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Biogen's Aduhelm controversy as a case study for accelerated approval biomarkers in Alzheimer's and related diseases

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HIGHLIGHTS

- The recent approval of Aduhelm, a medicine indicated for Alzheimer's disease, sparked controversy in part due to reliance on biomarkers instead of primary data showing cognitive improvement
- The use of biomarker surrogate endpoints enables medicines to make it from bench to bedside faster but reduces the certainty that these medicines show clinical efficacy
- Future policy should build on the lessons from the Aduhelm approval, consider how biomarkers are chosen, and balance the risk of using biomarkers with their potential benefit to patients with neurodegenerative diseases

In June 2021, the United States Food and Drug Administration (FDA) approved Biogen's Aducanumab (brand name Aduhelm) as the first purported therapy to directly impact Alzheimer's disease (AD) progression. While such a therapy was a long-awaited goal in AD treatment, Aduhelm's approval quickly became controversial due to the fact that its approval was based upon the drug's ability to clear protein aggregates rather than any observed clinical outcomes for patients. These aggregates had been established as a *surrogate endpoint*, a probable marker of future clinical outcomes, but the decision to do so was controversial. Furthermore, now that Aduhelm has been approved, considerations about the precedent set by these surrogate endpoint choices now have ramifications for future AD drugs, drugs for other neurodegenerative diseases, and the FDA's Accelerated Approval Program. In this review, we introduce the concept of biomarkers for surrogate versus *clinical endpoints*, explain why surrogate endpoints are necessary for many diseases like AD, why the endpoints selected for Aduhelm were controversial, and discuss how more appropriate biomarkers can be chosen for future AD and Accelerated Approval drugs.

The Food and Drug Administration's (FDA) recent approval of Aduhelm, the first drug designed to directly target Alzheimer's disease (AD), was a much-anticipated event for the 6.2 million Americans suffering from the disorder [1]. However, the approval has been hotly contested by multiple stakeholders, many of whom are concerned about the implications of an apparent contradiction. Aduhelm has been shown to effectively clear AD patients' brains of *amyloid-beta aggregates*, protein particulates which have been thought to play a key role in the disease. However, at the same time, the drug has demonstrated no clear effect on delaying or reversing AD dementia patients' cognitive decline, a primary clinical symptom of underlying neurodegeneration [2].

One controversy is fundamentally grounded in clinical trial design and the FDA's policies regarding *endpoints*, which are pre-established variables that are measured to objectively determine whether or not a therapeutic intervention is beneficial [3]. *Clinical endpoints* concern direct expressions of the disease; for AD, these often constitute performance on cognitive examinations. However, for diseases like AD, the timescale of progression, complexity of pathogenic mechanisms, or eventual fatal nature of the disease may render it infeasible to conduct trials primarily on such data. To overcome these hurdles, the FDA permits the use of *surrogate endpoints*, which are measurements thought to predict, as opposed to directly constitute, clinical benefit [3, 4]. These are often biomarkers such as laboratory measurements, physical signs, or biomedical images. Biomarkers are categorized as *validated*, *reasonably likely*, or *candidate* based on the level of scientific and clinical evidence tying said endpoint to a clinical outcome [4, 5]. According to the FDA, a *validated* surrogate endpoint has both a clear "mechanistic rationale" and strong clinical evidence linking changes in said endpoint to a specific clinical benefit. In contrast, a *reasonably likely* surrogate endpoint merely requires "empirical evidence" of the "biological plausibility of the relationship between the disease

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and the biomarker and the magnitude of observed change in the biomarker that supports the relationship" [5, 6]. *Candidate* surrogate endpoints are those whose ability to predict clinical benefit are currently under evaluation.

