PATIENTS RISING NOW

May 25, 2021

Steven D. Pearson, MD, MSc, FRCP
President, Institute for Clinical and Economic Review
One State Street, Suite 1050
Boston, MA 02109 USA

RE: Draft Evidence Report "Aducanumab for Alzheimer's Disease: Effectiveness and Value"

Dear Dr. Pearson:

Patients Rising Now advocates for patients with serious and chronic conditions to have access to life-improving and life-saving therapies and services. Access to such treatments and services is essential for them and their families. Importantly, such access spans affordability, insurance coverage, physical access, and in the case of Alzheimer's Disease, access to hope that every incremental improvement will be followed by larger advances in the future. For families of people with Alzheimer's like mine, that hope is not just about direct benefits to the person who has Alzheimer's, or the reduced burden on their caregivers, but also hope that as they age, there will be better treatments, ways to prevent Alzheimer's, or even a cure.

To support improved access, we are committed to engaging patients, caregivers, clinicians, media, health policy experts, payers, providers, and others to foster people-centered discussions about the entire U.S. health care system. That is, our goal is a balanced dialogue that illuminates the truth about health care innovations and advancements in a just and equitable way.

As the draft report's introductory discussion of patient and caregiver perspectives indicates, Alzheimer's is a horrible disease. I also know this from first-hand experience. Over the past decade, the death rate from Alzheimer's has climbed.[i] Alzheimer's is endemic, and U.S. society has habituated to this disease as a way of life – or more accurately, as part of the end of life for many people. Unfortunately, it is becoming so common that it likely has touched most Americans directly or indirectly. That reality is the lens through which new treatments for Alzheimer's should be viewed and valued by all sectors of society.

We include the above comments to help frame our views, because several things described in the draft report are not new, including the significant number of potential treatments for Alzheimer's that have found to not be beneficial in clinical testing,[ii] and the related finding that the assumption that beta-amyloid is the root cause of Alzheimer's is now seriously questioned.[iii] Is Alzheimer's caused by the amyloid itself? Is it the tau protein tangles? Is it a combination of the two? Is it something else that also results in the amyloid plagues or tau protein tangles, i.e., are they signs but not causative? Despite all that uncertainty, as of February 2020 there were over 100 compounds in clinical development based on different biological mechanisms of action.[iv] Hopefully some of them will both prove to be effective treatments and help illuminate the underlying pathological mechanisms causing Alzheimer's.

Given the evolving uncertainty as to the underlying disease mechanisms leading to Alzheimer's

and its progression, it is not too surprising that past treatment prospects have failed. Which brings us to aducanumab. Unlike some other potential breakthrough treatments – such as gene therapies or treatments that replace gene functions, where the impact and effectiveness can be very dramatic – as discussed in the draft report, what was seen in the aducanumab clinical trials was subtle, with the results initially not seen as positive, leading to the trials being stopped for "futility."[v] In the subsequent extensive review of the data from the trials, there does seem to have been some clinical benefit – albeit not consistent across the two Phase 3 trials. As the draft report notes, at the current time the totality of the data may be considered inconclusive. We also note that the data uncertainty and post-hoc analyses led to some controversy about the FDA advisory committee's decision, with an apparent split between the FDA's panel, outside patient advocates, and perhaps even between FDA officials.[vi] This unusual situation also appears to have led to the initiation of another follow-on study of aducanumab[vii] to try and elucidate clinical benefits over a longer period.

Thus, the situation with aducanumab is both very unusual and murky: Clinical trials terminated because of a belief the treatment didn't work; post-hoc analyses potentially reversing that conclusion; and scientists and patients coming down on opposite sides about the entire situation. Which leads us to ICER now weighing in about an experimental compound about which the FDA has yet to make any decisions.

It is within that context that we provide our comments on ICER's May 5th Draft Evidence Report "Aducanumab for Alzheimer's Disease: Effectiveness and Value." Our comments about the draft report are organized below into sections about People, Caregiver and Society-Centered Perspectives; Uncertainties and Assumptions; and Additional Points.

