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"May the words of my mouth and the meditation of my heart be pleasing in your sight, O Lord, my Rock and my Redeemer." Psalm 19:14

Editorial

FDA Approval of Aduhelm for Alzheimer's Disease is the Wrong Decision!

Very few other medical challenges create the level of fear among patients and their families as a diagnosis or probability of Alzheimer's disease. As one who has written, spoken, and celebrated the development of important new therapeutic agents for more than 50 years, I would be delighted to be describing the benefit and value of a highly effective treatment for this devastating condition. Aducanumab (Aduhelm) is NOT that drug. At best, the FDA decision to approve this drug for the treatment of Alzheimer's disease is greatly premature!

The drugs that have been previously approved for the treatment of patients with Alzheimer's disease include the cholinesterase inhibitors such as donepezil (e.g., Aricept) and the N-methyl-D-aspartate (NMDA) receptor antagonist memantine (e.g., Namenda). Unfortunately, the clinical benefit of these agents is very limited. Progress has been made in identifying pathophysiologic features of Alzheimer's disease, although uncertainties and differences of opinion persist among the experts regarding the importance of these characteristics and potential treatments. The identification of accumulated amyloid beta plaques in the brains of patients with Alzheimer's disease has resulted in investigations of agents that reduce the number of these plaques. However, to date, studies of these investigational agents have failed to demonstrate clinical effectiveness, with the consequence that the studies have been discontinued.

Aducanumab

Aducanumab-avwa is a human monoclonal antibody directed against forms of amyloid beta. It was evaluated by Biogen in two placebo-controlled studies in patients with confirmed presence of amyloid pathology and mild cognitive impairment or mild dementia. There is agreement that the drug consistently reduces amyloid beta plaques in the brain in a dose- and time-dependent manner. The reduction in this surrogate marker is thought to predict clinical benefit but is not itself a measure of clinical benefit.

In both studies patients were randomized to receive aducanumab low dose, aducanumab high dose, or placebo intravenously every 4 weeks for 18 months. At a point during the trials a "futility analysis" was conducted that appeared to indicate that aducanumab was not likely to be more effective than placebo and, in March 2019, Biogen terminated both trials prior to their planned completion. In the context of previous clinical trial failures of other amyloid-targeted investigational agents, the failure of yet another agent thought to have potential benefit was very disappointing but not shocking. It is reasonable to think that, if there was *any* possibility that these studies of aducanumab would show clinical benefit in the treatment of a devastating disease, and also have the potential for many billions of dollars of revenue, Biogen would *not* have terminated the studies early.

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But this was only the first of a series of controversial decisions.

Following early termination of the clinical trials, Biogen continued to review and reanalyze the available data/results. In one of the clinical trials, no statistically significant differences on the primary efficacy endpoint were observed between the aducanumab-treated (high dose or low dose) and placebo-treated patients. However, in the other clinical trial the high dose (but not the low dose) of aducanumab was thought to reduce clinical decline, as reflected by a statistically significant treatment effect on the primary and secondary efficacy endpoints compared to placebo. Notwithstanding the failure to identify clinical benefit in one of the studies, Biogen announced in November 2019 that it would use information from its additional analysis of data from the other uncompleted study to support the development of a biological license application (BLA) to submit to the FDA.

Following receipt of Biogen's application for approval of aducanumab, the FDA convened its Peripheral and Central Nervous Systems Drugs Advisory Committee to review the information submitted and provide recommendations. The Committee met in November 2020 and voted overwhelmingly that the information reviewed did not justify approval of the drug. Although FDA officials are not required to make decisions that are consistent with the recommendations of its Advisory Committees, they usually do so and the resultant expectation that the application for approval would be rejected prompted intense publicity and lobbying in support of approval of aducanumab from patients and advocacy groups, as well as those with financial and political interests.

On June 7, 2021 the FDA announced that it approved aducanumab under the provisions of the accelerated approval process that is based on a drug's effect on a surrogate endpoint that is reasonably likely to predict a clinical benefit for patients. Because the FDA's action was not based on the demonstration of clinical benefit, it also required Biogen to conduct a post-approval trial to verify that the drug provides the expected clinical benefit. Those who support the FDA's decision say that it provides hope for and perhaps actual clinical benefit, greater and more timely access to treatment for patients with Alzheimer's disease, as well as incentives for pharmaceutical companies and investors to expand research efforts that will result in more medications that will provide effective treatment.

