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Original Research

Assessing the Cost-effectiveness of a Hypothetical Disease-Modifying Therapy With Limited Duration for the Treatment of Early Symptomatic Alzheimer Disease

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ABSTRACT

Purpose: Clinical trials have produced promising results for disease-modifying therapies (DMTs) for Alzheimer's disease (AD); however, the evidence on their potential cost-effectiveness is limited. This study assesses the cost-effectiveness of a hypothetical DMT with a limited treatment duration in AD.

Methods: We developed a Markov state–transition model to estimate the cost-effectiveness of a hypothetical DMT plus best supportive care (BSC) versus BSC alone among Americans living with mild cognitive impairment (MCI) due to AD or mild AD. AD states included MCI due to AD, mild AD, moderate AD, severe AD, and death. A hypothetical DMT was assumed to confer a 30% reduction in progression from MCI and mild AD. The base case annual drug acquisition cost was assumed to be $56,000. Other medical and indirect costs were obtained from published literature or list prices. Utilities for patients and caregivers were obtained from the published literature and varied by AD state and care setting (community care or long-term care). We considered 3 DMT treatment strategies: (1) treatment administered until patients reached severe AD (continuous strategy), (2) treatment administered for a maximum duration of 18 months or when patients reached severe AD (fixed-duration strategy), and (3) 40% of patients discontinuing treatment at 6 months because of amyloid plaque clearance and the remaining patients continuing treatment until 18 months or until they reached severe AD (test-and-discontinue strategy). Incremental cost-effectiveness ratios (ICERs) were calculated as the incremental cost per quality-adjusted life-year (QALY) gained.

Findings: From the health care sector perspective, continuous treatment with a hypothetical DMT versus BSC resulted in an ICER of $612,354 per QALY gained. The ICER decreased to $157,288 per QALY gained in the fixed-duration strategy, driven by large reductions in treatment costs. With 40% of patients discontinuing treatment at 6 months (test-and-discontinue strategy), the ICER was $125,631 per QALY gained. In sensitivity and scenario analyses, the ICER was the most sensitive to changes in treatment efficacy, treatment cost, and the initial population AD state distribution. From the modified societal perspective, ICERs were 6.3%, 20.4%, and 25.1% lower than those from the health care sector perspective for the continuous, fixed-duration, and test-and-discontinue strategies, respectively.

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Implications: Under a set of assumptions for annual treatment costs and the magnitude and duration of treatment efficacy, DMTs used for a limited duration may deliver value consistent with accepted US cost-effectiveness thresholds. (*Clin Ther.* 2022;000:1–14.)

Key words: Alzheimer's disease, cost-effectiveness analysis, disease-modifying therapy, economic evaluation.

INTRODUCTION

In 2020, the estimated societal cost of Alzheimer's disease (AD) and related cognitive disorders in the United States exceeded $300 billion, and their projected annual economic cost will exceed $1500 billion by 2050.[45,1] Current pharmacologic AD therapies may be categorized into those that treat AD symptoms (symptomatic) or those that modify its underlying biology to slow its progression (disease-modifying therapies [DMTs]). To date, aducanumab is the only DMT approved by the US Food and Drug Administration (FDA).

A recent economic analysis of aducanumab questioned the economic value of treatments that slow progression of early symptomatic AD to more advanced states.[2–4] Notably, this analysis found that cost-effectiveness results were highly sensitive to therapy costs. Other recent economic analyses of DMTs found favorable economic impacts of including their effects on the quality of life of informal caregivers and limiting treatment duration.[5,6]

Building on prior economic analyses, several variables could affect the cost-effectiveness of DMTs. One primary difference among DMTs in ongoing clinical trials is treatment duration, which could be expected to have a substantial impact on treatment costs. Additional variables that may affect the cost-effectiveness of DMTs include treatment efficacy, treatment cost, duration of treatment benefit, and impacts on informal caregivers. Therefore, in anticipation of FDA approval of additional DMTs for AD, quantifying their potential cost-effectiveness under a range of scenarios will enhance our understanding of the potential clinical and economic value of DMTs with different possible treatment profiles. The objective of this study is to assess the cost-effectiveness of a hypothetical DMT with a limited treatment duration but sustained clinical benefit. In addition, we use several sensitivity and scenario analyses with varying treatment characteristics and assumptions to investigate the main drivers of the cost-effectiveness of such a hypothetical DMT.

PARTICIPANTS AND METHODS

Model Overview

We developed a Markov state–transition model in Microsoft Excel to estimate the cost-effectiveness of a hypothetical DMT plus best supportive care (BSC) versus BSC alone among Americans living with mild cognitive impairment (MCI) due to AD or mild AD. Best supportive care includes nonpharmacologic and symptomatic pharmacologic interventions but excludes DMTs. The model uses 5 AD states to track disease progression, including MCI due to AD, mild AD, moderate AD, severe AD, and death (Figure 1). The model also reflects the care setting for the patient with AD, including community care and long-term care (LTC).

The model structure and inputs mirror the approach taken in the economic evaluation of aducanumab conducted by the Institute for Clinical and Economic Review.[4] We follow their detailed methods, which have previously been well documented.[4]

Results were based on a patient's lifetime time horizon with a model cycle length of 3 months. Following US cost-effectiveness standard practice, costs and outcomes were discounted annually at 3%.[7] Analyses were conducted from both the health care sector and modified societal perspectives. The health care sector perspective included treatment, administration, LTC, and patient direct medical costs (Table I). The modified societal perspective included the health care sector costs, direct medical costs of the informal caregiver, and productivity costs of both the patient and the informal caregiver. Health outcomes were reported as life-years and quality-adjusted LYs (QALYs). Whereas the health care sector perspective focused on patient QALYs, the modified societal perspective also included informal caregiver QALYs. Incremental cost-effectiveness ratios (ICERs) were calculated as the incremental cost per QALY gained.

