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Reply to Ayton et al “Amyloid Related Iatrogenic Atrophy of the Brain (ARIA-B…”

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Corresponding Author:	Nick C Fox, MD FRCP FMedSci University College London London, UNITED KINGDOM
First Author:	Christopher R. S. Belder
Order of Authors:	Christopher R. S. Belder
	Delphine Boche
	James Nicoll
	Zane Jaunmuktane
	Henrik Zetterberg
	Jonathan Schott
	Frederik Barkhof
	Nick C Fox, MD FRCP FMedSci
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We agree with Ayton and colleagues and, indeed, state in our paper that it is vital that participant-level data on brain volume changes from existing (and future) clinical trials of anti-amyloid therapies are fully reported and carefully evaluated. Long-term outcome data and more post-mortem neuropathology from treated patients are also required to understand better the consequences and causes of these changes.

In our paper, we address the possibility that excess volume changes could be due to accelerated neurodegeneration. Having carefully evaluated the totality of available clinical, imaging and biomarker evidence we do not believe the data support this proposition. Instead, we argue that the volume changes associated with therapy are most compatible with amyloid plaque removal and resolution of associated inflammatory changes – hence the term ***pseudoatrophy.***

Ayton and colleagues suggest that microglial activity around plaques in treated patients challenges the notion that volume loss could be due to reduced inflammation. It is important, however, to note that while microglia are indeed involved in the active phase of removal of plaques, in the longer-term microglial activity has been shown to be *reduced* relative to untreated AD.[1] As in many areas of medicine, resolution of inflammatory changes, and downstream tissue remodelling may take some time after removal of the initial inflammatory stimulus, and indeed these findings may also help explain the "temporal disconnect" seen between brain volume reductions and amyloid removal.

The cerebral volume changes that take place during amyloid removal are qualitatively different to those that occur in untreated Alzheimer's disease. They are also very different to the changes seen with β-secretase inhibitors which are associated with rapid (within 13 weeks for verubecestat), and non-progressive, volume loss.[2]

It is also important not to lose sight of the fact that, unlike with the secretase inhibitors, amyloid removal induced by both lecanemab and donanemab is associated with clinical benefit which occurs alongside the increased brain volume decreases.

Our suggestion of the term Amyloid Removal Related Pseudoatrophy (ARPA) is not to minimise the complexity or importance of the issue or to suggest a single, reductive explanation. Our aim is to draw attention to the phenomenon and to encourage more complete, clear and transparent reporting of brain volume outcomes in these important trials.

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

References

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