EDITORIAL

FDA's green light, science's red light

Alzheimer's disease (AD) afflicts some 6 million Americans with progressive cognitive impairment and personal anguish while imposing a huge economic burden on society. Everyone wants to find a way to help slow or even halt this disease. But there will be no quick fix. Responding to mounting pressure, the United States Food and Drug Administration (FDA) jumped the gun by granting accelerated approval this month to Biogen's pricey, questionably effective, and possibly harmful new drug aducanumab—a decision supported by not one of the 11 members of the agency's Expert Advisory Committee. Even worse, the approval may divert funding into a therapeutic dead end and away from approaches that might actually work.

As a member of this advisory committee, who resigned in protest over the decision to grant approval, I am still trying to fathom how this happened. No doubt, the FDA faced a difficult decision. The public pressure must have been immense, and the influence of industry on the FDA in general has been a growing concern. Any trickle of hope about this drug has been magnified far beyond the facts. The Alzheimer's Association has pushed this bandwagon and already stated that aducanumab "demonstrates that removing amyloid from the brain may delay clinical decline in people living with Alzheimer's." The science does not support such a delay.

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There is a scientific basis for trying to develop this type of drug. Rare genetic forms of AD caused by mutations result in early-onset dementia related to substantial brain deposition of amyloid-β or tau protein. Yet, most people with AD do not suffer from a genetic form. Rather, sporadic forms feature early deposition of abnormal amyloid-β long before cognitive problems arise and later develop abnormal deposition of tau that more closely coincides with cognitive impairment. Many studies investigating drugs designed to clear abnormal brain amyloid-β in people with sporadic AD failed to demonstrate clinical benefit (the alleviation of symptoms).

Despite these bad odds, a drug targeting amyloid-β was presented for approval to the FDA. On 6 November 2020, our FDA advisory committee reviewed Biogen's application for aducanumab, primarily on the basis of a two-part study that had been stopped early because of futility—the chances of clinical benefit were very small if the study continued to the planned conclusion.

But then, the data were reanalyzed and Biogen proposed that because one part of the study was positive, though the other was not, that was sufficient for FDA approval. Never mind that the side effects of the proposed dose included localized brain swelling in 35% of clinical trial participants and microhemorrhages in 20%.

When all this was put to a vote by the advisory committee, 10 voted no, 1 voted uncertain, and no one voted yes.

And yet, the FDA granted accelerated approval of aducanumab for treatment of AD, merely requiring Biogen to do a prospective study over the next 9 years to confirm if there is some clinical benefit. Even worse, the FDA changed the standard for determining this benefit from clinical evidence that the drug actually helps to evidence that the drug simply reduced brain amyloid-β.

Although all of this may be well and good for Biogen with a potential $56 billion dollars for the first year of treatment in 1 million people with AD, this decision may impair future research into better treatments for AD. Studies may be required to compare a new drug with aducanumab rather than placebo, which could potentially bias the research. Furthermore, enthusiasm from potential volunteer participants or funders for new treatments may wane owing to the false belief that effective treatment already exists. And, the matter of economics cannot be overlooked. The billions of dollars spent on aducanumab may be better invested in developing stronger evidence for aducanumab or alternative therapies. These potentially serious issues could delay investigation and implementation of a truly effective therapy for AD.

The FDA and the advisory committee have a responsibility to help protect vulnerable patients and their families, not just from sketchy drugs but also from false hopes. That can mean making hard decisions that disappoint them in the short term to increase the chances of ultimately finding drugs that work.

–Joel S. Perlmutter

PHOTO: MONICA PERLMUTTER

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