	No increase
Bapineuzumab (Study 302; n=1121)[22,23]‡	0·5 mg/kg every 13 weeks	71 weeks	1·4 mL (0·1%)	Not reported	1·8 mL§	0·01 mL	115 CL¶	−9·5 CL§¶	15·3%
Gantenerumab (GRADUATE I; n=985)[9]	510 mg subcutaneously every 2 weeks	116 weeks	4·2 mL (0·32%)§	3·3 mL (0·64%)§	5·1 mL§	0·02 mL in left hippocampus,§ no observed difference in right	94 CL	−66 CL§	22%
Gantenerumab (GRADUATE II; n=980)[9]	510 mg subcutaneously every 2 weeks	116 weeks	4·7 mL (0·36%)§	3·3 mL (0·64%)§	4·9 mL§	No observed difference	96 CL	−56·4 CL§	22%
Aducanumab (ENGAGE high dose; n=1647; similar results in EMERGE)[24]	Target 10 mg/kg every 4 weeks	78 weeks	1 mL (no difference in EMERGE)	Not reported	2·5mL (2·7 mL in EMERGE)§	No observed difference	77 CL (76 CL in EMERGE)	−62 CL (−54 CL in EMERGE)§	36%
Lecanemab (phase 2; n=856)[26]*	Various; up to 10 mg/kg every 2 weeks‖	79 weeks	4·8 mL (0·48%)§	Not reported	1·6 mL§	0·01 mL	80 CL†	−46 CL†§	9·9%
Lecanemab (Clarity-AD; n=1795)[12,25]*	10 mg/kg every 2 weeks	79 weeks	4·1 mL (0·41%)§	Not reported	1·8 mL§	−0·02 mL (less loss than placebo)§	78 CL	−59 CL§	12·6%
Donanemab (TRAILBLAZER-ALZ phase 2; n=257; NCT03367403)[27]*	700 mg for first three doses then 1400 mg; every 4 weeks	76 weeks	4·6 mL (0·47%)§	2·7 mL (0·69%)§	2·3 mL§	0·01 mL	108 CL	−85 CL§	27·5%
Donanemab (TRAILBLAZER-ALZ 2 low to medium tau population; n=1182)[13,28]	700 mg for first three doses then 1400 mg; every 4 weeks	76 weeks	6·3 mL (0·65%)§	Not reported	2·5 mL§	−0·01 mL (less loss than placebo)	102 CL	−88 CL§	24%
Donanemab (TRAILBLAZER-ALZ 2 combined population; n=1736)[13,28]*	700 mg for first three doses then 1400 mg; every 4 weeks	76 weeks	6·7 mL (0·69%)§	Not reported	3 mL§	−0·02 mL (less loss than placebo)§	103 CL	−87 CL§	24%
AN1792 (Phase 2a; n=372)[10,17]	AN1792 225 µg plus QS-21 50 µg	52 weeks or early termination	10 mL (1·01%)§	Not reported	6 mL§	0·02 mL	Not reported	Not reported	22% of responders developed encephalitis

Data are mean differences between treatment and placebo. PiB=Pittsburgh compound B. SUVR=standardised uptake value ratio. *If baseline volumes were not reported, representative baseline values have been imputed from those reported for TRAILBLAZER-ALZ2 (presented at the Alzheimer's Association International Conference 2023)[28] to establish estimates of percentage volume change. When exact numerical outcomes were not available, estimates have been drawn from figures. The MRI analysis methods used in different trials varied and so absolute volumes should be interpreted with caution. †Estimated from SUVRs florbetapir using the conversion 183 × SUVR − 177 after Navitsky and colleagues.[29] ‡Converted from annualised rates presented by Novak and colleagues.[23] §Volume changes reported as statistically significant in the trials. ¶Estimated from SUVR PiB using the conversion 100 × ([11]C-PiB SUVR − 1·009)/1·067 from Rowe and colleagues.[30] ‖Lecanemab phase 2 outcomes presented as weighted mean of results from the 10 mg/kg every 2 weeks and monthly participant groups due to changes in randomisation of *APOE* ε4 carriers during the trial.