Critics of the decision, including this writer, contend that a clinical benefit has not been clearly demonstrated, that the FDA should have required completion of another clinical trial to verify a clinical benefit before approving the drug, that the earlier failures of multiple amyloid-targeted investigational agents to have demonstrated clinical benefit do not inspire confidence that the experience with aducanumab will be any different, that the FDA has reduced its standards for approving new drugs and also reduced the credibility of the approval process and the role of Advisory Committees, and that ready access to aducanumab will increase the difficulty in recruiting patients, who might be assigned to a placebo group, to participate in clinical trials of potential effective treatments for Alzheimer's disease. Soon after the FDA announcement, three members resigned from the Advisory Committee that had recommended against approval, with one stating that the decision was "probably the worst drug approval decision in recent U.S. history," and another indicating that the decision would undermine public trust and medical innovation.

The recommended maintenance dosage of aducanumab is 10 mg/kg administered by intravenous infusion every 4 weeks, and the anticipated cost of the medication for one year would be approximately $56,000 for each patient. An analysis conducted by the Kaiser Family Foundation estimates that if 500,000 Medicare recipients (of the approximately 6.2 million Americans with Alzheimer's disease) are prescribed aducanumab, it would cost the Medicare program nearly $29 billion a year, much more than any other medication. Some patients who are treated with the drug could have copayments of about $11,500 annually, and Medicare premiums are likely to be increased.

The FDA has the authority to approve a medication based on improvement in a surrogate marker, but I consider it unwise to reject the almost unanimous recommendation of its Advisory Committee in taking the action it did. The FDA has stated that failure of aducanumab to meet the efficacy endpoint in the post-approval trial it has required Biogen to conduct could result in removal of the drug from the market. However, I can't imagine that would happen because, even if clinical benefit is not demonstrated in the relatively small controlled clinical trial, the uncontrolled experience in the much larger number of patients for whom it can now be prescribed will become a de facto study in which some patients, caregivers, and prescribers will insist that benefit has been provided. The opposition to removing the drug from the market will be far greater than the support for approving it now.

For a drug for which the FDA provides accelerated approval based on improvement in a surrogate marker, and not clinical benefit, the experience of the patients for whom it is prescribed will be an important factor in the decision as to whether the drug will be permitted to remain on the market. A pharmaceutical company should make such a drug available without charge until the clinical benefit is demonstrated.

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New Therapeutic Agents Marketed in the United States in 2020

Generic name	Trade name (Manufacturer)	Therapeutic classification	Route of administration	FDA classification[a]	New Drug Comparison Rating[b]
Amisulpride	Barhemsys (Acacia)	Antiemetic	Intravenous	1-S	3
Artesunate	(Amivas)	Antiparasitic agent	Intravenous	1-P,O	5
Atoltivimab/maftivimab/odesivimab-ebgn	Inmazeb (Regeneron)	Antiviral agents	Intravenous	P,O[c]	5
Avapritinib	Ayvakit (Blueprint)	Antineoplastic agent	Oral	1-P,O	5
Belantamab mafodotin-blmf	Blenrep (GlaxoSmithKline)	Antineoplastic agent	Intravenous	P,O[c]	4
Bempedoic acid	Nexletol (Esperion)	Lipid-regulating agent	Oral	1-S	4
Berotralstat	Orladeyo (BioCryst)	Agent for hereditary angioedema prophylaxis	Oral	1-S,O	4
Brexucabtagene autoleucel	Tecartus (Gilead)	Antineoplastic agent	Intravenous	[d]	5
Capmatinib hydrochloride	Tabrecta (Novartis)	Antineoplastic agent	Oral	1-P,O	4
Cedazuridine/decitabine	Inqovi (Taiho)	Antineoplastic agent	Oral	1-P,O	4
Cefiderocol sulfate tosylate[e]	Fetroja (Shionogi)	Antibacterial agent	Intravenous	1-P	4
Cenobamate[e]	Xcopri (SK Life)	Antiepileptic drug	Oral	1-S	2
Eptinezumab-jjmr	Vyepti (Lundbeck)	Agent for migraine	Intravenous	S[c]	2
Fam-trastuzumab deruxtecan-nxki[e]	Enhurtu (Daiichi Sankyo)	Antineoplastic agent	Intravenous	P[c]	4
Fostemsavir tromethamine	Rukobia (Viiv)	Antiviral agent	Oral	1-P	4
Inebilizumab-cdon	Uplinza (Viela)	Agent for neuromyelitis optica spectrum disorder	Intravenous	S,O[c]	4
Isatuximab-irfc	Sarclisa (Sanofi)	Antineoplastic agent	Intravenous	S,O[c]	4
Lasmiditan hemisuccinate[e]	Reyvow (Lilly)	Agent for migraine	Oral	1-S	4
Lemborexant[e]	Dayvigo (Eisai)	Hypnotic	Oral	1-S	3
Lonafarnib	Zokinvy (Eiger)	Agent for progeria syndrome	Oral	1-P,O	5
Lumasiran sodium	Oxlumo (Alnylam)	Agent for primary hyperoxaluria type 1	Subcutaneous	1-P,O	5
Lumateperone tosylate[e]	Caplyta (Intra-Cellular)	Antipsychotic agent	Oral	1-S	2
Lurbinectidin	Zepzelca (Jazz)	Antineoplastic agent	Intravenous	1-P.O	4
Margetuximab-ckmb	Margenza (MacroGenics)	Antineoplastic agent	Intravenous	S[c]	3
Naxitamab-gqgk	Danyelza (Y-mABs)	Antineoplastic agent	Intravenous	P,O[c]	4
Nifurtimox	Lampit (Bayer)	Antiparasitic agent	Oral	1-P,O	5
Oliceridine fumarate	Olinvyk (Trevena)	Analgesic	Intravenous	1-S	2
Opicapone	Ongentys (Neurocrine)	Antiparkinson agent	Oral	1-S	3
Osilodrostat phosphate	Isturisa (Novartis)	Agent for Cushing's disease	Oral	1-S,O	4

