RESEARCH ARTICLE

Perspectives on the clinical use of anti-amyloid therapy for the treatment of Alzheimer's disease: Insights from the fields of cancer, rheumatology, and neurology

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Abstract

Introduction: The advent of disease-modifying therapies for Alzheimer's disease (AD) has raised many questions and debates in the field as to the clinical benefits, risks, and costs of such therapies. The controversies have resulted in the perception that many clinicians are apprehensive about prescribing these medications to their patient populations. There also remains widespread uncertainty as to the economic impact, cost benefit ratio, and safety oversight for use of these medications in standard clinical care settings.

Methods: To contextualize such issues, the present study compared anti-amyloid biologic therapy (lecanemab) to four commonly used biologic agents in other fields, including trastuzumab for breast cancer, bevacizumab for lung cancer, etanercept for rheumatoid arthritis, and ocrelizumab for multiple sclerosis.

Results: The data presented demonstrate comparable costs, clinical benefits, and risks for these biologic agents in their disparate disease states.

Discussion: These results provide context for the costs, clinical benefits, and safety regarding the mainstream use of anti-amyloid biologic agents for the prevention of cognitive loss. While the era of disease-modifying therapies for AD is now in its infancy, there is an expectation that these discoveries will be followed by improved therapies and combination treatments leading to greater efficacy in ameliorating the clinical trajectory of AD.

KEYWORDS
Alzheimer's disease, anti-amyloid therapy, biologic agents, mild cognitive impairment

Highlights

- Anti-amyloid therapy costs are comparable to other commonly used biologics.
- Anti-amyloid therapy efficacy is comparable to other commonly used biologics.
- Anti-amyloid therapy safety is compatible with other commonly used biologics.

1 | INTRODUCTION

The development and United States Food and Drug Administration (FDA) approval of disease-modifying therapies for Alzheimer's disease (AD) has raised many questions and sparked debates in the field regarding the clinical benefits, risks, and costs of such therapies.[1] While full approval from the FDA for the first anti-amyloid therapy, lecanemab, has led to approval for reimbursement from the Centers for Medicare and Medicaid Services (CMS), albeit requiring a Coverage Eligibility Determination (CED), indicating that the center remains unconvinced of the long-term benefits and cost-effectiveness of lecanemab in routine practice. In addition, many third-party payors operating outside CMS guidance have not committed to reimbursing such medications. This may in part be due to current controversies in the field regarding the clinical meaningfulness of the statistically significant findings that have led to drug approval for lecanemab.[1–3] There remains widespread uncertainty as to the economic impact and cost benefit ratio for use of these medications in standard clinical care settings.[1–5] In addition, the present controversies have resulted in the perception of many clinicians becoming apprehensive about prescribing these medications to their patient populations.[1] Despite such perceptions, trials of both amyloid-targeting and non-amyloid-targeting agents remain active in the field.[6]

AD is an inexorably progressive disease in which personhood is slowly lost over several years and was the seventh leading cause of death in the United States (2021), affecting a significant proportion of the over 6 million individuals living with the diagnosis of dementia today.[7] However, this number may be a significant underrepresentation, as mild cognitive impairment (MCI) due to AD more than doubles the estimated prevalence of AD.[7] AD has many known risk factors but can affect us all, with at least 15% of the population eventually developing this disease.[7] A widespread perception that any worthwhile treatment should completely cure the disease has perhaps been an obstacle to incremental progress.[2,3] However, we have witnessed remarkable clinical progress in drug discovery for the treatment of individuals with diseases such as breast cancer, lung cancer, rheumatoid arthritis, and multiple sclerosis, which has raised hopes that we can do the same for AD and other related dementias.[8–11] Importantly, we note that acceptance of incremental increases in treatment efficacy, together with the concept of combination therapies, was instrumental to the successful pursuit of better therapeutic and clinical approaches for these and a spectrum of other conditions. However, the controversies that surround AD-modifying therapies may discourage similar therapeutic advancement unless recognized and addressed appropriately.