Table: **Neuroimaging outcomes in selected trials of amyloid β immunotherapy**

shown excess brain volume changes of a magnitude less than 1% of brain volume (table and figure 1A, B). A reasonably consistent pattern of volume change has emerged, with proportionally greater excess volume change in the ventricular system than whole brain volume, and in the cortex compared with the brain as a whole (NCT03367403).[9] Importantly, there is no consistent evidence for excess hippocampal volume loss. Indeed, in trials showing slowing of cognitive decline, there was slight attenuation of hippocampal volume loss.[13,25] All amyloid-removing antibodies were associated with ARIA, although incidence varied widely between agents; ARIA-E was also associated to some extent with ventricular volume change (figure 1C, D). There are notable differences between anti-amyloid monoclonal antibodies that remain unexplained, such as the relatively minimal excess whole brain volume change observed with aducanumab despite successful amyloid lowering.

Brain volume loss due to other amyloid-targeting therapies

Excess volume changes have also been seen with other amyloid-targeting therapies, principally with small molecule inhibitors of enzymes involved in amyloid β

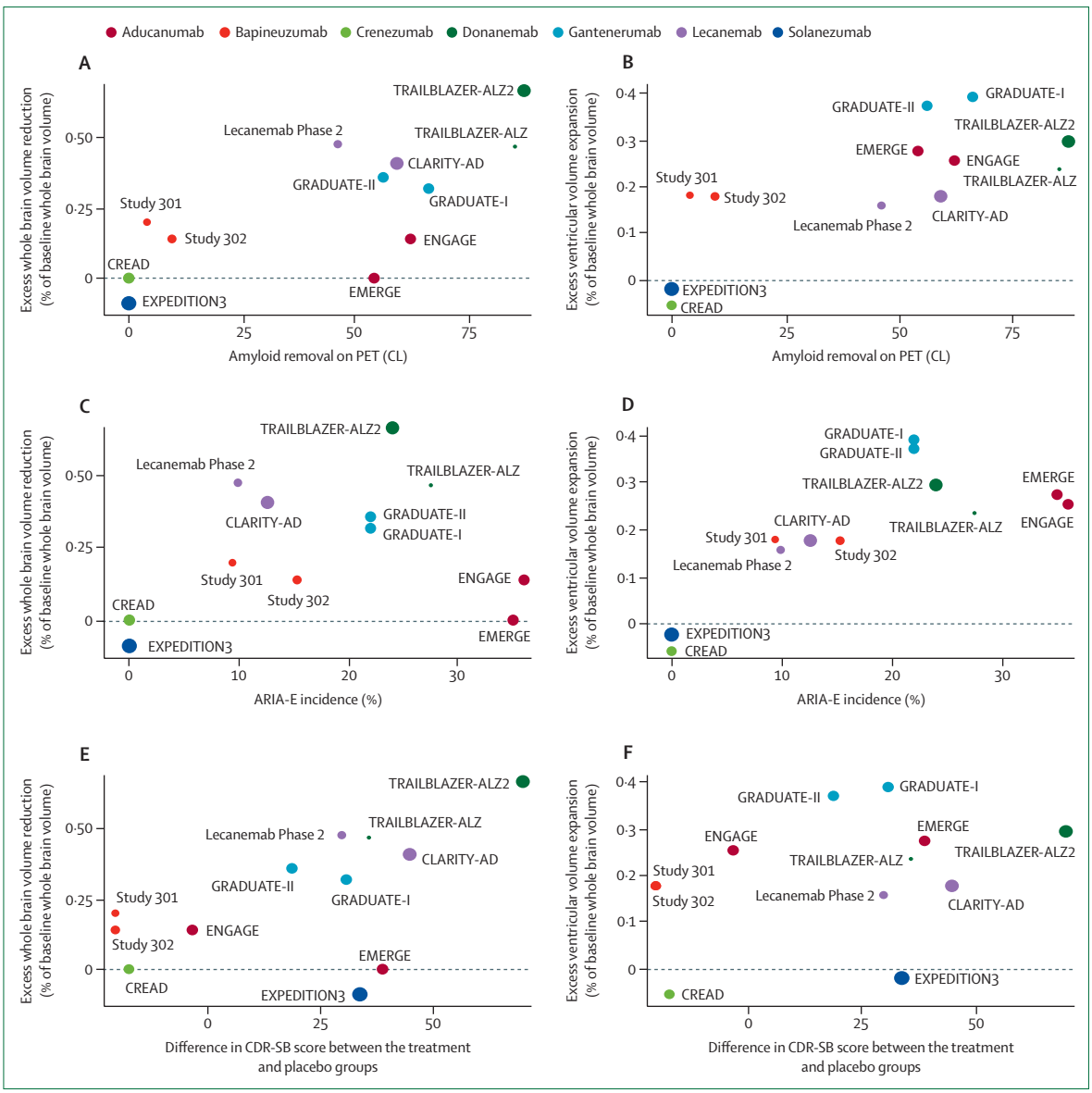

Figure 1: **Whole brain volume and ventricular volume outcomes in key trials, shown as treatment group minus placebo group**
(A) Whole brain volume excess reduction as a percentage of baseline whole brain volume plotted against amyloid removal on PET. (B) Ventricular volume excess expansion as a percentage of baseline whole brain volume plotted against amyloid removal on PET. (C) Whole brain volume excess reduction as a percentage of baseline whole brain volume plotted against ARIA-E incidence. (D) Ventricular volume excess expansion as a percentage of baseline whole brain volume against ARIA-E incidence. (E) Whole brain volume excess reduction as a percentage of baseline whole brain volume plotted against the mean difference in CDR-SB score. (F) Ventricular volume excess expansion as a percentage of baseline whole brain volume against the mean difference in CDR-SB score; the bapineuzumab trials (Study 301 and 302) are overplotted due to an identical point estimate. Mean difference in CDR-SB score is presented as it was the primary outcome for six of 12 depicted studies, and reported as a secondary endpoint for the remainder; for consistency, this mean difference in