Editorial commentary Neurology-2022-187233 Ayton

Do anti-amyloid antibodies cause pseudo-atrophy?

Frederik Barkhof and David Knopman

The prevailing theory about the pathogenesis of Alzheimer's disease (AD) is the amyloid cascade, where abnormal amyloid-beta (Aβ) metabolism leads to deposition of amyloid plaques in the brain, with subsequent formation of tau-tangles and neurodegeneration. Indeed, cognitively normal subjects with amyloid (and tau) pathology are destined to decline [ref Ossenkoppele]. In later stages of the disease, neurodegeneration will manifest brain volume loss (atrophy) on MRI scans and for example hippocampal atrophy on MRI is frequently used as the neurodegeneration (N) biomarker in the so-called ATN staging system [ref Jack].

The past decades have seen increasingly successful efforts to prevent amyloid build up or remove it from the brain using Aβ antibodies. Recently 2 of these antibodies have been given accelerated approval by the FDA [refs Budd & van Dyck], leading to fierce debate as the clinical benefit is small and there are significant safety concerns due to the occurrence of ARIA. Currently, there is a lack of longer-term treatment studies to determine what the real clinical benefit of Aβ antibody therapy might be. An important element to close this gap would be to determine its effect on downstream biomarkers within the ATN framework and beyond.

Both aducanumab and lecanemab have beneficial effects on plasma tau levels, NFL and GFAP, signifying that normalisation of Aβ does not come in isolation but has positive downstream effects in the amyloid cascade. The question thus is whether these drugs also slow the process of neurodegeneration, including rate of atrophy on MRI. In this issue of Neurology, Ayton and colleagues review the effects of amyloid-lowering antibody therapy on MRI across a series of published AD trials. Overall, the rate of atrophy did not differ between placebo and active treatment arms, suggesting a lack of effect on neurodegeneration.

Can we be sure that indeed amyloid-removal does not prevent neurodegeneration? The positive effects on NFL and other biomarkers seem to be contradictive and call into question how accurate a reflection MRI rates of atrophy are under amyloid therapy. While the relationship between degree of MRI atrophy and pathological findings of neurodegeneration have been confirmed and the rates of brain-volume change have prognostic value in untreated AD populations, little is known about its accuracy of measuring (rates of) brain volume during treatment.

An alternative explanation could be that MRI brain volume changes under Aβ antibody treatment reflect other processes beyond neurodegeneration and that we cannot simple equate rates of MRI volume changes with rates of atrophy. For example, amyloid may increase grey matter volume in early stages of amyloid deposition [ref Ingala or similar],

which may be due to microglia activation or alterations in the glymphatic pathways. It is conceivable that removal of amyloid might reverse this process and lead to a shrinkage of brain volume, which would be indistinguishable from brain volume loss due to neurodegeneration. Such a pseudo-atrophy phenomenon is frequently observed in multiple sclerosis, where highly effective treatments accelerate brain volume loss in the first year of treatment, with a subsequent slowing of atrophy rates only after longer periods of treatment.

The current treatment trials with A-beta antibodies have been too short to answer this and other important questions about the long-term efficacy and effectiveness of these expensive drugs. Intriguing differential effects were found by Ayton and colleagues for classes of drugs, with monoclonal Aβ-antibodies giving more ventricular enlargement that secretase inhibitors. This class of drugs is also accompanied by the occurrence of amyloid-related imaging abnormalities (ARIA), which are thought to be due to linked to abnormal perivascular drainage [Petrarca]. In doing so, ARIA may also affect CSF dynamics and hence brain volume. More detailed analyses of available trial data looking at the dynamics of brain volume changes around the occurrence of ARIA may shed light on this relationship.