J Prev Alz Dis 2023;3(10):336-338
Published online June 13, 2023, http://dx.doi.org/10.14283/jpad.2023.71

Viewpoint

Balancing the Conflicting Goals for Treatment of Alzheimer's Disease with Monoclonal Antibodies

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Abstract

The recent conflicting recommendations on coverage and use of monoclonal antibody treatments for Alzheimer's Disease (AD) in the United States provide an opportunity to better define the concepts of safety, efficacy, reasonableness, and necessity. The translation of current science into clinical practice may require additional studies that enroll patients like those seen by primary care providers. Regarding recently published clinical trials as a step forward toward an AD cure is critical, as is wide collaboration between researchers and clinicians, and public and private sectors, to ensure that new effective therapies can be easily provided in clinical practice settings.

Key words: Alzheimer`s disease, monoclonal antibody, mild cognitive impairment, regulatory bodies, side effects and cost.

The recent reviews by the Food and Drug Administration (FDA) and the Centers for Medicare and Medicaid Services (CMS) and the United States Veteran's Administration (VA) on amyloid directed monoclonal antibodies appear to produce contradictory results. CMS notes that the FDA must approve the efficacy and safety for a treatment modality, and that CMS determines payment coverage for only what is reasonable and necessary (1).

The notions of efficacy, safety, reasonableness, and necessity are not as easy to define in clinical medicine, but clinicians in practice must apply these concepts every time we order a medication for a patient. We, generally assume that such medications are effective, safe, reasonable, and necessary in our treatment plan.

We hope here to highlight the challenges facing clinicians who are taking care of patients, and not to take a stand in what has been characterized as the "CMS vs. FDA debate."

Efficacy is defined by the FDA to "refer to the findings in an adequate and well-controlled clinical trial or the intent of conducting such a trial (2)." We understand that decreasing the care burden for both the patient and his relatives can be considered a form of efficacy. To slow by 25 to 30 percent the progression of a long-term diseases like Alzheimer's disease (AD) appears to be significant progress toward our quest for a cure. However, we need to better define the relevant timeframes involved in slowing disease progression. The 25 to 30 percent reduction in progression has also shown to result in a three-month slowing of progression of mild cognitive impairment (MCI) and a one month slowing of mild AD progression (3). In our conversations with families and patients, they see a 30 percent reduction as very promising, while three-month prolongations may seem trivial to them. In addition, most of our patients often do not qualify for these studies due to multiple comorbidities and other demographic characteristics, making it more difficult to apply the conclusions to our patient populations. For example, we treat a patient population that is 45 percent Hispanic, a group that has been significantly underrepresented in the monoclonal antibody studies to date. Much longer randomized, controlled trials with a population more representative of the clinical and demographic characteristics of Alzheimer's disease patients, in more standard clinical practice settings will be needed to convince clinicians that these new treatments will be truly effective in our patients.

Safety refers to the balance of intended benefits and untoward side effects for a given drug. The National Institutes of Health states, "Drug safety is the main aspect of medical therapy that can play a major role in deciding which drug should be given to a patient. Also, considering the concept of benefit–risk balance, we found that drugs with a high-risk profile should be avoided unless needed (4)." While minor side effects may not cause significant physiologic decompensation, many of them can impair patient and caregiver quality of life. More serious side effects such as amyloid-related imaging abnormalities with vasogenic edema and/or microhemorrhage (ARIA-E and ARIA-H) can rarely advance from asymptomatic to severe and be responsible for many additional diagnostic studies, which may also result in reductions of the quality of life of the patient and their caregiver, use valuable healthcare personnel resources, and increase the cost of the patient management. We also recognize that delaying the progression of AD can reduce or at least delay the costs

Received March 28, 2023
Accepted for publication April 19, 2023

of more intensive healthcare resources, such as trips to Emergency Departments, hospitalizations and nursing home stays.

A recent meta-analysis of monoclonal antibody treatments in AD showed overall risk ratios of 10.65 for ARIA-E and of 1.75 for ARIA-H (5). ARIA occurred in 26 percent of lecanemab treated patients (5), although the large majority of this group were asymptomatic.

CMS, in a new rule released in 2021, has provided a definition for "reasonable and necessary." The definition has three main elements, according to the final rule, including that an item or service 1) be safe and effective, 2) not experimental or investigational, and 3) appropriate for Medicare patients (7). Since "safe and effective" are also the domain of the FDA, and the FDA approval essential means that these biologics are no longer experimental, CMS has the sole role to determine appropriateness for Medicare patients.