CDR-SB between treatment and placebo is presented so that a positive value represents benefit in the treatment group relative to controls. Points are coloured by agent and their area scaled by number of participants included in the imaging analysis of the trial. In each trial, if multiple doses were used, the highest dose group was included, except for the data from the lecanemab phase 2 trial, which are reported as a weighted mean of the 10 mg/kg once every 2 weeks and monthly treatment groups due to changes in randomisation of *APOE* ε4 carriers during the trial. Data are from CREAD,[18] EXPEDITION3,[20,21] Study 301 and 302,[22,23] GRADUATE I and II,[9] EMERGE and ENGAGE,[24] Lecanemab phase 2,[26] CLARITY-AD,[12,25] TRAILBLAZER-ALZ (NCT03367403),[27] and TRAILBLAZER-ALZ2.[13,28] ARIA-E=amyloid-related imaging abnormalities with oedema and effusions. CDR-SB=Clinical Dementia Rating Scale Sum of Boxes.

production. In trials studying BACE inibition (eg, with lanabecestat, verubecestat, or atabecestat), excess whole brain and hippocampal volume reduction was seen, compared with placebo, with relatively little change in ventricular volume.[11,31,32] With verubecestat, there was an excess brain volume reduction of 4·8 mL (0·5% of baseline), excess hippocampal volume reduction of 0·015 mL (0·6% of baseline), minimal change in ventricular volume (0·39 mL excess), and little change in amyloid burden (approximately 3·7 CL reduction with

verubecestat).[33] These excess volume reductions were observed by week 13, with no additional excess volume change through to week 78 with ongoing treatment.[33] With atabecestat, excess whole brain volume reduction was observed, and treatment at a group level was associated with worse cognitive outcomes, which reversed after treatment cessation.[31] Semagacestat, a γ-secretase inhibitor, was associated with increased ventricular volume and a small but not statistically significant increase in hippocampal volume reduction, although this trial was discontinued early so there is uncertainty around these outcomes.[34] The distinct temporal and spatial patterns of brain volume change observed in the trials of these therapies, compared with the changes observed in trials of anti-amyloid β immunotherapy, suggest that different mechanisms underlie these observations. These enzymes have numerous substrates other than amyloid β that could mediate these volume changes in the brain when their functions are inhibited.[35,36]