People, Caregiver and Society-Centered Perspectives

Alzheimer's Disease (AD) is an insidious, slowly progressing, horrible disease for patients, caregivers, family, friends and society. That point bears repeating. And from a societal perspective, Alzheimer's is common and very costly, with disproportionate burdens for women and people of color. As the draft report states, without effective disease-altering therapies, "[t]reatment of AD remains largely supportive, including creation and implementation of individualized dementia care plans (e.g., treatment of dementia symptoms, medication and home safety assessments, advance care planning), caregiver education and support, care navigation, care coordination, and referral to community-based organizations for services (e.g., adult day care, caregiver training, etc.)."[viii]

Moving forward, the goal is better treatments. However, it needs to be recognized that hitting a major league home run during the first at-bat is extremely rare in biomedical research. Much more common is a series of progressive improvements – often utilizing one mechanism of action, and then another, and then combinations. This has been seen with treating HIV infections and in oncology, and perhaps the best comparison for Alzheimer's is autoimmune diseases like rheumatoid arthritis, where over the course of many years, treatments progressed from solely relieving symptoms to treatments that modified – or halted – progression of the disease. And then subsequent disease-modifying treatment options were developed that were more effective with reduced side effects.

Given the tremendous societal impact of Alzheimer's, we were shocked to note the draft report's failure to conduct a Benefit Price Benchmark analysis from the societal perspective – which the draft report already recognized in the Long-Term Cost Effectiveness section's threshold analysis.[ix] This rather obvious omission is cause for concern and casts confusion and doubt on all the processes that ICER may have in place to undertake such reviews.

Finally, we would like to point out that in the clinical trials of aducanumab – as has been the case with many other potential treatments for Alzheimer's – a major focus has been on quantifying amyloid plaques, which may be because of the presumed central role of beta-amyloid as the cause of Alzheimer's. Of course, amyloid plaques are easier to measure than patients' memory and other cognitive capabilities. The problem with that analytical dichotomy is that it potentially drives research into new treatments toward treating amyloid plaques rather than the actual care and treatment of people with Alzheimer's. Therefore, we urge ICER to encourage researchers to pursue more robust patient function factors in their future work.

Uncertainties and Assumptions

The uncertainties in the underlying information – and biology and pathology of Alzheimer's – as discussed in the draft report are voluminous. Therefore, the extent of the assumptions that the draft report includes brings into serious question the utility of the draft report's quantitative conclusions.

However, we do find that there is one set of connected analyses in the draft report that is very illuminating – namely, the clinical benefits of aducanumab and ICER's potential budget impact analysis. **Specifically, the draft report makes it very clear that under ICER's "framework," the more effective a treatment is, the fewer people should receive it to avoid exceeding ICER's affordability definition.** This ethical paradox occurs because under ICER's cost effectiveness methodology, the more clinically effective a treatment is (i.e., increased QALYs), a higher price can then be justified (which is consistent with value-based pricing or reimbursement). But then, because of ICER's budget impact analysis scheme, each dose at that higher price should be given to fewer people to stay under ICER's artificial total spending limit. If ICER's budget impact formula were applied to the current COVID-19 vaccines – assuming that we wanted to vaccinate everyone in one year, rather than the five years ICER usually allows for its analysis – then the "acceptable cost" per dose of vaccine would be about $2.48 per vaccinated person, or $1.24 per dose for vaccines given as two shots.[x] If the federal government had used ICER-like calculations to help drive development of the COVID-19 vaccines (which were pre-purchased from several companies, including some where the government provided up-front payments to support and accelerate development and production), then it is likely we would still be waiting for vaccines.[xi]

Once again, the fallacy of ICER's Budget Impact analysis is exposed. The actual societal benefit of an effective treatment for Alzheimer's would be ***huge*** – and by ICER's own methodology, the more effective a medicine is then the higher the price that could be justified. **But under ICER's value assessment methodology, because of budgetary concerns, the more effective a treatment is, the fewer people should get it. That is the essence of ICER's moral stance on how to manage access to health care in the United States.**

On a related note, we also want to point out that prices for first treatment options for a disease sets the landscape for incentives for developing future treatments. That is, the price for the first treatment available – and any access or patient affordability restrictions – provides ongoing incentives (or disincentives) for development of future treatments. In the current situation, aducanumab might be the proverbial camel's nose under the edge of the tent; if the price that ICER – or others, such as actual health care payers or providers – determines to be "fair" is below a threshold the company needs to be able to practically manufacture and distribute a sterile biologic medicine after approval by the FDA, then it will be a missed opportunity with numerous negative repercussions.

Additional Points

- We note that the placeholder price of $50,000 was based on a news article referencing another source, and that source's analysis was conducted prior to the FDA's advisory committee meeting, vote, and subsequent controversy.[xii]
- The supplemental materials about the methodology for the Budget Impact Analysis state that the formula is based upon "the average number of new drug approvals by the FDA over the most recent two-year period." However, looking at the ICER's website, it seems that ICER's methodology uses a five-year period (2014-2018) rather than a two-year period.[xiii] This also raises the question about why ICER has not updated this information using the FDA's data for approvals in 2019 and 2020,[xiv] which would produce an annual average number of approvals of 54.6 (rather than the 42.6 for 2014-2018), resulting in a lower threshold for ICER's acceptable budget impact analysis.