The development and practical use of biologic agents for the treatment of human disease is a relatively new approach that has revolutionized treatment for many diseases that previously lacked effective therapies or disease-modifying treatments. Biologic agents can target specific molecules involved in disease pathways for distinct sets of patients and have facilitated precision medicine in oncology and are rapidly expanding across other disease states. Such therapies, however, are expensive to develop, test, move through the therapeutic pipeline, and eventually deliver to the population in need. Given the

RESEARCH IN CONTEXT

1. **Systematic Review**: There has been much debate as to the efficacy, safety profile, and cost of the recently approved anti-amyloid therapy, lecanemab, for Alzheimer's disease (AD), The present study compares anti-amyloid biologic therapy (lecanemab) to four commonly used biologic agents in other fields, including trastuzumab for breast cancer, bevacizumab for lung cancer, etanercept for rheumatoid arthritis, and ocrelizumab for multiple sclerosis.

2. **Interpretation**: The data presented demonstrate comparable clinical benefits and risks for these biologic agents in their disparate disease states, and we further discuss relative costs and assumptions. These results shed light on the controversies regarding the mainstream use of anti-amyloid biologic agents for the prevention of cognitive loss.

3. **Future Directions**: While the era of disease-modifying therapies for AD is now in its infancy, there is an expectation that these discoveries will be followed by improved therapies and combination treatments leading to greater efficacy to ameliorate the scourge of AD.

extensive effort and costs associated with their development (often many failures for each success),[12] there is an associated high cost involved in their distribution and use for care. Most biologic therapeutic medicines appear relatively safe from a general standpoint[13]; however, the disease pathways that they target can lead to unintended (generally on-target related) changes in necessary biologic function(s), and so carry risks that may only become known after prolonged use. These considerations are currently inherent in the debate and discussions on disease-modifying therapies for AD, that is, anti-amyloid therapies.

To provide context for this important discussion, the current manuscript compares and contrasts perceptions on treatment with disease-modifying biologic agents across disparate conditions.[4,8–11] The data presented include 2023 disease prevalence and mortality estimates for the United States and cost comparisons of five different biologic therapies used for multiple disparate and distinct disease states. The data provide important comparative insights into how the clinical meaningfulness and cost-effectiveness of these therapies are driving clinical decision-making today, as well as context for decision-making relevant to AD-oriented biologics.

2 | METHODS

The Centers for Disease Control and Prevention (CDC) WONDER and Pub Med databases were searched for contemporary estimates of disease prevalence and mortality associated with AD, breast cancer,

lung cancer, rheumatoid arthritis, and multiple sclerosis—five common diseases where the field adapted the use of biologic agents as optimal therapies for their treatment as of 2023. The FDA and IPD Analytics databases were searched for contemporary estimates of risk, benefit, and cost for five commonly used biologic agents including lecanemab for AD, trastuzumab for breast cancer, bevacizumab for lung cancer, etanercept for rheumatoid arthritis, and ocrelizumab for multiple sclerosis. These data were used for comparisons of need, clinical meaningfulness, potential risks, and costs for these biologic agents for the treatment of their underlying disease conditions. The agents selected are all currently used state-of the art biologic therapies. While lecanemab is the first disease-modifying therapy for AD, comparisons to other first-of-their-kind disease-modifying therapies would not provide relevant cost or comparative safety and efficacy measures allowing a modern comparison that is the intent of this manuscript.

3 | RESULTS

Table 1 describes estimated US prevalence and mortality for the five conditions in 2023. AD is the most prevalent of all the conditions included in the present study with 6,700,000 persons affected.[7] Mortality related to AD surpasses that of the comparison disease states including breast cancer, lung cancer, rheumatoid arthritis, or multiple sclerosis.

Annual drug costs are lower for lecanemab compared to the other four included biologic agents (trastuzumab, bevacizumab, etanercept, and ocrelizumab). Etanercept is the highest-priced agent at $96,224 per year followed by bevacizumab at $82,882 annually, ocrelizumab at $78,858 annually, and trastuzumab at $79,479 annually.[14–17] While drug costs remain only part of the equation, the costs associated with establishing candidacy for treatment, drug delivery, and safety monitoring are also important considerations. Lecanemab falls mid-range within the scope of costs associated with these current-day biologic therapies.