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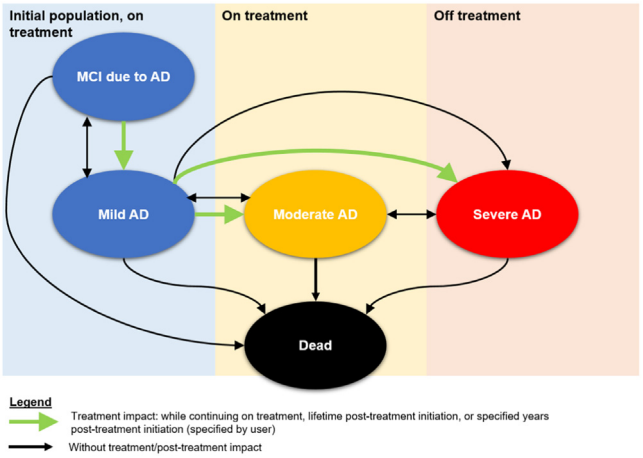

Figure 1. Model diagram. Across all treatment duration strategies, patients are assumed to discontinue treatment on reaching the severe Alzheimer's disease (AD) state. In the fixed-duration scenario, patients continue to receive treatment for 18 months, whereas in the test-and-discontinue strategy 40% of patients discontinue treatment at 6 months because of amyloid plaque clearance. In addition, the model assumes that 10% of patients stop treatment because of adverse events within the first 6 months of treatment. The base case model assumes that the treatment impact continues until progression to moderate AD. MCI = mild cognitive impairment.

Clinical Inputs

At baseline, patients were assigned to MCI (55%) and mild AD (45%) states, with 92% of patients in the community care setting and 8% in the LTC setting.[8,9] Patients subsequently transitioned to more severe states as their disease progressed. Patients could also transition from the community to LTC setting, where they remained until death.[10]

Treatment was assumed to involve an infusion given every 4 weeks (ie, 13 times per year). Treatment effects were represented as relative risks (RRs) applied to baseline AD transitions (Supplemental Table I). The RR of AD progression for a hypothetical DMT was 0.70 for all progressions from MCI and mild AD to more advanced states, resulting in a 30% reduction in the BSC transition probabilities. This 30% reduction was informed by recent clinical trials in AD progression, as well as a European Union consensus statement on clinically meaningful modifications in AD progression.[11] The model assumes no impact of treatment on the rate of disease progression from the moderate AD state.

We considered a set of 3 base strategies reflecting different DMT treatment durations: (1) treatment administered until patients reached severe AD (continuous strategy), which aligns with the Institute for Clinical and Economic Review's previous analysis[4]; (2) treatment administered for a maximum duration of 18 months or until patients reached severe AD (fixed-duration strategy); and (3) 40% of patients discontinued treatment at 6 months because of amyloid plaque clearance and the remaining patients continued treatment until a maximum of 18 months or until they reached severe AD (test-and-discontinue strategy). The fixed-duration and test-and-discontinue strategies are promising treatment approaches supported by clinical and biomarker responses observed in recent clinical trials that suggest that some antiamyloid DMTs produce disease-modifying benefits that persist beyond the period of treatment.[12,13] The fixed-duration strategy reflects a conservative treatment approach wherein practitioners are unable or choose not to order a diagnostic test (eg, positron emission tomography [PET]) to establish amyloid clearance. In comparison, the test-and-discontinue strategy mimics a treat-to-clear approach, which has been implemented in clinical trials through the use of amyloid PET. Across all treatment strategies, the treatment benefit was

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Table I. Key model inputs.

Model Input	Value	Perspective		Source
		Health Care Sector	Modified Societal	
Clinical Inputs				
Relative risks, hypothetical DMT and BSC vs BSC alone				
Progression from MCI	0.7	X	X	Assumption
Progression from mild AD	0.7	X	X	Assumption
Progression from moderate AD	1.0	X	X	Assumption
Annual transition probabilities to long-term care, %				
MCI due to AD	2.40	X	X	Whittington et al,[4] 2002
Mild AD	3.80	X	X	Neumann et al,[11] 1999
Moderate AD	11.00	X	X	
Severe AD	25.90	X	X	
Relative risk of death by AD state				
MCI due to AD	1.82	X	X	Andersen et al,[44] 2010
Mild AD	2.92	X	X	
Moderate AD	3.85	X	X	
Severe AD	9.52	X	X	
Probability of treatment discontinuation due to ARIA, %	10	X	X	FDA AdComm Briefing Document[14]
Utility Inputs				
Patient disutilities, community setting				
MCI due to AD	−0.17	X	X	Neumann et al,[19] 1999
Mild AD	−0.22	X	X	Neumann et al,[10,19] 1999
Moderate AD	−0.36	X	X	
Severe AD	−0.53	X	X	
Patient disutilities, long-term care setting				
MCI due to AD	−0.17	X	X	Assumption
Mild AD	−0.19	X	X	Neumann et al,[10, 19] 1999
Moderate AD	−0.42	X	X	
Severe AD	−0.59	X	X	
Caregiver disutilities, community setting and long-term care setting				
MCI due to AD	−0.03		X	Neumann et al,[19] 1999
Mild AD	−0.05		X	Neumann et al,[10] 1999
Moderate AD	−0.08		X	Mesterton et al,[30] 2010
Severe AD	−0.10		X	

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Table I. (*continued*)

Model Input	Value	Perspective		Source
		Health Care Sector	Modified Societal	
Cost Inputs, $				
Hypothetical DMT annual cost, year 1[a]	47,488	X	X	Assumption
Hypothetical DMT annual cost, year 2 or later[a]	59,360	X	X	Assumption
Annual direct medical cost	8840	X	X	Leibson et al,[26]
Direct medical multiplier costs				
MCI due to AD	1.12	X	X	Leibson et al,[26]
Mild AD	1.56	X	X	
Moderate AD	1.93	X	X	
Severe AD	1.93	X	X	
Long-term care cost per month	7186	X	X	Administration on Aging[27]
Caregiver direct medical costs per month				
MCI due to AD	447		X	Robinson et al,[29]
Mild AD	938		X	Assumption based on
Moderate AD	1501		X	Robinson et al,[29] and
Severe AD	1876		X	Mesterton et al,[30]
Brain MRI cost per scan	255.33	X	X	CMS physician fee schedule[22]
Amyloid PET cost per scan	4467	X	X	MediSpan PriceRx[23]; The New IDEAS Study[24]
Cost per intravenous administration	74.58	X	X	CMS physician fee schedule[22]

AD = Alzheimer's disease; ARIA = amyloid-related imaging abnormality; BSC = best supportive care; CMS = Centers for Medicare & Medicaid Services; DMT = disease-modifying treatment; FDA = Food and Drug Administration; MCI = mild cognitive impairment; MRI = magnetic resonanc imaging; PET = positron emission tomography.