In the case of Aduhelm, the surrogate biomarker endpoints were derived from the long-dominant *amyloid hypothesis*. Specifically, this hypothesis holds that AD is triggered by the accumulation of *amyloid-beta* in the brain; by extension, a person's risk of developing AD should be related to the amount of such particles found throughout their brain [7]. As the FDA considered the amyloid hypothesis scientifically sound, they classified neuroimaging scans of amyloid-beta brain burden as a reasonably likely surrogate biomarker endpoint of AD upon which drug trials could be evaluated [2]. This classification allowed Aduhelm to be tested through FDA's *Accelerated Approval Program*. In this program, surrogate endpoints are accepted as a basis of evaluation with the aim of speeding up the approval process of drugs targeting serious medical conditions with no or limited treatments. In addition, the FDA frequently requires post-market confirmatory trials on clinical endpoints to verify patient benefit for therapies developed this way [3].

Aduhelm was approved due to its effects on surrogate endpoints, despite having negligible or undetermined effects on clinical endpoints across two major Phase III clinical trials [2, 8, 9]. Biogen, the parent company, has made the drug available on United States (U.S.) markets and is mandated to perform confirmatory trials by 2030. Despite receiving FDA approval, the Centers for Medicare & Medicaid Services (CMS) released a National Coverage Determination stating that Aduhelm and other similar medicines would only be covered under their programs for use outside clinical trials if approved through traditional FDA approval mechanisms, not Accelerated Approval [10]. These tensions provide an opportunity for an in-depth case study to inform current and future policy discussions on the use of surrogate biomarker endpoints.

Clinical trials and current policies on biomarkers as surrogate endpoints

The FDA assesses new medicines using a three-phase trial format. The first in-human trials, Phase I trials, investigate the safety of a new medicine in a small group of healthy individuals over the course of months [11]. Owing to many years of work assessing the new therapeutic in the lab, the majority of new medicines are able to continue past Phase I trials [11]. Phase II follows to assess safety, side effects, and initial efficacy in small-scale studies of patients who have the disease the new medicine was designed to treat. Phase II trials typically last several months to a few years and represent a significant hurdle for new medicines, with only about one third progressing to Phase III [11]. Phase III clinical trials investigate the efficacy of the new medicine compared to a placebo in hundreds to thousands of patients over the course of one or more years. During Phase III, clinical endpoints in patients may be assessed directly, or biomarkers may be measured instead. The traditional FDA approval mechanism only allows the use of validated biomarker surrogate endpoints in clinical trials. These biomarkers have been extensively studied, usually over many years in large independent research studies, and are accepted as reliable predictors of clinical outcomes in patients [12].

While it may initially seem that clinical outcomes should be the primary way to assess the efficacy of new medicines, biomarker surrogate endpoints serve an important role in clinical trials. Providing novel medicines with the shortest delays from bench to bedside is of clear importance, but the often lengthy course of disease progression is an impediment. Relying solely on the primary outcome of a disease would lead clinical trials to become unwieldy in terms of duration, cost, and patient retention [12]. For example, a treatment for heart disease would be required to be studied until participants did or did not have a major cardiac event. Instead, biomarkers can be easily measured and predict clinical outcomes as surrogate endpoints, instead of relying on primary endpoints alone [12]. To extend the example above, the concentration of cholesterol in the blood could be used as a biomarker to predict cardiac protection. Biomarker surrogate endpoints are a mainstay of the modern therapeutic approval process that greatly facilitate the discovery and implementation of new therapeutics.

However, biomarkers meeting the exacting standard of validation used for traditional FDA approval do not exist for AD [13]. When validated biomarkers do not exist for serious and life-threatening diseases with few or no therapies, such as AD, the FDA can choose to assess new medicines through the Accelerated Approval Program [14, 15]. The Accelerated Approval Program seeks to reduce the duration of clinical trials in these serious and life-threatening diseases that do not have biomarkers with adequate validation to support a typical approval. Biomarkers used for Accelerated Approval are required to be *reasonably likely* to predict clinical improvement in patients, a statute that leaves considerable room for interpretation concerning the degree of biomarker validation [14, 15]. The measurement of amyloid-beta burden in the brain using positron emission tomography (PET) for the Aduhelm clinical trials is an example of this type of biomarker. While the use of less-validated biomarkers may decrease the certainty that a new medicine will show clinical efficacy, developing new therapeutics more quickly for serious diseases can be very beneficial to patients without other treatment options. Increased use of Accelerated Approval in recent years necessitates close examination of how biomarker surrogate endpoints are selected and interpreted (Fig. 1).