Possible mechanisms for cerebral volume loss with treatment

There are different mechanistic explanations that have been proposed for the brain changes observed following immunotherapy targeting amyloid β. First, we address whether these volume changes could be explained by bulk clearance of amyloid β plaques and associated cellular responses, and then consider alternative mechanisms, including those related to neurodegeneration and fluid shifts.

Amyloid removal

Given that therapies that induce the most amyloid clearance are associated with the greatest change in cerebral and ventricular volume, could the excess volume loss be explained by removal of amyloid β pathology? Although the total mass of amyloid β peptide in the brain of people with Alzheimer's disease has been estimated to be far less than is necessary to account for these volume changes,[37] it is important to note that amyloid plaques occupy a volume much greater than that due to the amyloid β protein itself. Each plaque also contains a host of other proteins and dystrophic neurites, and is associated with reactive glia and fluid, all of which occupy volume. The dry weight of amyloid β in the brain is therefore unlikely to be a good guide to the volume changes expected because of extensive plaque removal.

Post-mortem estimates of the area fraction (and corresponding volume) occupied by amyloid β plaques vary depending on the methodology used to measure them. Some studies have examined one cortical region, whereas others have assessed multiple lobes. Estimates of amyloid β plaque-related volume in post-mortem brains of people with Alzheimer's disease include: 5–8% of a range of cortical and subcortical regions;[38] 1% of neocortex;[39] 6·9% of frontal cortex and 10·1% of entorhinal cortex;[40] 6·7% of frontal cortex and visual cortex;[41] 6·7% of supramarginal gyrus;[42] 11% of temporal cortex;[43] 6% of temporal, frontal, parietal, and cingulate cortices;[44] and 8·7% of frontal, 6·5% of temporal, and 4·5% of caudate.[45] Together, these studies suggest that a reasonable estimate of the proportion of cortical grey matter occupied by amyloid β plaques in the post-mortem brains of people with Alzheimer's disease is around 6–8%, which is around 2–3% of total brain volume. This value is much higher than, and more than enough to account for, the excess volume losses in cortical grey matter and in the whole brain (<1%) seen in the clinical trials of immunotherapies, noting that although the trial cohorts comprise individuals with mild cognitive impairment or mild dementia, all participants have substantial amyloid β pathology.

There are relatively few autopsy estimates of the amyloid β plaque reduction in patients treated with immunotherapies. Brain tissue from the autopsy of a patient previously treated with aducanumab was shown to have markedly reduced amounts of temporal neocortical amyloid β plaque compared with untreated controls with Alzheimer's disease (area fraction 0·17% *vs* 2·5–12%).[46] Post-mortem neuropathological analyses of a subset of patients immunised with AN1792[47] showed substantially lower plaque burden, even some years after the treatment, compared with untreated controls with Alzheimer's disease (inferior parietal lobule mean amyloid β area fraction 1·7% *vs* 7·2%).[48]

A key area that requires explanation is the apparent temporal disconnect between the amyloid PET changes and the volumetric MRI changes, with amyloid removal occurring early at a group level and then plateauing, whereas the volume changes continue throughout the duration of the trials.[12,13] This finding suggests that amyloid removal is not the sole explanatory factor: complete removal of plaques (including dystrophic neurites, etc) and resolution of the associated inflammatory cell response might both be important and might both lag behind reductions on amyloid PET.