[a] Annual cost includes $56,000 drug acquisition cost and 6% markup for infusion. Year 1 annual cost includes 80% dose titration.

maintained until the patient reached moderate AD. The duration of the treatment benefit was varied in scenario analyses.

Irrespective of the treatment strategy, patients may discontinue treatment because of amyloid-related imaging abnormality (ARIA) adverse events, which are associated with antiamyloid monoclonal antibodies.[14] These events are assumed to last 12 weeks,[14] which aligns with clinical trial data for antiamyloid monoclonal antibodies indicating that the typical ARIA duration ranges from 3 to 8 months [12,15–17] Because most ARIA events occur within the first 3 to 6 months of treatment,[12,15–17] the model allows patients to discontinue treatment because of symptomatic ARIA adverse events at a rate of 10% during the first 6 months of treatment. The model assumes that 50% of these discontinuations because of ARIA events occur at 3 months and the remaining 50% occur at 6 months, with no subsequent treatment or benefit in those who discontinue. For the test-and-discontinue strategy, all ARIA-related treatment discontinuations are assumed to occur before the PET scan at month 6 to

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account for the shortened treatment benefit for patients who discontinue before amyloid plaque clearance. This approach deviates from the Institute for Clinical and Economic Review's analysis, which assumed 10% of patients discontinued because of ARIA adverse events within the first 18 months of treatment,[4] but is more consistent with timing of ARIA events observed in clinical trials.[4,12,15,18]

Health Utility Inputs

Patient utilities stratified by AD severity and care setting were obtained from the published literature (Table I).[10,19] The modified societal perspective included informal caregiver disutilities—one type of family spillover.[7] Informal caregiver disutilities were assumed to be the same for community and LTC settings. The QALYs lost due to informal caregiver disutilities were subtracted from patient QALYs gained to calculate overall net QALY impact.

A disutility of −0.14 was implemented for patients experiencing symptomatic ARIAs using headache (the most common symptom of ARIA) as a proxy.[20] The daily disutility was applied for the assumed 12-week duration of symptomatic ARIAs.

Costs

All costs in the model are reported in 2020 US dollars (Table I). Patient and informal caregiver direct medical costs were included for each AD state. In addition, the model includes drug costs, adverse event management costs, monitoring costs, and LTC costs.

Given that the intervention is a hypothetical treatment, an annual drug acquisition cost of $56,000 was tested in the 3 base strategies, which was consistent with Biogen's initial price for aducanumab and aligns with the final Institute for Clinical and Economic Review report.[4] A lower annual price of $28,000 was tested in scenario analyses, which is consistent with Biogen's recently revised price for aducanumab.[21] In the first year, an 80% dose titration was applied, leading to reduced treatment costs. In addition, a 6% markup for infusion was included each year, leading to annual treatment costs of $47,488 in the first year and $59,390 in subsequent years. Treatment administration costs were applied 13 times per year with a cost of $74.58 per administration.[22]

In the test-and-discontinue strategy, all patients incurred a $4467 diagnostic testing cost at 6 months. This amount is consistent with the cost of amyloid PET (currently the only diagnostic test that is able to establish plaque clearance) and includes current Centers for Medicare & Medicaid Services (CMS) reimbursement for amyloid PET and the mean amyloid radiopharmaceutical wholesale acquisition cost.[23,24]

We assumed that patients experiencing ARIA adverse events received 3 brain magnetic resonance images, once every 4 weeks for 12 weeks. In addition, monitoring requirements for both treatment arms included 3 brain magnetic resonance images in the first year while undergoing treatment. The cost of a magnetic resonance image was obtained from the CMS.[22]

Annual inpatient and outpatient direct medical costs stratified by AD severity were used to calculate a direct medical cost multiplier for each AD state.[46,26] For patients in the LTC setting, an additional annual LTC cost of $86,232 ($7186 per month) was applied.[27]

For the modified societal perspective, patient and informal caregiver productivity costs were estimated by summing lost productive hours and multiplying them by the 2020 national mean gross hourly wage for workers ($29.58).[28] Employed patients with AD (MCI, 20.4%; mild AD, 11.1%)[29] reporting reduced work productivity were assigned 20 lost hours per week. Community-dwelling caregivers of patients with AD were assigned AD health state–based lost productivity hours per month. The modified societal perspective also included informal caregiver direct medical costs.[29,30]

Statistical Analysis

We estimated the cost-effectiveness of a hypothetical DMT across the 3 base treatment strategies from the health care sector and modified societal perspectives using the Microsoft Excel–based Markov state–transition model developed for this study. Sensitivity and scenario analyses were performed on a set of defined variables from the health care sector perspective.

RESULTS

Alternative Intervention Strategies From the Health Care Sector Perspective

Comparing a hypothetical DMT used continuously (continuous treatment strategy) to BSC from the health care sector perspective led to an incremental total cost of $285,165, with 0.466 total QALYs gained and 0.462 total life-years gained (Table II). Most incremental costs were attributed to incremental treatment costs ($275,177), whereas there were relatively small

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Table II. Base treatment strategy results for DMT vs BSC from the health care sector perspective.

Results Category	Incremental Results for Continuous Treatment vs BSC	Incremental Results for Fixed-Duration Treatment vs BSC	Incremental Results for Test-and-Discontinue vs BSC	Total Results for BSC[a]
Costs, $				
Total costs	285,165	73,279	58,531	221,858
Treatment costs	275,177	66,684	48,254	0
Long-term care costs	1577	1587	1587	139,192
Patient direct medical costs	3741	3743	7760	82,666
Undiscounted mean time in AD states, y				
MCI Due to AD	0.667	0.667	0.667	2.027
Mild AD	0.452	0.452	0.452	1.807
Moderate AD	-0.181	-0.181	-0.181	1.172
Severe AD	-0.323	-0.323	-0.323	1.699
Life-years	0.462	0.462	0.462	5.937
QALYs	0.466	0.466	0.466	3.489
Incremental cost per QALY gained, $	612,354	157,288	125,631	NA

AD = Alzheimer's disease; DMT = disease-modifying treatment; BSC = best supportive care; NA = not applicable; QALY = quality-adjusted life-year.