Biomarker surrogate endpoints used for Accelerated Approval must be known in the field as reasonably likely to predict clinical outcome, and medicines approved through this mechanism are no more likely to be removed from the market than those approved under other guidelines [14, 15]. Furthermore, drug products approved through the Accelerated Approval Program are frequently required to conduct post-market studies, also known as Phase IV Trials, in the years following approval to confirm improved patient outcome and long-term safety [14, 15]. These trials are

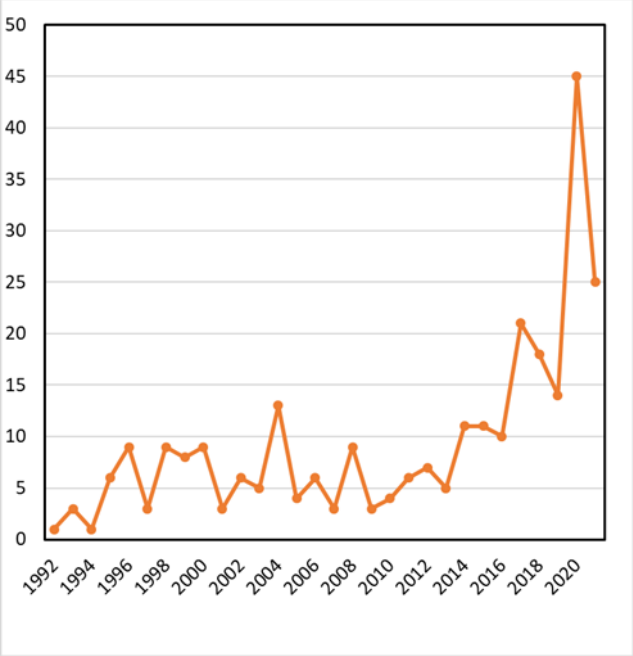

Figure 1: Number of drugs approved each year via the Accelerated Approval Pathway. Note the considerable increase in recent years [16].

completed by a majority of applicants within four years of the initial Accelerated Approval date and the majority publish their findings in academic journals or on ClinicalTrials.gov, the FDA's clinical trial data reporting website [17].

However, these confirmatory studies do not completely eliminate the risk to patients who may take the new medication before Phase IV data is obtained. If the chosen biomarker does not accurately predict patient improvement, patients may be subjected to ineffective treatment for years. This can be made worse if a new medicine has a significant side effect but is ultimately determined to have no clinical benefit. To this point, only about one fifth of cancer drugs, a class of medicines well known for severe side effects, that received Accelerated Approval were later found to increase patient survival in Phase IV studies [18]. Beyond efficacy, patients may also face significant financial burden to obtain the therapeutic or experience distress if they have been treated with a therapeutic that is later found not to impact clinical outcome as expected. In contrast, if the chosen biomarker is predictive of clinical improvement, patients may have access to life-changing therapies potentially years before they otherwise would have through Accelerated Approval. Aduhelm went through this Accelerated Approval pathway, and both the choice of biomarker surrogate endpoint and the decision to overrule a unanimous panel of experts who found the drug had no benefit to patients were controversial, for reasons discussed in the following sections [19, 20].

The neurodegeneration therapeutic development space and biomarkers for Alzheimer's disease

AD is a neurodegenerative disease, part of a large, heterogeneous class of fatal neurological disorders characterized by the progressive loss of neurons in the brain and spinal cord [21]. Other members of this family include Parkinson's disease, amyotrophic lateral sclerosis (ALS, or sometimes Lou Gehrig's disease in the U.S. and motor neuron disease in other countries), and Huntington's disease, among many rarer illnesses. These diseases share a range of traits that have made drug development more difficult. Aduhelm claims to be the first disease-modifying therapy for any adult-onset form of neurodegeneration [22]. We make this distinction and elaborate on challenges facing neurodegeneration as a whole here because many of the challenges and controversies surrounding Aduhelm will provide lessons not only for AD therapy, but also for how surrogate endpoint use should be considered across this whole family of illnesses.