Changes in the cellular response

The cellular response to amyloid β deposition is highly complex and includes, among other processes, reactive astrogliosis and microglial activation (figure 2).[49] In addition to the volume changes that might be explained by direct plaque removal, another contributing factor could be attenuation of the cellular response to aggregated amyloid β. There is some evidence that immunotherapy-induced clearance of plaques might reduce some elements of this cellular response—for instance, donanemab and lecanemab reduce plasma GFAP, a marker of astrocytosis.[12,50] In a post-mortem study, increased microglial plaque engagement was seen in a patient who had been treated with aducanumab, although the total burden of microglia was not reported.[46]

With active immunotherapy, an initial increase in microglial activity has been proposed as a key mechanism of plaque clearance, which would be followed by microglia

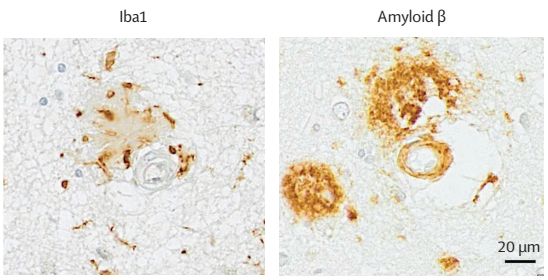

Figure 2: **Microglia clustering around amyloid β plaques**
Neuropathological analysis of the cortex of the inferior parietal lobule in an 84-year old woman diagnosed with Alzheimer's disease. The antibodies used in the staining were anti-Iba1 (microglia, Wako), and anti-amyloid β (pan-Aβ 4G8, Covance). Slides were counterstained with haematoxylin and eosin, and images were digitised on an Olympus VS110 slide scanner (Olympus America). Brain tissue was sourced from the South West Dementia Brain Bank (NRES Committee South West Central Bristol, REC reference 08/H0106/28+5).

dispersal and downregulation after amyloid β clearance.[51,52] Histological studies in patients who received AN1792 showed that the percentage area of cerebral cortex occupied by microglia was halved, compared with that in the cortex of patients with untreated Alzheimer's disease (CD64 microglial marker: AN1792 treated Alzheimer's disease 0·4% *vs* untreated Alzheimer's disease 1·1%).[52] These changes could contribute either directly or indirectly to the volume reduction observed by use of MRI. Qualitative observations suggest that plaque-associated astrocytes also become less activated and that the astrocytes also reduce in size. Although these astrocyte changes have not been quantified in a similar manner to those of the microglia, it seems likely that changes in astrocytes could also contribute to the volume changes observed.[53] There is also neuropathological evidence that this astrocytic response is not attenuated until there is complete plaque removal, which could be a factor accounting for the temporal disconnect between amyloid PET and MRI measures.[54]

Excess cerebral volume loss has been observed in trials of anti-inflammatory agents, such as resveratrol, in patients with Alzheimer's disease.[55] Analogies have also been drawn between the excess volume loss in immunotherapy for Alzheimer's disease and the volume loss observed in people administered highly active disease-modifying treatments for multiple sclerosis (eg, natalizumab), in whom an initial accelerated volume loss occurs with treatment (referred to as pseudoatrophy), and is presumed to be due to a reduction in inflammation or fluid shifts, followed by a slowing of brain volume loss with treatment, probably due to disease modification.[15,56,57] Longer follow-up data are required to find out whether similar patterns occur in patients with Alzheimer's disease treated with effective immunotherapy.

If amyloid β removal and attenuation of the cellular response do account for the excess brain volume losses seen in these trials, it is reasonable to ask whether amyloid β deposition (albeit over a much longer timeframe) is associated with volume increases. There is some evidence in support of this association, with increased cortical thickness reported in the early stages of the Alzheimer's continuum, before subsequent atrophy rates increase and likely obscure any volume effects of continuing amyloid accumulation.[58–62] The early increases in cortical thickness are also associated with markers of cellular response, including MRI, PET, and CSF markers of reactive astrogliosis and microglial activation.[62–64]

Neuronal changes and accelerated neurodegeneration

The possibility that the excess volume loss seen with immunotherapies might reflect accelerated neurodegeneration (ie, an increased rate of neuronal loss) is, of course, the greatest concern. Possible mechanisms for this accelerated neurodegeneration could include deleterious effects of amyloid β oligomer release following plaque clearance, or could be a consequence of ARIA, or of unknown off-target effects.[11]