Initiation of lecanemab treatment requires a clinical visit to establish CED criteria for CMS approval, which also entails an magnetic resonance imaging (MRI) scan of the brain performed in the past year, recommended apolipoprotein E genetic testing to establish individual risk profiles, and confirmation of amyloid status by either spinal fluid examination or amyloid-PET scanning. Bi-weekly infusions also add to costs, and there are required safety MRI scans prior to the 5th, 7th, and 14th infusions to monitor for amyloid-related imaging abnormalities (ARIA) which can include edema, hemorrhage, or both. If safety concerns are seen on imaging, monthly monitoring with MRI is recommended to guide further therapy. Such costs may be significant, and these additional expenses should be factored into the cost-benefit analysis of anti-amyloid therapy.

The requirements for additional screening, monitoring, and clinical time are not unique to lecanemab. In comparison, initiation of trastuzumab and bevacizumab therapy requires tumor identification by imaging and tumor biopsy in addition to safety laboratory testing

and genetic profiling of tumor characteristics. Trastuzumab therapy also requires an echocardiogram at baseline and every 3 months, which is increased to once a month if a reduced left ventricular ejection fraction is noted. Echocardiograms are only indicated for bevacizumab therapy if clinical signs or symptoms of congestive heart failure (CHF) are noted. Routine testing of blood counts are also indicated for both trastuzumab and bevacizumab to monitor for neutropenia and bone marrow suppression. Interval monitoring of cancer progression, stability or regression is typically performed every 3 months by computed tomography (CT) and MRI which can be local or whole body depending on metastatic concerns. Infusions are conducted every 1–3 weeks in cycles. These additional costs for eligibility determination and monitoring treatment efficacy and safety are not included in Table 1, which solely focuses on cost of the medication. Clearly such costs are well in line with the infusion schedule and limited MRI scans required for safety monitoring of lecanemab therapy.

Ocrelizumab eligibility is determined clinically with the supporting clinical evidence of active multiple sclerosis by brain and spine MRI and spinal fluid testing. In addition, testing for immunoglobulin status and prior hepatitis B infection is required. Two infusions, 2 weeks apart, are then followed by infusions every 6 months. Routine monitoring of immunoglobulins and blood counts is recommended in addition to the routine practice of at least annual MRI scans to establish efficacy. Additional MRI scans are required for safety should neurologic symptoms suggestive of progressive multifocal leukoencephalopathy occur. The eligibility, associated care, and other costs associated with ocrelizumab are not negligible, but appear to be considerably less than required for lecanemab therapy.

Patients treated with etanercept should be screened for hepatitis B and tuberculosis. No other eligibility criteria have been established. Etanercept is available in self-injectable prefilled syringe, so this precludes costs associated with parenteral administration in an infusion center. Routine monitoring of blood counts is recommended to ensure adequate immune system function. Additional medical costs for monitoring safety are dependent on the clinical signs and symptoms of adverse side effects and are difficult to quantify for an individual patient. Of the biologics studied here, etanercept is the most cost-effective with regard to establishing eligibility and engaging biologic therapeutic intervention.

While a direct comparison of overall response rates is problematic given the disparate outcome measures used in the clinical trials supporting FDA approval of these biologic therapies, the present manuscript sought to best compare efficacy in response rates derived from the clinical trials in terms of slowing disease progression. The overall response rates reported in Table 1 provide only a limited perspective of the comprehensive outcome measures that have led to FDA approval for these disparate biologic therapies, each designed to treat very disparate disease states. Table 1 highlights response rates in terms of slowing of disease progression with these medications that ranges from 24% to 45%, similar across all agents. Primary efficacy outcomes for trastuzumab included a reduction in mortality by 33%.[18] Primary efficacy for bevacizumab includes a 28% to 38% response rate in cancer progression.[19] Etanercept can lead to a 31% remission and a 45%

TABLE 1 Comparison of disease states treated with lecanemab and four other commonly used biologic therapies