The first of these traits is that neurodegenerative diseases are all neurological disorders, meaning that most conventional approaches will attempt to deliver drugs to the brain. The nervous system is even more difficult to develop therapies for than normal because of the blood-brain barrier (BBB), a semipermeable defense mechanism the body uses to tightly control what compounds can and cannot reach the brain [23]. Few drugs can permeate the BBB naturally, and interventions to make it more permeable often have additional technological and safety considerations [24, 25].

Second, AD is a polygenic disease; that is, AD arises from complex interactions of multiple genetic risk factors [26]. In practice, this means that it is rare for patients to have inherited a mutation in gene X from one or both parents that causes the disease; rather, they may have smaller changes in genes X, Y, and Z which all increase the odds they develop it, and this can be exacerbated by lifestyle choices. There are dozens of genes implicated, many with several disease-associated variants, that are known risk factors, and far more which remain unknown. Because each of these genes may contribute to multiple biological processes, disease presentation and progression is extremely heterogeneous. Notably, the ways in which even the most highly-studied genetic risk factors contribute to disease progression remains inconclusive. This can make it very difficult for scientists to determine which biological pathways would make good drug targets and has even raised questions if AD should be considered one single disease. This is further exacerbated by the existence of rare monogenic forms of AD, which have overlapping clinical and pathological presentation to polygenic forms but often have an earlier age of onset [27]. While monogenic AD occurs due to mutations in genes related to the production of amyloid-beta, the relative rarity compared to polygenic forms, which may not have a known connection between implicated genes and amyloid-beta's production of function, suggest the contribution of other biological pathways which may require independent therapeutic targets.

A third factor is that AD and other neurodegenerative disorders follow a particularly long course of progression. AD-related pathology in the brain has been observed in patients 10–20 years before clinical symptoms emerge [26].

Patients live an average of eight years, though sometimes far longer, after diagnosis [1]. Given the considerable patient-to-patient variation mentioned above and the fact that AD most often occurs in elderly people with relatively high rates of comorbidities, clinical trials which demand direct measurement of long-term patient outcomes before approval would quickly become long, resource-intensive, and difficult to interpret.

Because of these traits, it is important to identify biomarkers which can be used as surrogate endpoints for clinical trials of therapies for neurodegenerative diseases, and often we look first towards disease pathology. Neurodegenerative diseases are often referred to as "proteinopathies" because many of them are associated with a hallmark protein pathology [28, 29]. These proteins form aggregates in the brains of patients. Generally, each neurodegenerative disease has one to two which appear in most patients but not as often in patients with other illnesses. For AD, two such proteins are known: amyloid-beta and tau [7].

AD pathology in the brain is defined by the accumulation of amyloid-beta aggregates and neurofibrillary tangles made of the protein tau. While these deposits were first described nearly a century ago, it was only in 1984 that amyloid-beta accumulation was proposed to be the trigger for AD [7]. The primary hypothesis is that such aggregation of amyloid-beta encourages aberrant changes in tau protein, leading to the formation of neurofibrillary tangles and damaging brain cells. This accumulation of protein aggregates is thought to initiate neurodegenerative processes resulting in cell death, and these in turn result in loss of memory and impaired cognition. From this model, a reasonable hypothesis is that the removal of amyloid-beta aggregates might impede or halt the progression of AD.