[a] BSC values are included as a reference and reflect total amounts rather than incremental amounts. Incremental results for all treatment strategies are calculated relative to the BSC totals.

increases in LTC ($1577) and medical costs ($3741) due to patients receiving the DMT living longer than patients receiving BSC alone. The projected ICER for the continuous treatment strategy was $612,354 per QALY gained.

A hypothetical DMT used for 18 months (fixed-duration treatment strategy) resulted in a total incremental cost for the DMT versus BSC of $73,279, driven by incremental treatment costs of $66,684. Because treatment effects were sustained until patients reached moderate AD, the life-year and QALY gains were equivalent to those in the continuous treatment scenario. The ICER for the fixed-duration treatment strategy was $157,288 per QALY gained.

With 40% of patients discontinuing treatment at 6 months (test-and-discontinue strategy), the incremental costs for the DMT versus BSC were $58,531, mainly due to incremental treatment costs of $48,254. The ICER for this strategy was $125,631 per QALY gained.

Alternative Intervention Strategies From the Modified Societal Perspective

When assessing the cost-effectiveness of the continuous treatment strategy from the modified societal perspective, incremental costs decreased by $14,026 relative to the health care sector perspective due to cost offsets for informal caregiver direct medical costs (−$2351) and informal caregiver productivity costs (−$11,889; Supplemental Table II). The inclusion of informal caregiver QALYs in the modified societal perspective also increased incremental QALYs by 0.007 relative to the health care sector perspective. The resulting ICER was $573,530 per QALY gained.

Similar trends were observed for the fixed-duration and test-and-discontinue treatment strategies. For the fixed-duration treatment strategy, the ICER was $125,276 per QALY gained, and for the test-and-discontinue treatment strategy, the ICER was $94,092 per QALY gained.

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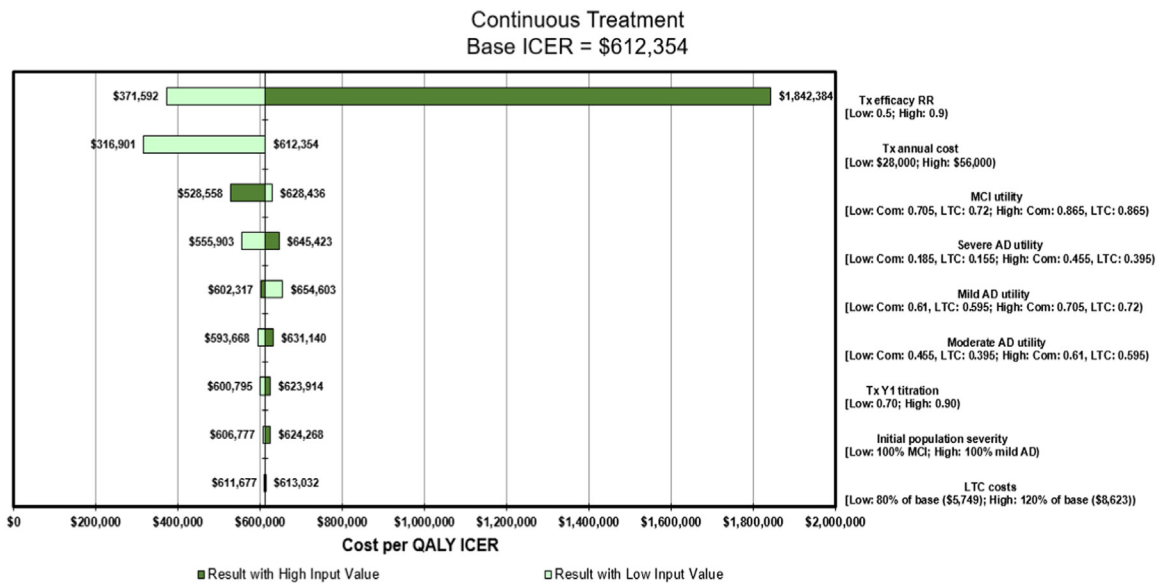

Figure 2. One-way sensitivity analysis results for the continuous treatment strategy. Tornado diagram depicting the most influential inputs on the incremental cost-effectivness ratio (ICER) for the continuous treatment strategy from the health care sector perspective. AD = Alzheimer's disease; Com = community based care; LTC = long-term care; MCI = mild cognitive impairment; QALY = quality-adjusted life-year; RR = relative risk.

Sensitivity and Scenario Analyses From the Health Care Sector Perspective

In sensitivity and scenario analyses varying a set of parameters from the health care sector perspective, the ICER in the continuous treatment strategy was most sensitive to treatment efficacy and treatment cost (Figure 2). In the other treatment strategies, the ICERs were most sensitive to treatment efficacy, treatment cost, and the initial AD state distribution (100% MCI vs 100% mild AD) (Figure 3; Supplemental Figure 1).

When the annual drug acquisition cost was reduced from $56,000 to $28,000, the ICER decreased by 41% to 48% across the 3 treatment strategies, with the largest ICER decrease observed in the continuous treatment strategy.

Reducing treatment efficacy to a RR of 0.9 (vs a RR of 0.7 in the base case) translated to more rapid disease progression for DMT than in the base case and therefore increased the ICERs by 201% to 225% across the 3 treatment strategies. Conversely, improving treatment efficacy by setting the RR to 0.5 reduced the ICERs by 39% to 43%.

When the duration of the treatment effect was set to a maximum of 4 years for the fixed-duration and test-and-discontinue treatment strategies, as opposed to maintaining the treatment effect continuously until moderate AD is reached, the ICERs increased by 46% and 44% due to reductions in QALY gains. When the duration of the treatment effect was reduced to 8 years, the ICERs for both strategies increased by 9%.

