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Commentary

The US Expert Panel on the Appropriate Use Recommendations of Aducanumab in Clinical Practice

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The authors of these recommendations must be congratulated on rapidly putting together a workable set of guidelines on the best use in clinical practice of the first drug approved (1) in a new class of medications acting on the excessive deposition of amyloid plaques in the brain of persons with early symptoms of Alzheimer's disease (AD). These guidelines have been written despite the current lack of peer-reviewed publications about the Phase III pivotal studies so changes may be required once all the data is available in the public domain (2, 3, 4).

There has been a good effort at suggesting clinical instruments that are familiar to clinicians and less time consuming than rating scales used in randomized clinical trials (RCT). Nevertheless, the Clinical Dementia Rating (CDR) scale is a comprehensive and reliable instrument that should be considered for annual follow-up visits and help determine if there is sufficient clinical stability to justify treatment continuation for another year.

`Start rules` are clearly defined, based on what is known of the participant populations in the Phase III studies. There are few comments about persons younger than 50 in the early symptomatic stages of familial autosomal dominant AD or with Down's syndrome, and these special populations require their own independent RCT to determine effective doses and safety profile, even with aducanumab. The exclusion of persons with `evidence of stroke` need more details since many patients with early symptomatic AD have asymptomatic lacunar infarcts in non-strategic brain regions.

There has been an effort at defining `stop rules`, including severe symptoms in the presence of ARIA, inability to reach therapeutic dose, loss of access to clinical and brain imaging monitoring, but the authors stopped short of stating that this treatment should be stopped when reaching a moderate stage of dementia. This will likely be a requirement from payers and the next set of use guidelines may operationally define moderate dementia such as CDR global score of 2, MMSE lower than 19 at least twice, having lost autonomy on key instrumental activities of daily living.

Optimal use of amyloid PET and CSF analysis is very well documented in these guidelines, and the authors hint at potential time and cost savings using ApoE genotype and plasma p-tau isoforms as a case-finding tool to identify patients that are amyloid positive. There is indeed realistic hope that a significant number of candidates for anti-amyloid drugs will not need amyloid PET or CSF analysis if they are ApoE4 homozygotes or have elevated plasma p-tau 181.

Future recommendations could address the need of confirmatory data on clinical efficacy, taking advantage of the FDA requirement for another placebo-controlled study: it is an opportunity to establish if anti-amyloid therapy can be stopped once the amyloid load has been rectified, through a repeat PET amyloid scan after 12 or 18 months, followed by randomization to continuation of aducanumab, to placebo, to an anti-tau drug or a combination of the two drug class. This randomized delayed start factorial design may go a long way in influencing future therapy of AD, as well as adaptive designs as described by Bateman et al, 2016 (5) .

Although written to answer the specific needs of clinical use of aducanumab right now in the USA, these guidelines will likely serve as blueprint for other drugs of that class. This is one big step for our field.

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