Alzheimer's and Aducanumab:
Unjust Profits and False Hopes

by LEONARD M. FLECK

The U.S. Food and Drug Administration's decision to approve use of aducanumab for the treatment of Alzheimer's disease has generated at least three major ethical issues that need to be recognized and addressed: Medicare resources (which is to say, taxpayer dollars) are at risk of being unjustly squandered, physicians are being placed in the position of choosing between facilitating this unjust squandering and denying desperate patients and families access to this drug, and patients and families are having false (sometimes costly) hopes legitimated and encouraged when physicians give them access to aducanumab.

First, some background. A phase I trial of aducanumab had very promising results, so promising that Biogen, the company that had developed the drug, initiated two phase III trials, known as ENGAGE (301) and EMERGE (302). ENGAGE yielded negative results, however, and EMERGE yielded somewhat positive results. The trials were not actually completed because Biogen concluded that they were not justified by the meager results. Shortly thereafter, though, Biogen researchers took another look at ENGAGE and concluded that the negative data were flawed because the trial included high-dose "rapid progressors"—people whose disease progressed rapidly for whom the drug was not expected to work. If the rapid progressors were excluded from the trial data, the trial looked a bit positive. This motivated Biogen to seek FDA approval.

Had the drug been proven effective? The short answer is that no one really knows. Most researchers will tell you there is no justification for relying upon the sort of post hoc analysis that altered the ENGAGE result.[1] And why did it still show only slightly positive results? One clear fact is that aducanumab reduces β-amyloid plaque in the brain significantly. Other drugs for Alzheimer's have been able to do that as well. What matters is the clinical outcome. Did aducanumab halt or reverse cognitive decline in these patients? Not obviously, and clearly not by much. In the high-dose EMERGE group, the absolute gain (compared to placebo) was 0.39 on an 18-point scale used to assess cognitive function.[2] Most researchers would judge a gain of 1 or 2 points to be clinically significant. This result is far below that minimal standard.

I will spare the reader the complex statistical analysis that yields the conclusion that this drug is minimally effective at best in some patients with mild cognitive impairment. Instead, consider what patients and researchers are saying about the drug. At the positive end there is Phil Gutis, who developed early-stage Alzheimer's at age fifty-four, has been on aducanumab for five years through a clinical trial, and reports, "There was just a fogginess I remember having a couple years ago that I don't really feel I have now."[3] But other patients are quoted as saying that they did not really feel that the drug had made much of a difference. Various advocates for approving aducanumab concede that the trial data is "far from perfect," as Stephen Salloway, director of neurology and the Memory and Aging Program at Butler Hospital in Providence, Rhode Island, put it. But Salloway defends aducanumab on grounds of its novelty: "To get the best in class, you have to have first in class."[4] Is that sufficient justification for FDA approval?[5]

At present, 6.2 million Americans have been diagnosed with some degree of Alzheimer's dementia, with projec-

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Prescribing aducanumab would represent a substantial injustice: profits for Biogen and its stockholders, illusory benefits for patients.

tions to 2050 of more than doubling this number. Roughly half of them are diagnosed as being in the mild stage. This is the patient group that is supposed to have the greatest likelihood of deriving some benefit from aducanumab. No one is claiming that this drug has any degree of effectiveness for any patient in more advanced stages of the disease. More importantly, these patients are desperate for anything that might positively alter the direction of this mind-destroying disease process. Nothing else is out there that can promise what aducanumab seems to promise. Some people conclude from these facts that a just and caring society must make this drug available to all these patients. But this is the wrong conclusion, for the three reasons I suggested at the beginning of this essay. Let's consider those reasons more carefully.

Biogen has announced that the price of this drug, which is given by monthly infusion, would be $56,000. This is cheaper than some new drugs—only 30 percent of what most of the new targeted cancer drugs cost. However, at least 3.1 million Americans would be candidates for it. The vast majority of these patients would be older and covered by Medicare, whose projected expenditures for 2021 are a little over $900 billion.[6] If all 3.1 million of those individuals had that drug paid for, either by Medicare or some private insurer, the total cost would be $174 billion per year. And that is just the beginning of the expenses, since the drug is given by infusion. In addition, 40 percent of patients on the high dose of the drug (the dose that Biogen believes is most efficacious) are at risk for brain swelling or small-vessel brain bleeds. It is estimated that infusion costs and brain scans will add $30,000 per patient for the first year and half that for every year thereafter.[7] That represents an additional $93 billion in health care costs.[8] If the drug reversed and cured Alzheimer's, it would make ethical and economic sense to fully fund access to it, in my view. But it does not do that.

