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Lecanemab Is Not the Savior Drug for Alzheimer Disease

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As I set out to pen the original draft of this opinion piece, its first sentence read, "lecanemab, in phase III clinical trials for Alzheimer disease (AD), appears to be on the cusp of approval by the FDA." Little did I realize just how fine the margins of that cusp would be.

Before I could finish that draft in January 2023, the FDA granted lecanemab (dubbed Leqembi) accelerated approval, a special dispensation "under which [it] may approve drugs for serious conditions where there is an unmet medical need and a drug is shown to have an effect on a surrogate endpoint that is reasonably likely to predict a clinical benefit to patients."1 Full FDA approval was granted in July 2023, to much media fanfare.

In the lead up to the initial FDA decision, excitement had been generated in late November of 2022 when scientists from Biogen and Esai, collaborators in the development of lecanemab, announced at the national Clinical Trials on Alzheimer's Disease conference in San Francisco, that they had achieved the primary endpoint of the trial, as well as key secondary endpoints in a sample of nearly 1,800 individuals diagnosed with early–stage AD. The next day, their results were published online in the prestigious New England Journal of Medicine.2 (A preview of their outcomes had been given in a September 27, 2022 press release3 intended exclusively for Biogen investors.)

Those data represented a breakthrough from all prior, essentially fruitless efforts involving dozens of molecules, more than thirty years of research, and untold millions, if not billions of dollars to develop an effective disease–modifying agent yielding meaningful benefits for AD sufferers, and by extension, to their families and caregivers.

The primary endpoint of the trial was patients' scores on the widely used Clinical Dementia Rating—

CDR—scale sums of boxes. This score represents a subjective determination by doctors regarding the extent of deterioration observed for persons with AD. Over a period of 18 months, CDR scores for those on lecanemab declined 27% more slowly than those who took placebo. The statistical probability of that difference being spurious was less than 5 in one–half million ($p = .00005$).

Sounds wonderful, right? Well, hold on.

First, to reiterate, CDR scores are subjective. The option to use the CDR as a primary endpoint was in itself somewhat controversial, reflecting a relaxation by the FDA of prior rules governing selection of endpoints, which had previously been limited to objective measures such as scores on tests of memory and the like.

Second, what does a 27% slower rate of decline actually translate to in real life? The range of scores on the CDR extends from 0—reflecting fully intact cognition and ability to engage in activities of daily living, to 18—total incapacitation. A CDR score of 0.5 reflects the presence of objective cognitive decline without functional impact; these patients remain independent in activities of daily living, equivalent to a diagnosis of mild cognitive impairment, or MCI. The range of scores observed in the study participants was far narrower—from 0.5 to 8.5, reflecting the fact that the study participants were mostly in the milder stages of the disease.

To put that into perspective, let's begin with the observation that the lecanemab and placebo groups each started the trial with CDR scores of about 3.2. At the end of the 18-month trial, the score for the folks on lecanemab worsened to 4.41 (remember that higher scores reflect greater impairment), whereas the placebo group dropped to 4.86. That 27% difference in CDR score equates to a difference of less than one–half point on a measure with a maximum score of 18. One would be hard-pressed to distinguish a hypothetical patient functioning at a CDR score of 4.41 from one scoring 4.86. There is a gulf of difference between findings which are statistically significant versus those which are clinically meaningful. Yet, this was the principle finding that provoked the accelerated approval by FDA.

Then there's the side-effects profile of lecanemab. This molecule is the latest in a series of monoclonal antibodies (MA) that bind to a segment of the misfolded amyloid-beta (Aβ) protein, one of the hallmarks of AD pathology, thereby neutralizing it and allowing for its clearance from the brain. All such AβMA have come with risks: cerebral edema as well as brain bleeds, ranging from microhemorrhages to large-vessel stroke, with some cases resulting in death. Collectively, the cerebral changes induced by AβMA as observed on radiologic studies are referred to as amyloid-related imaging abnormalities (ARIA). Two types of ARIA are recognized: edema is labeled ARIA-E, hemorrhage is ARIA-H.

Of the patients on lecanemab, 12.5% showed evidence of ARIA-E on brain imaging, although most had a mild form. While that is an improvement over aducanumab (Aduhelm, also Biogen), another MA approved controversially by FDA in June of 2021, it is still far from trivial. Further parsing of the lecanemab data shows adverse events occurred substantially more often among those with one or two copies of apolipoprotein E epsilon 4 allele (APOE4), the variant that confers the greatest risk of developing sporadic, late-onset AD. People who are heterozygous for APOE4 are about 4 to 5 times more likely to develop AD than those without APOE4; people who are homozygous have about a 10–fold higher risk. Thus, APOE4 carriers clearly have the greatest need for lecanemab. But that comes at a cost of the risk of worsening a recipient's brain status through ARIA, even beyond the ravages of Alzheimer disease itself. Moreover, Esai-Biogen came under some scrutiny in late 2022 for the manner in which it represented the adverse effects of lecanemab, particularly among study participants taking anticoagulant medication, thereby increasing their risk of cerebral hemorrhage—ARIA-H.4

Finally, there's the financial burden of the drug. Esai originally revealed that it would set the price for lecanumab at an eye-watering $26,500 per year. That figure is comparable to the average annual cost of $28,000 for aducanemab, which was a 50% reduction announced by Biogen in January 2022 in response to criticism over its expense. Because lecanumab is not covered by Medicare, out-of-pocket payment will undoubtedly be prohibitive for most, particularly when everyday disease-related expenses for AD sufferers are already extremely pressing.

The Department of Veterans Affairs, in a stunning move, decided to place aducanemab on its formulary. VA has not yet done the same for lecanumab, although it would seem reasonable to expect that to occur at some point. According to the 2020 US Census, people aged 65 or older make up 16.8% of the US population, about 55.8 million citizens. The proportion of this age group is projected to grow to 21% of the general population by 2040. As of 2021, military veterans made up about 8.1 million of those 65 or older, or about 14.5% of people 65 or older. Thus, in effect, more than 85% of elders will need to rely on private insurance or out-of-pocket payment for treatment with an AβMA. So, when I discuss the risk: benefit calculus with my patients, many demure, for good reason.

The numbers suggest lecanemab is a step forward in the war against a cruel, intransigent disease, one that ultimately robs those affected of their identity, and families of the steady presence of their loved ones. But with lecanemab, the devil is clearly in the details. All who are touched by Alzheimer disease are desperate for answers. Sadly, lecanemab simply is not it.

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