From a clinical perspective, and acknowledging that follow up data are limited, it is notable that, in phase 3 trials of lecanemab and donanemab, patients on treatment had—at a group level—less clinical decline despite showing increased brain volume reductions.[12,13] In a comparison of results across different drug targets in Alzheimer's disease trials, antibodies that remove amyloid β consistently show a dissociation between (excess) volume changes and (improved) cognitive outcomes (figure 1E, F), in contrast with other therapies, for which excess volume losses were associated with poorer cognitive outcomes.[65] It is conceivable that any clinical detriment associated with excess volume loss could be delayed, but based on the limited long-term data available, there is no evidence for this. In the lecanemab phase 2 open-label extension, in which treatment was interrupted before the open-label extension for a mean of 24 months (range 9–59), there was no delayed worsening in the treated group, although this finding should be interpreted cautiously due to selective attrition.[66]

Arguing against the volume changes associated with anti-amyloid β immunotherapy being due to accelerated neurodegeneration in patients with Alzheimer's disease is that the hippocampi—regions typically associated with some of the most pronounced neurodegeneration and volume loss in patients with Alzheimer's disease—are spared.

Another argument against the hypothesis of treatment-accelerated neurodegeneration as the principal explanation for brain volume loss is that CSF and plasma concentrations of neurofilament light (NfL) or total tau typically remained stable or decreased during treatment.[67] These markers can predict brain volume loss due to neurodegeneration measured by imaging,[68] are more sensitive than imaging measures to detect neuroaxonal injury in people with mild brain trauma,[69] and can be used to detect drug-related neurotoxic effects in research and clinical settings in other fields of neurology.[70–72] More

specifically, in people treated with lecanemab, a reduction in CSF total tau, a small reduction in plasma NfL, and stable CSF NfL concentrations were reported.[12] In the phase 3 trial of donanemab, plasma concentrations of NfL increased relative to placebo at week 24, but subsequently decreased in weeks 52 and 76.[28] In an analysis of phase 2 trial data of donanemab, increasing plasma concentrations of NfL correlated with reductions in brain volume, but this correlation did not separate excess volume change attributable to donanemab treatment from volume loss due to disease progression.[50] With gantenerumab, treatment was associated with lower CSF concentrations of NfL and total tau than placebo.[9]

Post-mortem studies of AN1792-immunised patients did suggest some increased neuronal loss and cortical spongiotic change (compared with controls with Alzheimer's disease), but also raised the possibility of improved health of residual neurons, with less neuritic curvature and the presence of fewer pro-apoptotic neurons in the immunised brains, interpreted as being due to the removal of damaged neurons.[54,73,74] This finding was consistent with the reduction in other amyloid β plaque-associated components, such as dystrophic neurites, intraneuronal hyperphosphorylated tau, Apo-E proteins, and an overall reduction in pro-apoptotic proteins.[47,73,75,76] In other words, the neuropathological findings were consistent with the hypothesis that there were changes in the cellular response to the presence of amyloid.

The role of ARIA

ARIA has been proposed as a cause for excess volume loss.[11] Although ARIA can cause acute clinical manifestations, and rarely death, no link between ARIA and long-term adverse cognitive outcomes has been established to date. *APOE* ε4 carriers have higher incidence of ARIA; however, these individuals appear to derive similar clinical benefits from immunotherapy to *APOE* ε4 non-carriers.[77] The benefits for *APOE* ε4 homozygotes are less clear than those in heterozygotes or non-carriers. These observed differences in outcome might be mediated by ARIA, or could be due to the relatively small number of participants who were *APOE* ε4 homozygotes (there were wide confidence intervals for these point estimates) and warrants further evaluation.[12,13] There is a correlation between ARIA-E incidence and treatment-related increases in ventricular volumes, although this association might be confounded by more pronounced amyloid removal than those without ARIA-E.[11] In a post-hoc analysis of the bapineuzumab trials, participants with ARIA-E had more amyloid removal on PET, a greater increase in ventricular volume, and greater hippocampal volume reduction than those who did not develop ARIA; however, the proportion of *APOE* ε4 carriers in the ARIA group was higher than that in the group of participants that did not develop ARIA, and other factors might have confounded these observations.[78] ARIA might lead to focal reductions in amyloid-PET, but whether this reduction translates into regional volume loss has, to our knowledge, not been evaluated.[79,80]