The large majority of researchers who have looked at the two trials conclude that it is highly uncertain that aducanumab will have even a marginal benefit for the vast majority of patients.[9] These researchers argue that a third clinical trial needs to be undertaken. It would take four to six years to get reliable results, and critics of this proposal argue that the delay would be inhumane and unjust to patients, who would be denied the alleged potential benefits of aducanumab and progress to later stages of Alzheimer's. This is an argument with emotional appeal but ethical disingenuousness. These patients could be on aducanumab for five years or longer, which means the size of the cohort increases each year, at a cost of more than $250 billion per year. Some fraction of those patients will have disease progression each year, and they will probably not be taken off the drug. Champions of the drug are likely to argue that the patients would progress even more quickly without it, and how could that argument be resisted when evidence to the contrary would be lacking and clinicians are looking into the eyes of desperate patients and families? The flip side of this point is that 29.5 percent of patients identified as having mild cognitive impairment will not progress to Alzheimer's proper, though they are part of the intended patient population for this drug.[10] In other words, their disease will not progress whether they are on the drug or not.

Overall, prescribing aducanumab represents a substantial and unjustifiable waste of health care resources. More precisely, it would represent a substantial injustice: profits for Biogen and its stockholders, illusory benefits for patients.[11]

Our second ethical problem pertains to professional ethics for physicians in the clinic. A number of them are quoted in the popular press as saying that they consider the evidence for aducanumab to be weak, but, like David Knopman, a neurologist at the Mayo Clinic who helped run one of the trials, they would tell their patients about their reservations but would feel ethically compelled to offer it.[12] But patients may not be able to weigh the evidence. Knopman described one conversation he had with a patient and her husband: "I presented the data . . . , and they didn't hear a word I said about my concerns. All they heard was that there might be a benefit."[13]

Why would physicians feel ethically compelled to provide access to aducanumab? One answer would be respect for patient autonomy. Physicians very familiar with the research on aducanumab have said that the risks of brain swelling and small brain bleeds far exceed any known or likely benefits associated with this drug. Still, the typical ethics argument goes, patients have to make their own assessment of the risks and benefits. The FDA's stamp of approval will encourage them to see aducanumab as safe and effective, of course. However, physicians have an additional ethical consideration to reflect upon. The Code of Ethics for the American College of Physicians holds that physicians are ethically obligated to make just and prudent uses of health care resources. They are expected to be parsimonious in their use of such care resources.[14] And there is nothing just or prudent about potentially wasting hundreds of billions of dollars over several years on a drug with no proven benefit, only an alleged benefit. Further, respect for patient autonomy does not warrant granting patients anything and everything that they believe might provide a medical benefit for them, regardless of social cost.

That brings us to the third point. The FDA, physicians who decide to prescribe aducanumab, and the Alzheimer's

Association (which vigorously campaigned for approval of aducanumab) are in all likelihood providing desperate patients with false hopes. This is neither kind nor just.[15] What can be done?

The FDA is requiring Biogen to do a phase IV trial of the drug. This will take years, and recruiting patients to participate in such a trial will be very difficult. In the past, pharmaceutical companies given similar requirements had only spotty success in completing such trials. And Biogen is poorly motivated to complete such a trial in a timely manner; if it is reaping tens of billions of dollars in profits while the trial is under way, and if it has any fear that the trial's results will be undesirable and unprofitable, then why would it press ahead with a trial?

I believe that this state of affairs can still be remedied, though it will require strong political support, federal action, and maybe judicial action. Biogen should be required to provide aducanumab at the pure cost of producing the drug plus a maximum profit of 5 percent. In other words, no research costs, no overhead, no marketing costs, nothing except the actual factory costs of producing the drug and this modest profit would be allowed. This would likely yield a number somewhere between $2,500 and $5,000 for a one-year supply of the drug for each patient. This represents reasonable reimbursement, given the uncertainty around the safety and effectiveness of aducanumab. Medicare is forbidden by law to refuse to approve a drug that is safe and effective because of the price of the drug. However, aducanumab clearly has safety issues (indeed, many clinicians, such as Knopman, would judge that the risks outweigh the likely benefits). In addition, its actual effectiveness is uncertain. That would justify Medicare's implementing my proposal. Pharmaceutical companies would object in court, which is why judicial review would likely be necessary.