Two scenarios tested the impact of varying the AD state distribution for the initial model cohort. In a scenario where 100% of the cohort entered the model in the MCI state, patients took longer to reach moderate AD and experienced a longer treatment effect. In this scenario, the ICER decreased by 15% in the fixed-duration and test-and-discontinue treatment strategies. When 100% of the cohort entered the model in the mild AD state, patients received the treatment benefit for a shorter amount of time relative to the base strategies and experienced a lesser gain in health outcomes. Therefore, the ICER increased by 32% in the fixed-duration and test-and-discontinue strategies. For the continuous treatment strategy, ICERs varied by <2% when the initial AD state distribution was varied.

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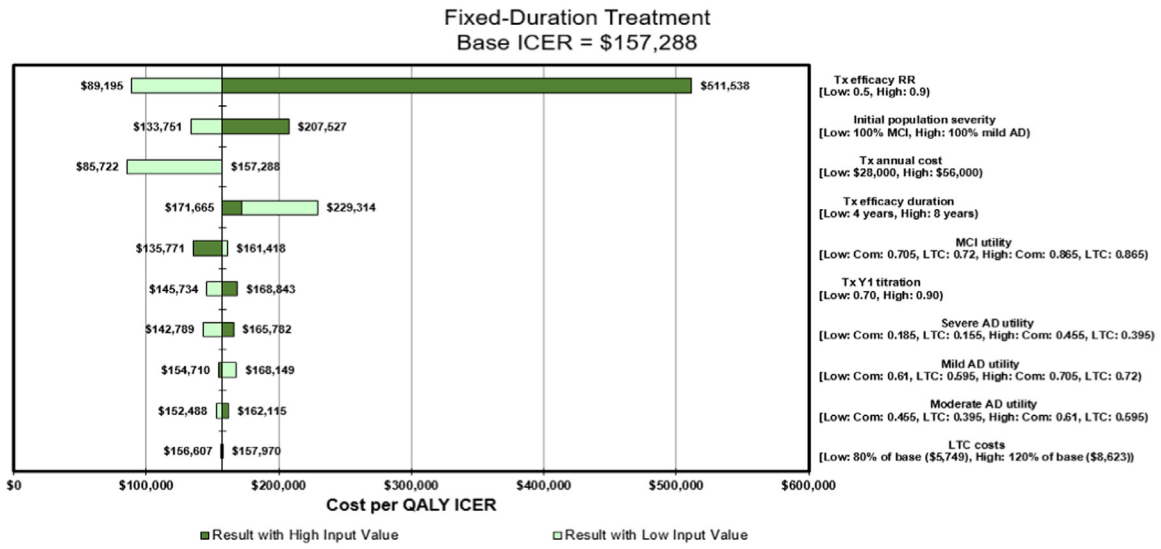

Figure 3. One-way sensitivity analysis results for the fixed-duration treatment strategy. Tornado diagram depicting the most influential inputs on the incremental cost-effectivness ratio (ICER) for the fixed-duration treatment strategy from the health care sector perspective. AD = Alzheimer's disease; Com = community-based care; LTC = long-term care; MCI = mild cognitive impairment; QALY = quality-adjusted life-year; RR = relative risk.

The ICERs were less sensitive to changes in additional variables that were tested in scenario analyses, including the percentage discontinuing treatment (applied in test-and-discontinue strategy only), the amount of treatment titration in the first year, LTC costs, and AD state utilities. Across these additional scenarios, the ICER varied by ≤16%.

DISCUSSION

Our results from the health care sector perspective at an annual drug acquisition cost of $56,000 indicated that a fixed DMT treatment duration of 18 months substantially reduced treatment costs relative to a continuous treatment duration, resulting in a 74% ICER reduction. In the test-and-discontinue strategy, discontinuing treatment for patients who have sufficient amyloid plaque clearance at 6 months resulted in relatively low incremental treatment costs and an ICER that fell below the commonly cited US willingness-to-pay threshold of $150,000 per QALY gained.[31]

Our findings are consistent with a recently published study by Ross et al.,[6] which found that a limited-duration dosing scheme resulted in greater health economic value and that this approach may allow clinically effective antiamyloid DMTs to be economically viable in the United States, even when priced similarly to other biologics.[6] When modeling a test-and-discontinue strategy (27% and 55% of patients suspend treatment at 6 and 12 months, respectively) with an annual drug cost of $28,200, a hazard ratio for disease progression of 0.68, screening costs of $17,096 per patient, and twice-yearly PET, this study reported a base case ICER of $193,000 per QALY gained.[6] When removing the high upfront screening costs to identify eligible patients, which were not included in our model, the ICER decreased to $151,000 per QALY gained.

When we incorporated informal caregiver medical costs, informal caregiver quality of life, and patient and informal caregiver productivity costs in the modified societal perspective, the ICERs for the fixed-duration and test-and-discontinue treatment strategies were 20% and 25% lower, respectively, when compared with the health care sector perspective. These notable ICER reductions indicate the importance of considering informal caregiver impacts when evaluating the cost-effectiveness of AD treatments because of

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the significant reliance of patients with AD on their informal caregivers for daily functioning.[32] A recent study by Ito et al.[5] assessed the cost-effectiveness of a hypothetical DMT and found that the inclusion of informal caregiver quality of life and productivity reduced the ICER by >60%. When compared with our study, this larger ICER reduction found by Ito et al.[5] is in part due to their quantification of lost leisure time for informal caregiver nonworkers, whereas our model only accounted for lost informal caregiver productive time. On the basis of their findings, the authors recommended that informal caregiver effects be considered in the economic modeling of AD treatments,[5] which will require the collection of high-quality data on informal caregiver impacts.

Sensitivity and scenario analyses found that the ICER was most sensitive to changes in treatment efficacy, treatment cost, and the initial population AD state distribution, which indirectly affects the duration of the treatment effect, particularly among the fixed-duration and treat-to-discontinue strategies. Notably, when the treatment efficacy decreased (RR = 0.9), the ICERs increased by >200%. The impact of treatment efficacy on DMTs was also found by the review of aducanumab performed by the Institute for Clinical and Economic Review, which found that the ICER was most sensitive to variation in treatment efficacy.[4] Similar findings were found by Ross et al.,[6] who found that ICERs for aducanumab and donanemab from the health care sector perspective were most sensitive to treatment efficacy.