However, the amyloid hypothesis has never been universally accepted. Common counter-arguments include the fact that many cognitively normal elderly people have amyloid-beta plaques in their brains, although proponents of the amyloid hypothesis claim these subjects died with a pre-symptomatic stage of AD [30]. In addition, multiple studies have found that the cognitive symptoms of AD are more correlated with the distribution and quantity of tau proteins than those of amyloid-beta aggregates [7, 30]. Finally, since 2002, over 20 amyloid-targeting AD drugs have been tested in Phase III trials, and each has failed to show any efficacy relative to placebos on measurements of cognitive decline [30]. This is despite the fact that many of these trials simultaneously demonstrated that their respective amyloid-targeting drugs successfully engaged with the intended targets—the protein itself or enzymes associated with its production, accumulation, or modification—as measured through amyloid-beta concentrations in cerebrospinal fluid and/or brain imaging techniques [30]. Some trial participants also suffered from side effects specific to treatment with amyloid-lowering drugs called Amyloid-Related Imaging Abnormalities (ARIA), which are associated with brain swelling and hemorrhages [2]. Such severe side effects become particularly concerning when the ability of a medicine to impact primary endpoints in addition to biomarker surrogate endpoints is in doubt, such as with Aduhelm. The questionable and continued testing of the amyloid hypothesis can be attributed to the fact that the National Institutes of Health historically largely avoided funding exploratory studies or those proposing to test hypotheses unrelated to amyloid-beta [30]. In addition, interest in the hypothesis is kept alive by the unresolved suspicion that amyloid-targeting treatments may only be effective at the very earliest, pre-symptomatic stages of AD before the amyloid has triggered a cascade of deleterious downstream effects.

Aduhelm targets and claims to clear amyloid-beta. However, considerable debate exists over the choice of targeting amyloid-beta or tau. Contention extends to whether either is an appropriate biomarker or has been sufficiently validated to justify its use [22]. The next section will expand upon this debate, highlighting the arguments for and against amyloid-beta, tau, or alternative biomarkers, and the Aduhelm controversy more specifically.

Aduhelm controversy and past examples of Accelerated Approval in neurology

Aduhelm, a monoclonal antibody meant to clear amyloid-beta aggregates from the brain, is certainly a product of the amyloid hypothesis. Building on smaller successful trials of the drug, Biogen initiated two essentially identical phase-three clinical trials, ENGAGE and EMERGE. Each included around 1600 people with AD [2]. Halfway through the trials, an independent data monitoring committee performed a futility analysis to preliminarily assess drug viability; it was concluded that while both trials showed significant evidence of Aducanumab decreasing amyloid burden, a surrogate endpoint, both had less than a 20% chance of demonstrating a significant impact on cognitive decline by their projected end. As a result, Biogen stopped both trials at 50% completion in March 2019 [2, 20]. However, merely six months later, Biogen announced that an analytical error had been made, claiming that participants treated with Aducanumab in the EMERGE trial had in fact had a statistically significant improvement on a clinical dementia rating scale (relative to individuals treated with placebos). In contrast, corresponding participants in the ENGAGE trial experienced a statistically significant cognitive decline [2, 20].

In light of claims that insufficient data had been collected due to the premature end of the trial, the two studies' incongruous result, and reports of concerning side effects, the FDA's Peripheral and Central Nervous System Drugs Advisory Committee nearly unanimously voted against the approval of Aduhelm [9]. However, despite the expert panel's conclusion, the FDA's Center for Drug Evaluation Research (CDER) deemed that Aduhelm met the requirements for the Accelerated Approval Program on the basis of the observed decrease in amyloid burden [19, 20]. Further adding to the controversy, the European Medicines Agency (EMA) voted