Indication	Lecanemab	Trastuzumab	Bevacizumab	Etanercept	Ocrelizumab
	Dementia (Alzheimer's disease as the leading cause)	Breast cancer	Lung cancer	Rheumatoid arthritis (all organ involvement)	Multiple sclerosis
No. of persons with disease in the US 2023	6,700,000	3,886,830	603,989	1,300,000	744,781
No. of deaths from the disease in the US 2018–2021[a]	619,539	216,237	603,253	474	28,716
Prevalence of disease (per 100,000 population)	1994.7	1157.2	179.8	387.0	221.7
Deaths due to disease (per 100,000 population) in the US 2018–2021[a]	47.0	16.4	45.8	0.0	2.2
Wholesale acquisition cost[b]	$26,500	$79,479	$82,882	$96,224	$78,858
Efficacy (derived from FDA package label)	27%–40% slowing of decline in cognitive and functional outcomes	Reduces mortality by 33%	20% improvement in PFS	31% remission; 45% low disease activity	46% reduction in relapse rate; 24% slowing in primary progressive MS
NNT	14–18	13–35	15	3–6	16
Black box warning (derived from FDA package label)	Amyloid related imaging abnormalities	Cardiomyopathy, infusion reactions, and Pulmonary toxicity	Gastrointestinal perforations; surgery and wound healing complications; and hemorrhage	Serious infections and malignancies	No black box warning
Risk of death due to drug (calculated from FDA package label)	0.1%	0.8%	2.5%	0.1%	0.3%
Risk of serious TEAEs (calculated from FDA package label)	7%	15%	31%	7%	18.1%

Abbreviations: FDA, United States Food and Drug Administration; NNT, number needed to treat; PFS, progression free survival; TEAE, treatment emergent adverse event.

[a]Data derived from IPD Analytics 2024.

[b]Data derived from Center for Disease Control and Prevention (CDC) WONDER representing provisional mortality rates.

shift to low disease activity in rheumatoid arthritis.[20] Ocrelizumab is a powerful agent for multiple sclerosis patients, leading to a 46% reduction in relapse rate for relapsing-remitting disease and a 24% slowing progression in primary progressive multiple sclerosis.[21] Overall, these agents lead to an approximately 24% to 45% mitigation of important disease-related outcomes, albeit the outcomes measured were very dissimilar across studies of the five biologic therapies compared in this manuscript.[18–22] Notably, the results for lecanemab (∼30% reduction of cognitive loss) falls squarely in the range of other diseases' widely-heralded biological remedies.

Alternatively, one could also consider the survival data demonstrating that 9% fewer lecanemab-treated patients declined one CDR grade after 18 months (one could consider this "progression free survival"), compared to a 20% reduction in progression free survival with bevacizumab, as evidence for suboptimal efficacy of lecanemab. Similar comparisons cannot be made in understanding the comparative effectiveness of trastuzumab and are less relevant to the comparisons with ocrelizumab and etanercept that also used reduction in disease-

related clinical and biomarker-related outcomes rather than survival outcomes.

Another way to understand clinical efficacy is through the use of analyses that derive the number needed to treat (NNT), although such analyses are also complicated by disparate outcome measures in disparate disease states. Recent analysis has suggested that the NNT for lecanemab is 14–18 persons,[23] compared to trastuzumab at 13–35,[24] bevacizumab at 15,[25] ocrelizumab at 16[26] and etanercept at 3–6 persons[27] (Table 1). Such comparison again supports a relatively comparable benefit for each of these biologic therapies given the caveats noted.

Black box warnings are included in the package label for four of these agents with the exception of ocrelizumab. The risk of death due to the drugs ranges from 0.1% to 2.5% with lecanemab deaths reported in only three patients to date.[1] As such, the risk of death due to lecanemab (0.1%) is the same or lower than any of the comparison biologicals (Table 1); while three of the other four drugs have risk of death >0.2%.