Treatment costs were also very influential on the ICER. When annual treatment acquisition costs were reduced by 50%, ICERs for the fixed-duration and test-and-discontinue treatment strategies decreased to <$100,000 per QALY gained. Finally, our model assumes that treatment effects are maintained until patients reach moderate AD, which is the functional equivalent of maintaining treatment effects for approximately 10 years in the base analysis. In scenarios that varied the duration of the treatment effect from 4 to 8 years, the ICERs increased from as much as 46% (4 years) to 9% (8 years) in the fixed-duration and test-and-discontinue treatment strategies, demonstrating the impact of sustained clinical benefits on the cost-effectiveness of DMTs. A similar finding was reported by Herring et al.[33] in a modeling study that assessed the lifetime clinical benefits of aducanumab plus standard-of-care treatment versus standard of care alone from the EMERGE (221AD302 Phase 3 Study of Aducanumab (BIIB037) in Early Alzheimer's Disease) trial. Although that study focused on health outcomes and did not consider costs, the authors found that when the treatment effects of aducanumab ended after 3 or 5 years (vs when patients reach moderate AD), median survival decreased among patients.

The results of this study should be considered in light of several limitations. Uncertainty remains regarding the efficacy and duration of treatment effects for DMTs in development. In addition, patient and informal caregiver utilities were obtained from cross-sectional studies that may not appropriately reflect utility changes over time. Furthermore, the generic health-related quality-of-life instruments used may not capture all relevant quality-of-life domains for patients with AD and their informal caregivers. Informal caregiver utilities were also assumed to be the same for community and LTC settings because of a paucity of published quality-of-life data for informal caregivers of patients with AD. This assumption is unlikely to reflect the real-world QOL impacts of informal caregivers for patients with AD in each setting. The model also only accounts for the impacts of 1 primary informal caregiver, which may underestimate the informal caregiver costs and effects when patients have multiple informal caregivers.[34] This analysis also did not consider delirium, which is significantly associated with long-term cognitive decline.[35] Delirium is a major driver of emergency department visits, hospitalizations, and follow-on complications for patients with AD. Therefore, both costs and mortality rates in this study, and hence the value of effective DMTs, are likely underestimated because they do not account for the higher incidence of delirium in hospitalized patients with AD.[36] This study also did not factor in any potential of a DMT to reduce delirium by delaying progression of the cognitive decline associated with AD. Future research should incorporate the impact of delirium on the overall costs and mortality of AD and examine whether DMTs have any impact on these clinical and economic outcomes. Finally, this analysis did not account for the possibility of widespread uptake of the evidence-based collaborative AD care model that found improvement in behavioral and psychological symptoms of both patients with AD and their informal caregivers in addition to

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increasing community living and reduction in acute care utilization.[37,38]

Additional research is needed to broaden the perspective of value assessments for AD therapies. One area of focus should be on the costs of different methods of screening large patient populations to identify patients with AD as soon as subtle symptoms appear and possibly even earlier. Our analysis indicates the importance of early diagnosis by the finding that a hypothetical DMT used for a limited duration would be more cost-effective when the initial cohort begins treatment earlier in their disease progression (ie, 100% MCI vs 100% mild AD). In addition, there is potential value in serial testing strategies; for example, using a sensitive but less expensive blood test, followed by more specific and expensive PET for those who screen positive as a strategy could cost-effectively identify patients eligible for DMTs. To date, most cost-effectiveness analyses of DMTs for AD have presupposed identification of the correct patients, but this is difficult to achieve in current real-world practice because of a mix of public policy, medical practice, and technological barriers. Today, in practice, accurate detection of the presence of amyloid is infrequent.[39] The economic value of antiamyloid treatments will depend in part on improved diagnostics to ensure that treatment-eligible patients are identified early in the disease course and treatment is initiated and monitored appropriately. The current health care system is ill-prepared for this unmet need and will need to adapt accordingly.

Future research is also required to address the limitations with applying traditional cost-effectiveness modeling approaches to DMTs for AD. To encourage a more holistic approach to value assessments, ISPOR developed a "value flower" framework that reflects the core elements of conventional cost-effectiveness analyses as well as newer elements related to changes in uncertainty (eg, insurance value, value of hope, and real option value).[40] This framework also highlights the importance of scientific spillovers that involve new treatments advancing the scientific field. When scientific spillovers occur, treatments that confer relatively small incremental benefits spur continued innovation when valued appropriately. An example of these spillover effects is the advances in squamous lung cancer treatment wherein incremental treatment improvements have resulted in a clinically meaningful impact for patients.[41] Recent formal mathematical explication of these new value elements highlights the importance of adjusting the cost-per-QALY threshold to capture the severity of the condition and acuity of need.[32] Because AD is a severe condition with limited treatment options affecting older populations, a higher cost-per-QALY threshold may be warranted.[42] A recent analysis of a hypothetical DMT that slowed AD by 30% concluded the treatment would be worth $5.5 trillion to US society— >$134,000 for each American who currently has MCI and >$18,000 for every adult American who does not have MCI but who would be willing to pay for the reassurance that a treatment exists.[43] Such figures suggest that willingness-to-pay thresholds may need to be adjusted higher for AD, yet future research is needed to inform how to accurately quantify nontraditional value elements (eg, scientific spillover, value of hope) and appropriately adjust willingness-to-pay thresholds.

CONCLUSIONS

This analysis found that under a reasonable set of assumptions for annual treatment costs and the magnitude and duration of treatment efficacy, DMTs with a limited duration of use and sustained clinical benefits until progression to moderate AD have the potential to deliver value consistent with currently accepted US cost-effectiveness thresholds. Treatment efficacy, drug costs, and the duration of the treatment benefit are important treatment characteristics that our study found to have a large impact on the cost-effectiveness of a hypothetical DMT. Future economic evaluations of DMTs should account for the economic impact of these treatment characteristics.

DECLARATION OF INTEREST

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.clinthera.2022.09.008.