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(cont.) New Therapeutic Agents Marketed in the United States in 2020

Generic name	Trade name (Manufacturer)	Therapeutic classification	Route of administration	FDA classification[a]	New Drug Comparison Rating[b]
Ozanimod hydrochloride	Zeposia (Celgene)	Agent for multiple sclerosis	Oral	1-S	4
Pemigatinib	Pemazyre (Incyte)	Antineoplastic agent	Oral	1-P,O	5
Pralsetinib	Gavreto (Blueprint)	Antineoplastic agent	Oral	1-P,O	4
Relugolix	Orgovyx (Myovant)	Antineoplastic agent	Oral	1-P	4
Remdesivir	Veklury (Gilead)	Antiviral agent	Intravenous	1-P	4
Rimegepant sulfate	Nurtec ODT (Biohaven)	Agent for migraine	Oral	1-S	3
Ripretinib	Qinlock (Deciphera)	Antineoplastic agent	Oral	1-P,O	4
Risdiplam	Evrysdi (Genentech)	Agent for spinal muscular atrophy	Oral	1-P,O	4
Sacituzumab govitecan-hziy	Trodelvy (Immunomedics)	Antineoplastic agent	Intravenous	P[c]	4
Satralizumab-mwge	Enspryng (Genentech)	Agent for neuromyelitis optica spectrum disorder	Subcutaneous	S,O[c]	4
Selpercatinib	Retevmo (Lilly)	Antineoplastic agent	Oral	1-P,O	4
Selumetinib sulfate	Koselugo (AstraZeneca)	Antineoplastic agent	Oral	1-P,O	5
Setmelanotide	Imcivree (Rhythm)	Antiobesity agent (for patients with certain genetic disorders)	Subcutaneous	1-P,O	5
Somapacitan-beco	Sogroya (Novo Nordisk)	Agent for growth hormone deficiency	Subcutaneous	S[c]	4
Tafasitamab-cxix	Monjuvi (Morphosys)	Antineoplastic agent	Intravenous	P,O[c]	4
Tazemetostat hydrobromide	Tazverik (Epizyme)	Antineoplastic agent	Oral	1-P,O	5
Teprotumumab-trbw	Tepezza (Horizon)	Agent for thyroid eye disease	Intravenous	P,O[c]	5
Triheptanoin	Dojolvi (Ultragenyx)	Agent for long-chain fatty acid oxidation disorders	Oral	1-S,O	4
Tucatinib	Tukysa (Seagen)	Antineoplastic agent	Oral	1-P,O	4
Ubrogepant[e]	Ubrelvy (Allergan)	Agent for migraine	Oral	1-S	4
Viltolarsen	Viltepso (NS Pharma)	Agent for Duchenne muscular dystrophy	Intravenous	1-P,O	3

[a]FDA classification of new drugs: 1 = new molecular entity; P = priority review; S = standard review; O = orphan designation

[b]The New Drug Comparison Rating (NDCR) system was developed by Daniel Hussar in 2002 and is used as an indicator of the relative importance of a new drug: 5 = importance advance; 4 = significant advantage(s); 3 = no or minor advantage(s)/disadvantage(s); 2 = significant disadvantage(s); 1 = important disadvantage(s)

[c]A biological approved through an FDA procedure that does not assign a numerical classification.

[d]A gene therapy considered in a separate category by the FDA.

[e]Approved in 2019 but not marketed until 2020.

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