The treatment-emergent serious adverse events resulting in stopping treatment range from 7% to 31% for these agents. Again, lecanemab falls at the lower end of this range at 7% for treatment-emergent serious adverse events. The major drug-related adverse events with anti-amyloid therapy include the development of ARIAs, which include both cerebral edema (ARIA-E) as well as hemorrhage (ARIA-H).[22] In the final phase 3 study, ARIA-E was seen in 13% of treated patients compared to 2% in the control group.[28] ARIA-H was seen in 14% of treated patients compared to 8% in the control group.[28] Both ARIA-E and ARIA-H are largely asymptomatic and can be effectively managed in most cases with a temporary pause in dosing and steroid treatment if the ARIA is significant. It should be noted, however, that some cases of ARIA require cessation of treatment and can have long-lasting serious consequences, and in some cases, even prove fatal.[4,22,28]

4 | DISCUSSION

AD is by far the most prevalent of the five disease states included in this comparison, although indeed each is a relatively common condition. The mortality of AD exceeds that of lung cancer, breast cancer, rheumatoid arthritis, or multiple sclerosis.[7] Indeed, AD is one of the most feared medical conditions in the United States.[7] Currently, AD is an inexorably progressive disease in which personhood is slowly lost over several years, resulting in significant morbidity and accelerated mortality. Only in the last several years have we begun to see the development of disease-modifying therapies for the millions affected. Despite these advances, there remains much debate as to whether or not the costs of anti-amyloid therapy are worth the potential benefits.[1-5] The debate on the clinical meaningfulness of these agents has been well vetted in the literature, although many third-party payors are not routinely covering such therapy despite coverage by CMS.[1-5]

Comparing these five disparate biologic agents for very different disease states is a complicated endeavor as described above in the Results section. As the primary efficacy outcomes varied significantly among the clinical trials of these agents, only a crude comparison of relative efficacy can be established. General efficacy rates based on different important outcomes for each disease population appear comparable overall, ranging from 20% to 46% amelioration of disease burden.

Much of the debate regarding the clinical meaningfulness of the disease slowing due to lecanemab centers on the primary outcome measure: the Clinical Dementia Rating Scale Sum of Box (CDR-SOB) score. Compared to placebo, treated participants declined 0.5 points over the 18-month study treatment period, representing a 27% slowing of decline.[1-5,28] Mean change in the CDR-SOB was 1.2 in the treatment group compared to 1.7 in the placebo group.[28] While an absolute change of 0.5 is low on a scale that includes a maximum of 18 points, the patients treated in the clinical trials were in the very early stages of disease with diagnosis of MCI or early AD, where the mean baseline CDR-SOB was 3.2.[28] Thus, this advantage of 0.5 points has been suggested to be quite meaningful at this early stage of disease,

often meaning the difference between maintenance of daily functional activities and the beginning of functional decline.[3] Indeed, the endpoint of activities of daily living, measured using the Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment, showed approximately 40% slowing in the treated versus placebo group, supporting the impact of the primary outcome change in CDR-SOB.[28]

Comparisons of safety data including risks for serious treatment-emergent adverse events and risk of death due to the study drug demonstrate that lecanemab is one of the safer biologic therapies among those included in the present manuscript.[18-22] Most ARIA is asymptomatic and serious symptoms were seen in only 0.7% of treated patients in the phase 3 study, suggesting an excellent safety profile despite concerns about permanent injury to the brain as a result of the use of these agents.[28] These safety data are reassuring compared to the other biologic agents included in the present manuscript that can cause cardiomyopathy, pulmonary toxicity, gastrointestinal perforations, wound healing complications, hemorrhage, serious infections, and malignancies.[18-21] Again, concerns over the safety of anti-amyloid therapy appear to be inflated in importance beyond the actual data, which suggests that this may be one of the safest biologic agents in clinical use currently.