The virtue of this proposal is that it gives Biogen an incentive to complete the phase IV trial quickly, because the company would be entitled to that $56,000 price only if that trial establishes that the drug yields enough benefit to justify that price. This approach allows desperate patients and families to have access to the drug at a reasonable societal cost. Physicians can prescribe it with a just-enough conscience and respect for the need to provide health care parsimoniously. If Biogen objects to the ticking of the patent clock during this reduced-payment phase, those years could be restored, assuming the drug is effective. We might still recognize this as wasteful health care spending, but maybe this is the best nonideal resolution we can achieve, given competing pressures from intense patient demands and the need for the just and prudent allocation of limited health care resources. In addition, it would set an important precedent for comparable drugs in the pipeline. Other pharmaceutical companies could expect the same crimped profits (and potential revenue losses from accrued research expenses) if they could not prove decisively that their drug yielded substantial clinical benefit at a reasonable cost. This would be unforgettable tough love.

1. G. C. Alexander, S. Emerson, and A. S. Kesselheim, "Evaluation of Aducanumab for Alzheimer Disease: Scientific Evidence and Regulatory Review Involving Efficacy, Safety, and Futility," *Journal of the American Medical Association* 325 (2021): 1717-18.

2. Ibid., 1717.

3. L. McGinley, "Alzheimer's Drug Sparks Emotional Battle as FDA Nears Deadline on Whether to Approve," *Washington Post*, May 31, 2021.

4. Ibid.

5. However, DeWayne Nash, seventy-one, was in the placebo group for eighteen months in one of these trials and reported that his cognitive scores improved on the placebo. P. Belluck and R. Robbins, "Alzheimer's Drug Poses a Dilemma for the F.D.A.," *New York Times*, June 5, 2021.

6. S. P. Keehan et al., "National Health Expenditure Projections, 2019-28: Expected Rebound in Prices Drives Rising Spending Growth," *Health Affairs* 39, no. 4 (2020): 704-14.

7. The brain scans are necessary for the initial diagnosis, for regular follow-up, and for monitoring of serious side effects.

8. P. Belluck and R. Robbins, "F.D.A. Approves Alzheimer's Drug Despite Fierce Debate over Whether It Works," *New York Times*, June 7, 2021.

9. The Institute for Clinical and Economic Review states, "Our review of the evidence was concordant with that of many independent experts: current evidence is insufficient to demonstrate that aducanumab benefits patients." Institute for Clinical and Economic Review, "ICER Issues Statement on the FDA's approval of Aducanumab for Alzheimer's Disease," June 7, 2021, https://icer.org/news-insights/press-releases/icer-issues-statement-on-the-fdas-approval-of-aducanumab-for-alzheimers-disease/.

10. "Half of Alzheimer's Disease Cases May Be Mild," National Institute on Aging, March 18, 2021, https://www.nia.nih.gov/news/half-alzheimers-disease-cases-may-be-mild.

11. Many preventive drugs for which reimbursement is provided are known not to benefit everyone to whom they are prescribed; it is enough that they might benefit some patients. The problem with aducanumab is that it might not significantly benefit *anyone*. One FDA Advisory Committee member, who resigned following the FDA's decision to approve aducanumab, said, "Biomarker justification [β-amyloid reduction] for approval in the absence of consistent clinical benefit after 18 months of treatment is indefensible." P. Belluck and R. Robbins, "Three F.D.A. Advisers Resign over Agency's Approval of Alzheimer Drug," *New York Times*, June 11, 2021.

12. Belluck and Robbins, "Alzheimer's Drug Poses a Dilemma for the F.D.A."

13. Belluck and Robbins, "F.D.A. Approves Alzheimer's Drug Despite Fierce Debate over Whether It Works."

14. L. S. Snyder and T. A. Bledsoe for the ACP Ethics, Professionalism and Human Rights Committee, "American College of Physicians Ethics Manual," 7th ed., supplement, *Annals of Internal Medicine* 170, no. 2 (2019): S1-S32, especially S19-S20.

15. M. Eijkholt, "Medicine's Collision with False Hope: The False Hope Harms (FHH) Argument," *Bioethics* 34, no. 7 (2020): 703-11.