Conclusions

Alzheimer's is an insidious, slowly progressing, horrible disease for patients, caregivers, family, friends, and society.

The goal for researchers and clinicians – and hope for patients – is to have effective, safe, and easy-to-administer treatments for Alzheimer's disease. But like almost everything in biomedical research, achieving that goal will likely have to proceed through less effective treatments that have side effects and may not be so easy to access – such as requiring infusions rather than swallowing a pill. However, if those first steps are not taken, then the journey is never made and the status quo of watching, and waiting, and withering of minds and spirits will continue. Therefore, we are very concerned that ICER's draft report will impair or delay development of other potential treatments for Alzheimer's Disease.

Sincerely,

Terry M. Wilcox

Terry Wilcox
Co-Founder & Executive Director, Patients Rising Now

[i] " 2021 ALZHEIMER'S DISEASE FACTS AND FIGURES," https://www.alz.org/media/documents/alzheimers-facts-and-figures.pdf

[ii] The draft report notes on page 17 that "EMERGE [one of the trials of aducanumab] is the first late-stage clinical trial of drugs targeting removal of amyloid—out of more than 25 randomized controlled trials examining such therapies—to show clinical efficacy."

[iii] As ICER's draft report notes on page 17, there have been 25 other failed late-stage clinical trials that targeted removal of amyloid.

[iv] "Alzheimer's disease drug development pipeline: 2020," [Review of ClinicalTrials.gov as of February 27, 2020], https://alz-journals.onlinelibrary.wiley.com/doi/10.1002/trc2.12050; and "Alzheimer's treatments: What's on the horizon?," Mayo Clinic, May 20,2021 https://www.mayoclinic.org/diseases-conditions/alzheimers-disease/in-depth/alzheimers-treatments/art-20047780

[v] Draft report, p 8

[vi] "The Most Promising Alzheimer's Drug in Years Took a Thrashing From an FDA Advisory Committee," Time, November 10, 2020 (https://time.com/5908589/alzheimers-drug-biogen-fda-committee/); "FDA advisers tear apart case for Biogen's Alzheimer's drug aducanumab ahead of final decision," Fierce Biotech, April 1, 2021 (https://www.fiercebiotech.com/biotech/fda-advisers-tear-apart-case-for-biogen-s-alzheimer-s-drug-aducanumab-ahead-final-decision)

[vii] EMBARK trial started in March 2021 - "open-label, single arm EMBARK study is enrolling Alzheimer's patients who participated in any of four aducanumab clinical studies terminated in March 2019"Ð'd"24-month open-label treatment phase in which all participants are titrated to a target dose of 10 mg/kg of aducanumab — the highest dose tested in the phase III trials — every four weeks intravenously, then 18 weeks of additional follow-up." ClinicalTrials.gov Identifier: NCT04241068 (https://clinicaltrials.gov/ct2/show/NCT04241068); "Biogen launches new trial of Alzheimer's drug," Aducanumab, McKnight's Long-Term Care News, April 29, 2021 (https://www.mcknights.com/news/clinical-news/biogen-launches-new-trial-of-alzheimers-drug-aducanumab/)

[viii] Draft report, p 2

[ix] Draft report, p 29

[x] ICER's budget impact threshold is $819 million [using FDA approvals for 2014-2018], and there are about 330 million people in the United States, so $819/330 = $2.48.

[xi] The U.S. government is paying $15/dose for the Moderna vaccine, $19.50/dose for the Pfizer-BioNtech vaccine (which did not receive any up front funding), and $10/dose for the Johnson & Johnson vaccine. https://www.managedhealthcareexecutive.com/view/the-price-tags-on-the-covid-19-vaccines

[xii] "Cowen estimates that 2.2 million Americans have mild dementia due to Alzheimer's disease. If one-third of these people were treated with aducanumab, priced at an estimated $50,000 per year, sales would reach $36 billion annually, according to the health care investment bank." https://www.statnews.com/2020/11/04/fda-scientists-appear-to-offer-major-endorsement-of-biogens-controversial-alzheimers-treatment/

[xiii] https://icer.org/our-approach/methods-process/value-assessment-framework/

[xiv] https://www.fda.gov/drugs/development-approval-process-drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products