Fluid shifts

The apparently disproportionate ventricular enlargement relative to brain volume reduction that occurs in people treated with anti-amyloid immunotherapy raises the possibility that immunotherapy might result in an alteration in CSF dynamics—eg, impaired CSF resorption, leading to ventriculomegaly.[11,15] Solubilisation and mobilisation of amyloid β to vessel walls, with associated inflammation, could be a shared pathway. Altered glymphatic function or leakage of intravascular fluid into the parenchymal interstitial space manifests as parenchymal ARIA-E, whereas involvement of leptomeningeal vessels leading to leakage of proteinaceous fluid into the subarachnoid space manifests as sulcal ARIA-E,[16] and each of these (parenchymal and sulcal ARIA-E) in turn could impede CSF resorption, and result in ventricular enlargement. In other areas of neurology, therapies can cause brain volume changes unrelated to neurodegeneration that are instead due to reduced inflammation or fluid shifts, such as with acute corticosteroid treatment, mannitol administration, or haemodialysis.[81–83]

Conclusions and future directions

The explanation for the observed brain volume changes in the cohorts of anti-amyloid β immunotherapy trials is

***Panel 2*: Gaps in current evidence and key areas for further evaluation**

On an individual patient level, is the excess volume reduction observed in participants treated with anti-amyloid immunotherapy linked with the same clinical and biomarker outcomes that volume loss has according to the natural history of Alzheimer's disease, or do these associations weaken, as has been noted at a group level?[65]

What happens to cerebral volumes beyond the duration reported in current trials? Do these observations represent a consistently increased rate of volume loss with ongoing treatment, or does the excess volume change plateau (or decrease) once optimal removal of amyloid is achieved? How do these volume changes relate to long term clinical outcomes?

What brain regions are driving these volume changes, given that the ventricular and whole brain volumes that have been most commonly reported are not region specific?

At the individual patient level, how related (both in extent and topography) are these excess brain volume changes to the amount of amyloid removed (as measured by PET) and the presence of ARIA?

Do markers of glymphatic function and CSF dynamics influence volume changes in the presence of amyloid-removing immunotherapy (or the converse)? Is the increase in ventricular volume associated with an adverse change in CSF dynamics?

incompletely understood and likely to be multifactorial. There are many unanswered questions, including the long term trajectory of volume changes and, crucially, whether excess volume change after amyloid β removal adversely influences long term outcomes. Given that these medications are undergoing regulatory evaluation and entering clinical practice, urgent examination and reporting of patient-level data from the existing large datasets from these trials are needed (panel 2). However, scrutiny of the available data does allow for a number of conclusions. First, excess volume loss is only seen with immunotherapies that achieve amyloid removal, and the magnitude of excess volume loss appears to be related to the extent of amyloid removal. Second, this excess volume loss spares the hippocampi, and is not associated with worse cognitive outcomes (at a group level), arguing against this loss being substantially due to accelerated neurodegeneration. Finally, the volume occupied by amyloid β plaques in the brains of people with Alzheimer's disease is not trivial (around 6% of cortex according to post-mortem studies). The extent of excess volume change seen in treated patients is considerably lower than this volume occupied by plaques and, even allowing for the fact that immunotherapy trials involve people at much earlier stages of the disease with lower plaque burdens than those analysed in post-mortem studies, the highly effective removal of amyloid β plaques could reasonably explain the changes, through plaque clearance and plaque-associated glial changes, likely accompanied by fluid shifts.