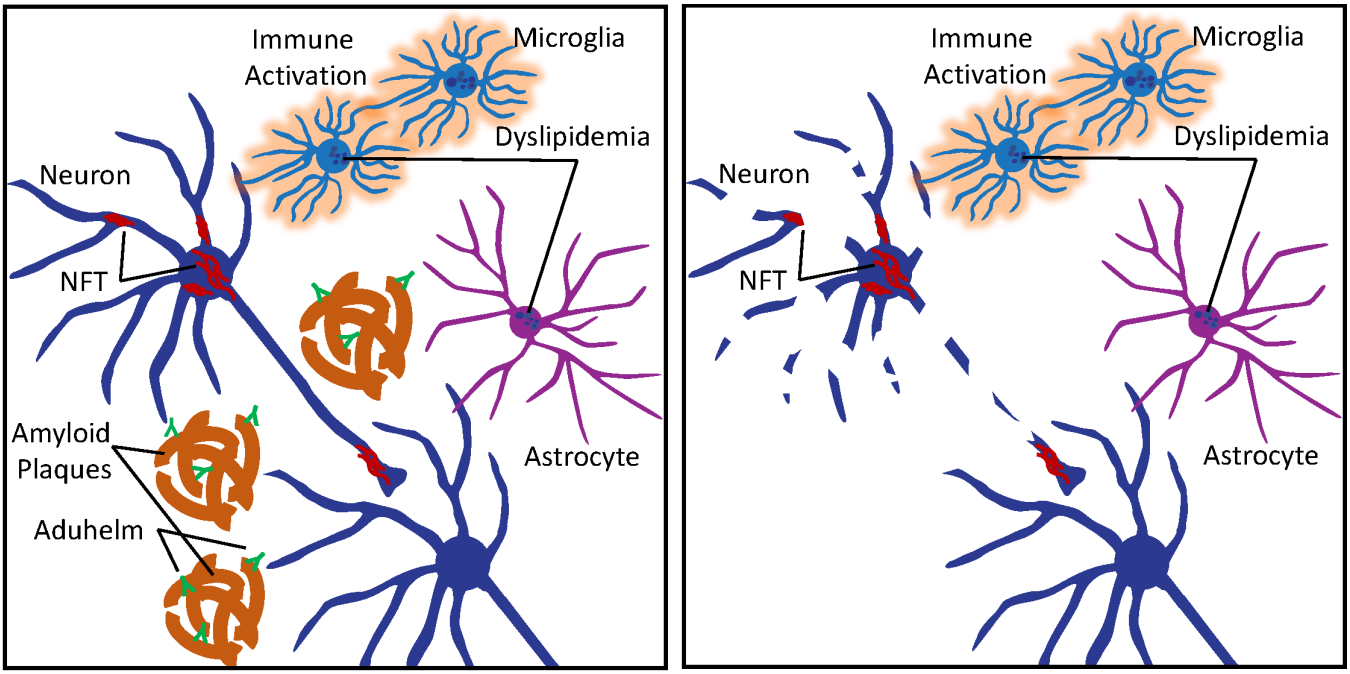

Figure 2: (Left) Amyloid plaques and neurofibrillary tangles (NFT) disrupt normal neuronal function in the AD brain. Aduhelm binds to and clears Amyloid plaques. Glial cells may accumulate lipids and become activated, further damaging neurons. (Right) After clearance of amyloid plaques by Aduhelm, neurons may still be damaged by NFT and dysfunctional glial cells. Dead neurons are largely not replaced.

not to approve Aduhelm despite usually concurring with FDA decisions [31].

While the approval of Aduhelm has been especially contentious, this is not the first time that medicines granted Accelerated Approval have faced controversy. For instance, concerns were raised about the interpretations of surrogate endpoints used for the approval of the Duchenne muscular dystrophy (DMD) treatment Eteplirsen (brand name Exondys 51) in 2016 [32]. DMD is a progressive disease linked to genetic mutations that disrupts dystrophin, a protein that stabilizes muscle fibers. Exondys 51 was designed to raise the levels of intramuscular dystrophin. It was tested using an Accelerated Approval process that relied on surrogate measures—specifically dystrophin increases in muscle biopsies—as primary endpoints and a six-minute walk test as a secondary clinical measure [33]. In the Phase III clinical trial, after 48 weeks of treatment, the median participant treated with Exondys 51 had achieved only a 0.1% increase in the surrogate measure—leaving them with about 0.44% of the intramuscular dystrophin levels a healthy subject would have [34]. No significant improvements were observed in the six-minute walking tests [33]. The FDA scientific reviewers of Exondys 51 opposed its approval; however, the director of CDER, Janet Woodcock, overruled them, arguing that "the extremely small increase in dystrophin might conceivably translate to a clinical benefit" and that "the greatest flexibility possible" should be adopted in evaluating the drug's efficacy given the lack of treatments and fatality of DMD [33]. The drug was granted an accelerated approval and, like Aduhelm, has been required to undergo post-market confirmatory trials. However, given that no placebo groups are mandated (or feasibly recruited), it is not clear how such a study could even hypothetically provide sufficient evidence leading to the removal of Exondys 51 from the market (bar the possibility of serious, unexpected safety problems) [33]. All in all, critics of both Aduhelm and Exondys 51 argue that the FDA's approaches to interpreting their respective surrogate endpoints have created incentives and precedents that unfairly favor companies that submit less rigorous and less clinically beneficial trials [33].