Annual treatment cost comparisons between the five agents studied demonstrate that lecanemab therapy at $26,500 annually is substantially lower than the other four biologic agents included in this manuscript.[14-17] This direct drug cost should be recognized as only part of the affiliated care needed for each of these agents as described above. Associated costs can vary significantly between agents and conditions included in this comparison, but notably lecanemab falls within the scope of such costs and does not appear to be an outlier, at least within the agents selected for comparison in this manuscript. Despite such overt cost comparisons, concerns have been raised about the economic impact of anti-amyloid therapy for the treatment of AD.[17] Such concerns have been supported by economic analyses, including those put forth by the Institute for Cost-Effectiveness Research, which typically equates cost to quality-adjusted life years (QALY), which is equivalent to 1 year of life in perfect health. Such analyses have not been conducted for the treatment of breast cancer by this Institute, but data and reports are available for all four of the other biologic agents compared in this manuscript. The analysis of bevacizumab suggests an overall cost-effectiveness of $100,000 to $150,000/QALY.[14] Cost-effectiveness for etanercept was set at $50,000-$150,000/QALY.[16] Cost-effectiveness for ocrelizumab was set at $100,000-$150,000/QALY.[15] In comparison, the cost-effectiveness of lecanemab was set at $8,900-$21,500 per year.[17] Cost/QALY were not provided for anti-amyloid therapy unlike the other biologic therapies used for comparison in this analysis.[17] Presumably, this is related to the fact that AD is incurable and the treatments do not actually improve the quality of life to a state of perfect health but rather sustain the quality of life in the given disease stage or slow disease progression without absolute increases in overall quality of life. QALY metrics appear to also be biased against older adults given their shorter life expectancy. As such, there is an

assumption that slowing of decline in quality of life per year following treatment is not meaningful for patients with MCI or early AD given the typically advanced age of those affected by degenerative dementia processes. Public comments on the ICER analysis and published expert opinions have aired some disagreements with such assumptions.[2–5,17] Ultimately, we endorse the idea that the elderly deserve access to relevant therapeutic options—including aggressive ones, and even risky ones—to guide their medical management.

Limitations of the current comparison include the difficulties of comparing cost, efficacy, and safety across a range of disparate disease states treated with agents that target different molecular pathways. While AD, breast cancer, and lung cancer result in accelerated mortality, multiple sclerosis and rheumatoid arthritis typically do not impact mortality significantly, although all these conditions are associated with high morbidity. Such distinctions greatly affect perceptions of acceptable risk profiles and efficacy considerations. Given the disparate molecular targets of the biologic therapies included in this manuscript, the side effect profiles and risks are significantly different beyond the commonality of infusion-related reactions which are similar in mechanism for all the biologics included in this comparison. It is problematic to compare ARIA to heart failure, immune compromise, gastrointestinal perforation, or fistula development. Comparisons of efficacy are also problematic in that outcome measures used in the clinical trials that led to FDA approval of these biologics conform to the condition studied and are distinct across these five agents. Focusing on disease progression is an oversimplification that limits the comparisons made. Cost analyses, beyond the overt drug costs, are also problematic as ancillary diagnostic testing, drug delivery logistics, and therapeutic/safety monitoring are distinctly different between the five chronic diseases studied and the mechanisms of action for the biologics compared. In addition, such costs are often part of standard care for disease states such as breast and lung cancer and might be required irrespective of treatment with a biologic therapy. We also note that a comparison of results for non-biological medications may have yielded different results, although that comparison would have been less relevant to AD therapeutics at this time. Despite such limitations, the present comparison provides a point of reference that may allow clinicians and scientists working in the area of aging and dementia to understand the caveats of biologic therapies given the recent approval of lecanemab which marks the first clinical use of a biologic therapy in the field.

In conclusion, the comparison of five different biologic agents for five distinct disease states included in this manuscript provide a framework for interpreting the utility of biologic agents with regard to the disease states being treated, including disease prevalence and mortality, as well as efficacy and safety concerns in relation to the costs of these biologic agents. This comparison demonstrates relative equivalent efficacy and safety for these agents and suggests a bias in the discussions of anti-amyloid therapies that have the promise of slowing AD progression. Anti-amyloid therapies may work best in the earliest stages of the disease, where quality of life and maintenance of function are critically important to those affected and their family members, who may have increasing burdens for caregiving in the later stages of disease. In light of these insights, a reconsideration may be in order as to how the field views treatments for the multiple degenerative causes of dementia in the aging population today. Since objective measures of efficacy and cost do not argue against them, disease-modifying agents to treat AD represent an important landmark in the history of medicine that should be embraced rather than discouraged.

CONFLICT OF INTEREST STATEMENT

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CONSENT STATEMENT

The data presented use only published sources of de-identified information and do not involve any direct or independent human subject engagement. As such, the present data are exempt from institutional review board and any additional human subject protection requirements.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.