We posit that available evidence suggests that this occurrence is neither paradoxical nor due to accelerated neurodegeneration, and pending longer term outcome data and further mechanistic insights, could now be referred to as amyloid-removal-related pseudo-atrophy. With this interpretation of the evidence, we do not aim to diminish the significance of the brain volume changes, but rather to facilitate a consistent terminology to be used for research and clinical trials. Analysis of patient-level clinical trial data is urgently needed, and long term follow up will be important to clarify whether these volume changes are an indicator of efficacy rather than a cause for concern—or neither. For future trials, MRI volume outcomes should be clearly and transparently reported as key safety measures alongside ARIA. We predict that effective therapies that slow neurodegeneration enough and for long enough will ultimately also slow rates of atrophy—the hypothesis with which incorporating serial MRI measurments in trials began.

Search strategy and selection criteria

We identified references in PubMed using the search terms "Alzheimer's disease" AND "amyloid" AND "immun*" AND "trial". We also searched ClinicalTrials.gov and AlzForum.org for immunotherapies (active and passive) targeting amyloid β in people with Alzheimer's disease and for publications covering clinical or biomarker endpoints. An initial search was performed for papers published between January, 2000, and March, 2023, by CRSB, with contributions from NCF. The search was repeated after the subsequent publications of findings from other relevant phase 3 trials (donanemab and gantenerumab), with the final search considering publications through to May, 2024. Conference presentations reporting relevant biomarker endpoints were also sought, if findings were not included in primary publications. Our selection of references is based on their relevance to the content of our Personal View. The reference lists within the articles that we found in our searches were also examined for their relevance to our discussion.

Contributors

CRSB: conceptualisation, literature review, writing the original draft, reviewing and editing the manuscript, and preparation of figures. NCF: conceptualisation, literature review, and reviewing and editing the manuscript. DB: conceptualisation, reviewing and editing the manuscript, and preparation of figure. JARN: conceptualisation and reviewing and editing the manuscript. ZJ: writing, reviewing, and editing the manuscript. HZ: writing, reviewing, and editing the manuscript. JMS: data interpretation, and reviewing and editing the manuscript. FB: conceptualisation, literature review, and reviewing and editing the manuscript.

Declaration of interests

DB has been a consultant or advisor relating to Alzheimer immunisation programmes for: Elan Pharmaceuticals (travel and accommodation) and Biogen (consultancy fees). JARN has been a consultant or advisor relating to Alzheimer immunisation programmes for: Elan Pharmaceuticals (travel and accommodation), GlaxoSmithKline (consultancy fees), Novartis, Roche (consultancy fees), Janssen (consultancy fees), Pfizer, Biogen (consultancy fees, travel, and accommodation), and Eisai. HZ has served at scientific advisory boards or as a consultant for AbbVie, Acumen, Alector, Alzinova, ALZPath, Amylyx, Annexon, Apellis, Artery Therapeutics, AZTherapies, Cognito Therapeutics, CogRx, Denali, Eisai, Merry Life, Nervgen, Novo Nordisk, Optoceutics, Passage Bio, Pinteon Therapeutics, Prothena, Red Abbey Labs, reMYND, Roche, Samumed, Siemens Healthineers, Triplet Therapeutics, and Wave; has given lectures in symposia sponsored by Alzecure, Biogen, Cellectricon, Fujirebio, Lilly, Novo Nordisk, and Roche; is chair of the Alzheimer's Association Global Biomarker Standardization Consortium; is a cofounder of Brain Biomarker Solutions in Gothenburg (Brain Biomarker Solutions), which is a part of the GU Ventures Incubator Program. JMS has received tracer from Avid Radiopharmaceuticals (a wholly owned subsidiary of Eli Lilly) and Alliance Medical and has consulted for Roche Pharmaceuticals, Biogen, and Eli Lilly. FB has received consulting fees from Combinostics, Roche, and IXICO; has participated in data safety monitoring or advisory boards for EISAI, Biogen, Prothena, and Merck; and is a cofounder of Queen Square Analytics. NCF reports consulting fees from Biogen, Eisai, Ionis, Lilly, Roche/Genentech, and Siemens—paid to University College London; he has served on a data safety monitoring board for Biogen. All other authors declare no competing interests.

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