However, more positive historical examples may provide complementary insight into useful strategies for future medicines seeking Accelerated Approval. One such example is Natalizumab, a monoclonal antibody developed by Biogen to reduce the frequency of relapses in some forms of multiple sclerosis (MS). Similar to Aduhelm, the development of Natalizumab was closely followed by the field, both because of the exciting new mechanism for an MS therapeutic and the rapid clinical development spanning only 12 years from identification of the target protein to approval [35]. Data from both primary endpoints and biomarkers in two key Phase III studies showed significant improvement over existing therapies and earned Natalizumab Accelerated Approval in November 2004 contingent upon the completion of the Phase III studies. However, within months of said approval, serious adverse events with the possibility of death or severe

disability were identified in two patients. These events led to the cessation of Natalizumab dosing shortly afterward. Comprehensive assessment of all patients treated with Natalizumab was performed immediately and eventually led to a reliable system to stratify patients based on the likelihood of experiencing these serious adverse events. Elimination of risk for adverse events has not been possible with Natalizumab, but careful collaboration among Biogen, the FDA, and clinicians has allowed thousands of patients to benefit from this novel therapy with proper screening. It remains to be seen whether a similar protocol can be developed for Aduhelm, but the Natalizumab story is an example of both the risks and benefits of Accelerated Approval in neurological conditions. Furthermore, the rapid and thorough assessment of adverse events and subsequent development of careful screening tools provides a strong framework to guide clinical and regulatory practices in the neuroscience disease space.

The transformative potential of biomarkers as surrogate endpoints in rare diseases

Biomarker surrogate endpoints present important opportunities for the development of new drug products but also come with challenges in properly assessing efficacy and safety. This is most applicable to biomarkers with less previous validation, such as those used in the Accelerated Approval Program. The risks associated with using such biomarkers, or Accelerated Approval more broadly, become particularly concerning when large or vulnerable patient populations may be negatively impacted if a new drug product is ineffective or leads to serious adverse events. These concerns are at the forefront of the discussion around Aduhelm's Accelerated Approval based on the highly-criticized biomarker surrogate endpoint data. Close examination of the Aduhelm data and use of Accelerated Approval in this case is necessary. However, it is also important to acknowledge the critical role of Accelerated Approval and biomarker surrogate endpoints in approvals for rare diseases. Future policy must carefully consider the impact that any significant changes resulting from the Aduhelm decision may have on these approvals.

One relevant disease area that has received recent attention is fatal familial insomnia (FFI), a highly penetrant genetic prion disease that progresses from first symptoms to profound disability to death typically within less than a year [36]. The age of onset for the most common genetic prion diseases, including FFI, is extraordinarily variable, creating another significant impediment to trial design in addition to rapid disease progression and small patient population [37, 38]. Of the double-blind, placebo-controlled clinical trials that have been conducted for FFI and other genetic prion diseases, all have failed due to high patient mortality early in the trial [38]. One recent study asserts that there simply are not enough patients converting from asymptomatic carrier status to active prion disease at any given time to conduct traditional clinical trials for preventative anti-prion therapeutics using a primary endpoint of delaying disease onset [37, 38].