REFERENCES

1. Committee on the Decadal Survey of Behavioral and Social Science Research on Alzheimer's Disease and Alzheimer's Disease-Related Dementias. *Reducing the Impact of Dementia in America: A Decadal Survey of the Behavioral and Social Sciences*. The National Academies Press; 2021 doi:10.17226/26175.
2. Franklin M. ICER report on Alzheimer's disease: implications from a patient perspective. *Journal of Managed Care & Specialty Pharmacy*. 2021;27:1618–1620. doi:10.18553/jmcp.2021.27.11.1618.
3. Synnott PG, Whittington MD, Lin GA, Rind DM, Pearson SD. The effectiveness and value of aducanumab for Alzheimer's disease. *Journal of Managed Care & Specialty Pharmacy*. 2021;27:1613–1617. doi:10.18553/jmcp.2021.27.11.1613.
4. Whittington MD, Campbell JD, Rind D, Fluetsch N, Lin GA, Pearson SD. Cost-effectiveness and value-based pricing of aducanumab for patients with early Alzheimer's disease. *Neurology*. 2022;98:e968–e977. doi:10.1212/wnl.0000000000013314.
5. Ito K, Chapman R, Pearson SD, Tafazzoli A, Yaffe K, Gurwitz JH. Evaluation of the cost-effectiveness of drug treatment for Alzheimer's disease in a simulation model that includes caregiver and societal factors. *JAMA Network Open*. 2021;4:e2129392. doi:10.1001/jamanetworkopen.2021.29392.
6. Ross EL, Weinberg MS, Arnold SE. Cost-effectiveness of aducanumab and donanemab for early Alzheimer's disease in the US. *JAMA Neurology*. 2022;79:478–487. doi:10.1001/jamaneurol.2022.0315.
7. Sanders GD, Neumann PJ, Basu A, et al. Recommendations for conduct, methodological practices, and reporting of cost-effectiveness analyses: second panel on cost-effectiveness in health and medicine. *JAMA*. 2016;316:1093–1103. doi:10.1001/jama.2016.12195.
8. Potashman M, Benea M, Gillis C, Gianinazzi M, Ikram MA, Maserejian N. Estimating the prevalence of Aβ-confirmed Alzheimer's disease using a funnel-based approach. *Value in Health*. 2020;23:S633–S634. Abstract PND59.
9. Johnson RW. ASPE Research Brief: What Is the Lifetime Risk of Needing and Receiving Long-Term Services and Supports? Office of the Assistant Secretary for Planning and Evaluation. US Dept of Health and Human Services. April 3, 2019. Available at: https://aspe.hhs.gov/reports/what-lifetime-risk-needing-receiving-long-term-services-supports-0. Accessed December 2021.
10. Neumann PJ, Hermann RC, Kuntz KM, et al. Cost-effectiveness of donepezil in the treatment of mild or moderate Alzheimer's disease. *Neurology*. 1999;52:1138–1145. doi:10.1212/wnl.52.6.1138.
11. Vellas B, Andrieu S, Sampaio C, Wilcock G. Disease-modifying trials in Alzheimer's disease: a European task force consensus. *The Lancet Neurology*. 2007;6(1):56–62. doi:10.1016/s1474-4422(06)70677-9.
12. Mintun MA, Lo AC, Duggan Evans C, et al. Donanemab in early Alzheimer's disease. *New England Journal of Medicine*. 2021;384:1691–1704. doi:10.1056/NEJMoa2100708.
13. Swanson C, Dhadda S, Irizarry M, et al. Clinical, Biomarker, and Safety Update from the Lecanemab Phase 2 Study. Lecanemab: An Assessment of the Clinical Effects, the Correlation of Plasma AB 42/40 Ratio with Changes in Brain Amyloid PET SUVr, and Safety from the Core and Open Label Extension of the Phase 2 Proof-of-Concept Study, BAN2401-G000-201, in Subjects with Early Alzheimer's Disease. Paper presented at: Annual Meeting of Clinical Trials on Alzheimer's Disease; November 2021; Boston, MA.

