Published in final edited form as:

Lancet Neurol. 2012 August ; 11(8): 661–662. doi:10.1016/S1474-4422(12)70143-6.

Primary or secondary prevention for AD: who cares?

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Your Editorial¹ in the July issue discusses the highly innovative clinical trial of the anti-amyloid monoclonal antibody crenezumab in carriers of a presenilin-1 mutation (*PSEN1* E280A) that causes early-onset familial Alzheimer's disease (EOFAD). The Editorial challenges the view that this placebo-controlled trial is actually a primary prevention trial, because participants will already have brain amyloidosis at baseline; furthermore, it suggests that only a true primary prevention trial—ie, one aimed at preventing brain amyloidosis—would be a definitive test of the amyloid hypothesis. We think that this interpretation of the trial is futile, because evidence about when the first amyloid β peptides or oligomers begin to accumulate in the brain is impossible to obtain at present. We think that the crucial issue regarding the interpretation of this trial is whether findings could be generalised to patients with sporadic Alzheimer's disease (AD).

The amyloid hypothesis states that AD starts with amyloid β deposition in the brain, followed by neurodegeneration and subsequent neuron loss that culminates in clinical symptoms.² This chain of events is comparable with that triggered by hypercholesterolaemia and causing coronary atherosclerosis, which leads to angina or infarction. Here, the disease to be prevented is coronary atherosclerosis, and cholesterol-lowering therapy is considered a primary prevention treatment. In AD, discussions about what should be defined as the disease state are ongoing; supporters of the amyloid hypothesis place brain amyloidosis at the pathophysiological core that triggers neurodegeneration. This view implies that any intervention in people who already have amyloidosis cannot be primary, but secondary prevention. Those who advance alternative hypotheses—for instance, that tau is more closely linked to neurodegeneration than is amyloid deposition—advocate for interventions that might block mechanisms of neurodegeneration more directly than do anti-amyloid therapies,³ regardless of whether those interventions could be considered primary prevention strategies or not.

If crenezumab prevents the onset of clinical symptoms in carriers of the *PSEN1* E280A mutation, then expectations from doctors and patients will be fully met, whether or not amyloid deposition had started at the time of treatment. If successful, the amyloid hypothesis will be verified. If unsuccessful, the hypothesis will be neither verified nor falsified on the

basis that even such early intervention might not be early enough, and that interventions might have to be started before deposition of the very first amyloid aggregate. If the results are negative, some people will argue that the only way to block neurodegeneration in AD is to interrupt progression of tau pathology.

An intriguing and crucial issue is that, even if successful, the findings might not be generalisable to sporadic AD, because early disruption of amyloid metabolism in sporadic AD is substantially different from that in EOFAD. Differences include: deposition of amyloid β in the neocortex in sporadic AD and in the striatum in EOFAD;⁴ topography of neurodegeneration, mapping to the medial temporal and lateral temporal cortex in sporadic AD and to the neocortex in EOFAD;⁵ and an absence of unequivocal evidence that amyloid β is overproduced in sporadic AD as it is in EOFAD.

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