In clinical practice, we consider treatments "reasonable" when efficacy and safety have been clearly established, and that the treatment will confer measurable and practical benefits to the patient and caregivers. Additionally, in the current market where the annual cost of individual drugs and biologics can often be thousands of dollars per year, the cost to the patient, families, and healthcare system must be carefully considered. There is also the ethical concern that such treatment options can out of reach for the most vulnerable or resource strapped communities. It is likely if insurance coverage is to help with the costs, additional hurdles such as prior authorization and specialty consultations will be added to the overall cost burden. Our patients do not consider any treatment "reasonable" when the cost of treatment forces them to choose between a drug and other necessities of life, such as food or housing.

However, for a devastating disease like AD, we may need to accept a moderate but real benefit that outweighs the side effects, and pay a reasonable price for the treatment, as we currently see in the high-cost treatments in rheumatology, oncology, and neurology, to name a few. In addition, the screening and safety monitoring investigations must be reasonable. Amyloid and tau PET scanning is costly and not widely available, and MRI scans can be stressful for older patients. Hopefully, in the near future, blood biomarkers can provide less costly and more convenient treatment monitoring.

In the category of necessary treatments, a significant clinical need exists for treatments that measurably slow and reverse the progression of MCI and mild to moderate AD, that can be shown to improve patient and caregiver quality of life. At the same time, more research is needed to determine whether costly treatments for those with multi-morbidity, poor global life expectancy, very advanced age, or the asymptomatic are warranted. We are hopeful that blood biomarkers soon can be used to screen and monitor our patients.

We have observed over a collective 60 years of clinical geriatric practice that AD patients and their caregivers have an inherent bias toward treatment with anything that can slow the progression of the disease. For the majority, such treatment tends to be seen as "necessary." At the same time, there seems to be an equal and opposing bias against drugs with troublesome side effects, whether serious or not. While each of the four criteria discussed here are the subjects of exam room discussion when initiating a new treatment, "necessity" seems most fraught with biases and the potential for a mismatch between patient, family, and provider points of view. It is also very important, from an equity perspective, to ensure that treatment coverage decisions be made without any systemic bias against the elderly, the infirm, and particularly those with AD.

Without additional studies, it may seem "necessary" to give every MCI and AD patient any available treatment without any subclassification based on effectiveness. If we can significantly slow the progression of the disease and at the same time increase quality of life by reducing burden for the patient and caregivers, we must pursue such treatments. However, the research-proven efficacy must be clinically significant, the monitoring tolerable, the side effects acceptable, and the price affordable.

Balancing all these factors for monoclonal antibodies is not easy from a policy perspective, as the discordance between FDA, CMS and VA recommendations has demonstrated. The decision-making for individual patients can be equally challenging. In clinical practice, only a few therapies are consistently effective without any side effects. In medicine we still use some therapies that may not be effective, necessary, or reasonable and we must continue to work to remove these from our various formularies and drug lists.

We cannot wait to have the final miracle drug for AD to prescribe treatments that are able to slow or reverse disease progression. More research is needed on efficacy and safety, and what is reasonable and necessary in clinical practice, and this will require deeper and stronger collaboration between patients and their caregivers, clinicians, payors, CMS and the FDA, pharmaceutical companies, and legislative bodies (8). We envision a "middle way" in which these communications can occur and at the same time transcend the inherent conflicts of interest in such collaborations.

There is established consensus on the difficulty of caring for and curing age related conditions like Alzheimer's disease; it remains our duty to pursue new avenues of treatment. We must work collaboratively on research to better establish efficacy and safety on more clinically relevant populations to help determine what is reasonable and necessary at both the public policy and individual patient levels. These recent debates related to the FDA, CMS and VA determinations are an ideal basis for further exploration and discussion.

Conflict of Interest Statement: Dr. Scrase has no conflicts of interest. Dr. Budhwar has no conflicts of interest.

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How to cite this article: D.R. Scrase, N. Budhwar. Balancing the Conflicting Goals for Treatment of Alzheimer's Disease with Monoclonal Antibodies. J Prev Alz Dis 2023;3(10):336-338; http://dx.doi.org/10.14283/jpad.2023.71