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14. Food and Drug Administration Peripheral and Central Nervous System (PCNS) Drugs Advisory Committee. Combined FDA and Applicant PCNS Drugs Advisory Committee Briefing Document: Aducanumab. November 6, 2020. Available at: https://www.fda.gov/media/143502/download. Accessed December 2021.
15. Haeberlein SB, Aisen PS, Barkhof F, et al. Two randomized phase 3 studies of aducanumab in early Alzheimer's disease. *The Journal of Prevention of Alzheimer's Disease*. 2022;9:197–210. doi:10.14283/jpad.2022.30.
16. Haeberlein SB, Gheuens S, Chen T, et al. Aducanumab 36-month data from PRIME: a randomized, double-blind, placebo-controlled Phase 1b study in patients with prodromal or mild Alzheimer's disease (S2.004). *Neurology*. 2018;90(15 Supplement).
17. Swanson CJ, Zhang Y, Dhadda S, et al. A randomized, double-blind, phase 2b proof-of-concept clinical trial in early Alzheimer's disease with lecanemab, an anti-Aβ protofibril antibody. *Alzheimer's Research & Therapy*. 2021;13:80. doi:10.1186/s13195-021-00813-8.
18. Sperling R, Salloway S, Brooks DJ, et al. Amyloid-related imaging abnormalities in patients with Alzheimer's disease treated with bapineuzumab: a retrospective analysis. *The Lancet Neurology*. 2012;11:241–249. doi:10.1016/s1474-4422(12)70015-7.
19. Neumann PJ, Kuntz KM, Leon J, et al. Health utilities in Alzheimer's disease: a cross-sectional study of patients and caregivers. *Medical Care*. 1999;37:27–32. doi:10.1097/00005650-199901000-00005.
20. Xu R, Insinga RP, Golden W, Hu XH. EuroQol (EQ-5D) health utility scores for patients with migraine. *Quality of Life Research*. 2011;20:601–608. doi:10.1007/s11136-010-9783-5.
21. Biogen Investor Relations. Biogen announces reduced price for Aduhelm to improve access for patients with early Alzheimer's Disease. Available at: https://investors.biogen.com/news-releases/news-release-details/biogen-announces-reduced-price-aduhelmr-improve-access-patients. Accessed April 12, 2022.
22. Centers for Medicare and Medicaid Services. Clinical Physician Fee Schedule Files. https://www.cms.gov/medicare/physician-fee-schedule/search/documentation.
23. Medi-Span PriceRx. Accessed February 23, 2022.
24. The New IDEAS Study. Medicare Reimbursement for Amyloid PET Scans. Accessed April 1, 2022. https://www.ideas-study.org/During-Study/Medicare-Reimbursement.
25. Institute for Clinical and Economic Review. *Aducanumab for Alzheimer's Disease: Effectiveness and Value. Final Evidence Report and Meeting Summary*; 2021.
26. Leibson CL, Long KH, Ransom JE, et al. Direct medical costs and source of cost differences across the spectrum of cognitive decline: a population-based study. *Alzheimer's & Dementia*. 2015;11:917–9132. doi:10.1016/j.jalz.2015.01.007.
27. Administration on Aging. Costs of Care. Accessed December 13, 2021. https://acl.gov/ltc/costs-and-who-pays/costs-of-care.
28. U.S. Bureau of Labor Statistics. *Table B-3. Average hourly and weekly earnings of all employees on private nonfarm payrolls by industry sector, seasonally adjusted - 2022 Q01 Results*; 2022. Accessed April 16, 2022 *https://www.bls.gov/news.release/empsit.t19.htm*.
29. Robinson RL, Rentz DM, Andrews JS, et al. Costs of early stage Alzheimer's disease in the United States: cross-sectional analysis of a prospective cohort study (GERAS-US). *Journal of Alzheimer's Disease*. 2020;75:437–450. doi:10.3233/jad-191212.
30. Mesterton J, Wimo A, By A, Langworth S, Winblad B, Jönsson L. Cross sectional observational study on the societal costs of Alzheimer's disease. *Current Alzheimer Research*. 2010;7:358–367. doi:10.2174/156720510791162430.
31. Neumann PJ, Cohen JT, Weinstein MC. Updating cost-effectiveness — the curious resilience of the $50,000-per-QALY threshold. *New England Journal of Medicine*. 2014;371:796–797. doi:10.1056/NEJMp1405158.
32. Makin C, Neumann P, Peschin S, Goldman D. Modelling the value of innovative treatments for Alzheimer's disease in the United States. *Journal of Medical Economics*. 2021;24:764–769. doi:10.1080/13696998.2021.1927747.
33. Herring WL, Gould IG, Fillit H, et al. Predicted lifetime health outcomes for aducanumab in patients with early Alzheimer's disease. *Neurology and Therapy*. 2021;10:919–940. doi:10.1007/s40120-021-00273-0.
34. Lin P-J, D'Cruz B, Leech AA, et al. Family and caregiver spillover effects in cost-utility analyses of Alzheimer's disease interventions. *PharmacoEconomics*. 2019;37:597–608. doi:10.1007/s40273-019-00788-3.
35. Davis DHJ, Skelly DT, Murray C, et al. Worsening cognitive impairment and neurodegenerative pathology progressively increase risk for delirium. *American Journal of Geriatric Psychiatry*. 2015;23:403–415. doi:10.1016/j.jagp.2014.08.005.
36. Khan BA, Zawahiri M, Campbell NL, et al. Delirium in hospitalized patients: implications of current evidence on clinical practice and future avenues for research—a systematic evidence review. *Journal of Hospital Medicine*. 2012;7:580–589. doi:10.1002/jhm.1949.
37. Boustani M, Alder CA, Solid CA, Reuben D. An Alternative Payment Model To Support Widespread Use Of Collaborative Dementia Care Models. *Health Affairs (Project Hope)*.

Please cite this article as: M. Boustani et al., Assessing the Cost-effectiveness of a Hypothetical Disease-Modifying Therapy With Limited Duration for the Treatment of Early Symptomatic Alzheimer Disease, Clinical Therapeutics, https://doi.org/10.1016/j.clinthera.2022.09.008

2019;38:54–59. doi:10.1377/hlthaff.2018.05154.
38. French DD, LaMantia MA, Livin LR, Herceg D, Alder CA, Boustani MA. Healthy Aging Brain Center improved care coordination and produced net savings. *Health Affairs (Project Hope)*. 2014;33:613–618. doi:10.1377/hlthaff.2013.1221.
39. Rabinovici GD, Gatsonis C, Apgar C, et al. Association of amyloid positron emission tomography with subsequent change in clinical management among Medicare beneficiaries with mild cognitive impairment or dementia. *JAMA*. 2019;321:1286–1294. doi:10.1001/jama.2019.2000.
40. Lakdawalla DN, Doshi JA, Garrison Jr LP, Phelps CE, Basu A, Danzon PM. Defining elements of value in health care-a health economics approach: an ISPOR Special Task Force Report. *Value in Health*. 2018;21:131–139. doi:10.1016/j.jval.2017.12.007.
41. Langer CJ, Obasaju C, Bunn P, et al. Incremental innovation and progress in advanced squamous cell lung cancer: current status and future impact of treatment. *Journal of Thoracic Oncology*. 2016;11:2066–2081. doi:10.1016/j.jtho.2016.08.138.
42. Lakdawalla DN, Phelps CE. Health technology assessment with diminishing returns to health: the generalized risk-adjusted cost-effectiveness (GRACE) approach. *Value in Health*. 2021;24:244–249. doi:10.1016/j.jval.2020.10.003.
43. Prados MJ, Liu Y, Jun H, Lam J, Mattke S. Projecting the long-term societal value of a disease-modifying treatment for Alzheimer's disease in the United States. *Alzheimer's & Dementia*. 2022;18:142–151. doi:10.1002/alz.12578.
44. Andersen K, Lolk A, Martinussen T, Kragh-Sørensen P. Very mild to severe dementia and mortality: a 14-year follow-up - the Odense study. *Dementia and Geriatric Cognitive Disorders*. 2010;29:61–67. doi:10.1159/000265553.
45. Alzheimer's Association2021 Alzheimer's disease facts and figures. *Alzheimer's & Dementia*. 2021;17:327–406. doi:10.1002/alz.12328.
46. Lin GA, Whittington MD, Synnott PG, et al. *Aducanumab for Alzheimer's Disease: Effectiveness and Value; Final Evidence Report and Meeting Summary, Institute for Clinical and Economic Review, August 5, 2021*. https://icer.org/assessment/alzheimers-disease-2021/.

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