For this reason, the ability to use a biomarker surrogate endpoint and a flexible trial design is critical for advancing therapeutics for FFI. Researchers in the field have proposed to use a reduction in concentration of prion protein in the cerebrospinal fluid as biomarker surrogate endpoint for anti-prion therapeutics and have conducted studies in rodent models to show that this is reasonably likely to delay disease onset [39]–[41]. This trial design is unlikely to meet the requirements for traditional FDA approval mechanisms but is consistent with the requirements for Accelerated Approval. This is just one of many examples of rare disease areas that could be negatively impacted if a high-profile controversy, such as with Aduhelm, leads to restrictions on the use of biomarker surrogate endpoints or the Accelerated Approval mechanism. Because traditional clinical trial design would make approval of such medicines more difficult or even impossible, there could be reduced investment in developing medicines for rare disease. Even without the enactment of additional restrictions, it is plausible that the risk of scandal alone could result in divestment from the already fraught neurodegenerative therapeutics development space. Likewise, increased incidence of CMS refusal to provide full coverage for therapeutics approved by the Accelerated Approval mechanism might disproportionately impact vulnerable patient populations, such as people with rare and serious diseases or the elderly. Any policy decisions following from the Aduhelm approval must balance the need to regulate the use of less-validated biomarkers and Accelerated Approval with the needs of patient populations that may benefit from their availability.

Conclusion

Use of biomarker surrogate endpoints in Accelerated Approval has the potential to bring therapies to patients much more quickly than traditional approval mechanisms. While there are inherent risks in using less-validated biomarkers, clear historical precedents demonstrate that collaboration among pharmaceutical companies and regulators can lead to successful mitigation of risk and ultimate success of neurological therapeutics through Accelerated Approval. The development of new treatments for neurological diseases, and AD specifically, is notoriously fraught owing to difficulty in delivering therapeutics to the brain, heterogeneity in disease progression, and incomplete understanding of underlying disease mechanisms. The long period of time over which cognitive decline occurs makes clinical trial design logistically difficult for AD and makes the use of biomarker surrogate endpoints particularly appealing.

The use of amyloid-beta as a biomarker surrogate endpoint supporting the eventual Accelerated Approval of Aduhelm has drawn significant criticism from some experts in the field, including the expert advisory committee who assessed Aduhelm ahead of the approval decision [9]. They argue that amyloid-beta clearance from the brain has not been sufficiently shown to predict improvement in patient cognition. Supporting this claim, data from the EMERGE and ENGAGE trials showed limited cognitive benefit from Aduhelm treatment [2]. While data from the forthcoming Phase IV trial will provide

more insight into the efficacy of Aduhelm as a treatment for AD, the approval process has already sparked significant debate and may impact future approvals, especially for neurological therapeutics. In the future, careful consideration of biomarkers and collaboration with leading experts will be instrumental to bringing new therapeutics to patients through Accelerated Approval, especially those with rare diseases that may not be amenable to traditional clinical trial designs.

There are now concerns that this new precedent will have unintended consequences for the AD drug development space. Upcoming amyloid-targeting AD drugs (including, for instance, Donanemab by Eli Lilly, Lecanemab by Esai, and Gantanerumab by Roche) are now likely to apply for Accelerated Approval using amyloid as a surrogate biomarker [42]–[44]. In addition, there may be attempts to resurrect amyloid-targeting drugs which failed traditional FDA approval programs via applications to the Accelerated Approval Program. All in all, this may lead to a proliferation of AD drugs solely validated on amyloid biomarkers, decreased pre-market availability of efficacy and safety data, and difficulties in recruiting and retaining participants in AD drug studies seeking traditional FDA approval, which may be more reliably beneficial to patients. Finally, there are also concerns that this precedent may divert funds from the wide gamut of alternative AD drug targets, including tau proteins, neuroinflammation, metabolomics, and more [45].

Looking forward, key considerations include how best to consider expert input for Accelerated Approval decisions and how best to identify biomarker surrogate endpoints for neurological therapeutics development.

Citation

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