Aducanumab: What about the Patient?

An enormous controversy has arisen regarding the clinical efficacy and the approval process surrounding aducanumab for the treatment of Alzheimer disease. Moghavem et al accurately recount the chronology of events and conclude that the data do not support its utility.1 The US Food and Drug Administration (FDA) granted accelerated approval of aducanumab on the basis of the removal of amyloid plaques as a surrogate marker in the setting of uncertain clinical efficacy.2 The key feature of the decision was the approval based on the impact on the amyloid biomarker, but the FDA indicated that more data were needed on the clinical efficacy. The subsequent firestorm has become extremely politically charged.3

In this controversial setting, however, the voice of the patient has been muted. Consider a 68-year-old woman with early mild cognitive impairment (MCI) who is amyloid positive and has been on an acetylcholinesterase inhibitor for 6 months. The patient is keenly aware of her change in cognition over recent years and has witnessed family members who have experienced the protracted course of Alzheimer disease. This is a fatal disease, and the clinical course can be devastating. This person, after hearing the discussion of the rationale for lowering the level of amyloid in the brain and the uncertain clinical benefit in the setting of the potential side effects of amyloid-related imaging abnormalities (ARIA), deserves the opportunity to participate in the decision.4 Although the ARIA can be serious in some instances, they can be managed effectively. As such, some may choose to be treated and some may not, but we need to involve the patients in the discussion rather than determining their fate for politically motivated reasons.

Clearly, the manner in which this information is presented to the patient is critical. Amyloid and tau constitute the defining features of Alzheimer disease. The recent proposal by the National Institute on Aging–Alzheimer’s Association panel concluded that amyloid and tau were sufficient to define the disease irrespective of the clinical presentations.5 Although not universally accepted at this point, other views incorporating clinical features with biomarkers for amyloid and tau have been proposed.6 Although not in complete agreement, both positions highlight the importance of biomarkers for amyloid and tau in defining the disease. As such, treating one of the fundamental elements of the disease appears quite rational. Amyloid is deposited in the brain over years to decades prior to the development of symptoms.7 With aducanumab and other amyloid monoclonal antibody therapies currently under investigation, the amyloid plaque levels are reduced to near normal over the course of 12 to 18 months.3,8 Is it reasonable to expect a dramatic clinical benefit from that reduction in the course of an 18-month randomized controlled trial considering the decades of neuronal damage that have accumulated? At best, we might expect a modest stabilization of the clinical progression in the MCI/mild dementia stages of the Alzheimer disease process, and that has been demonstrated by the more recent monoclonal antibodies.8 Although a dramatic clinical benefit is unlikely, any stabilization at that point in the process may be meaningful.

Alzheimer disease is a complex process, and it is highly improbable that we will find a single therapy that is likely to produce a large clinical benefit. There will be no penicillin for Alzheimer disease. The possibility of an effective tau therapy might demonstrate a more prominent clinical benefit due to the tighter correlation between the deposition of tau and clinical features, but these therapies are in their infancy. Ultimately, this complex disease will require combination therapy with one or more treatments for each element of the amyloid and tau processes coupled with therapies for other elements of the process such as inflammation in addition to symptomatic treatments. The bottom line is that we may be expecting too much of a clinical impact by any single Alzheimer disease therapeutic agent. This is not meant to argue for a lower standard for treatment of Alzheimer disease but may reflect the reality of this complex disease process. Combination therapy has become a standard in some cancers, hypertension, and human immunodeficiency virus–acquired immunodeficiency syndrome; we will likely be faced with a similar situation in treating Alzheimer disease.

The patient’s voice needs to be considered in this debate. By definition, persons with MCI have the capacity to participate in the decision-making process, and we need to hear them. Our 68-year-old woman deserves the
opportunity to participate in the decision. The clinical data with regard to aducanumab are equivocal and must be validated. The uncertain clinical benefit should be combined with a discussion of the clinical impact of other monoclonal antibodies under investigation for Alzheimer disease. The aggregate of these data suggests a modest clinical benefit that should be included in the discussion. The impact of potential ARIA ought to be considered in the conversation as well, and the entire objective picture needs to be discussed with the patient. Clinicians should avoid being too patronizing toward the patients and consider the clinical impact of the untreated fatal disease when discussing the politically charged environment. Monoclonal antibodies such as aducanumab likely constitute the initial phases of the development of disease-modifying therapies for Alzheimer disease. Tacrine was questionably effective as a symptomatic therapy for Alzheimer disease and had a short half-life on the market, but it opened this area of investigation, which led to the development of better therapies. The field is convinced that better therapies will evolve; allowing patients to participate in this early decision-making process will be beneficial for them and the field.

**Potential Conflicts of Interest**

R.C.P. reports grants from the National Institute on Aging (U01 AG006786, P30 AG062677) and the Alzheimer’s Association Zenith Award, and personal fees from Merck, Biogen, and Roche, and has served on a data monitoring committee for Genentech.

**References**

1. Moghavem N, Henderson VW, Greicius MD. Medicare should not cover aducanumab as a treatment for Alzheimer’s disease. Ann Neurol 2021;90:331–333.
2. Dunn B, Stein P, Cavazzoni P. Approval of aducanumab for Alzheimer disease—the FDA’s perspective. JAMA Intern Med (in press). 2021; https://doi.org/10.1001/JAMAINTERNALMED.2021.4607.
3. Jaffe S. US FDA defends approval of Alzheimer’s disease drug. Lancet 2021;398:12.
4. Mintun MA, Lo AC, Duggan Evans C, et al. Donanemab in early Alzheimer’s disease. N Engl J Med 2021;384:1691–1704.
5. Jack CR Jr, Bennett DA, Blennow K, et al. NIA-AA research framework: toward a biological definition of Alzheimer’s disease. Alzheimers Dement 2018;14:535–562.
6. Dubois B, Villain N, Frisoni GB, et al. Clinical diagnosis of Alzheimer’s disease: recommendations of the International Working Group. Lancet Neurol 2021;20:484–496.
7. Rowe CC, Ellis KA, Rimajova M, et al. Amyloid imaging results from the Australian Imaging, Biomarkers and Lifestyle (AIBL) study of aging. Neurobiol Aging 2010;31:1275–1283.
8. Rabinovici GD. Controversy and Progress in Alzheimer’s disease—FDA approval of aducanumab. N Engl J Med (in press). 2021; https://doi.org/10.1056/NEJMp2111320.