Cost-Effectiveness of a Hypothetical Gene Therapy for Alzheimer's Disease: A Markov Simulation Analysis

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Abstract

Background: Alzheimer's disease is a prevalent neurodegenerative condition causing significant health and economic burden. With limited therapeutic options, clinical trials have been investigating Alzheimer's disease treatment using more novel approaches, including gene therapy. However, there is limited evidence on the cost-effectiveness of such treatments.

Objectives: This research aims to explore the cost-effectiveness of a hypothetical gene therapy for patients with Alzheimer's disease at varying degrees of severity.

Methods: A Markov model with a 20-year time horizon was constructed for simulated cohorts with mild cognitive impairment due to Alzheimer's disease, assigned to receive either standard of care or a one-time gene therapy administration. Varying costs of care due to disease severity and treatment efficacy were utilized to determine the effect of those variables at different willingness-to-pay thresholds.

Results: Under the initial assumption that the hypothetical gene therapy grants a 30% risk reduction in disease progression and entry into institutional care, the maximum cost-effective price for gene therapy is $141,126 per treatment using the threshold of $150,000 per quality-adjusted life year (QALY). By increasing the treatment effectiveness to 50%, cost-effective price nearly doubled at each willingness-to-pay threshold (e.g., $260,902 at the $150,000/QALY threshold).

Conclusion: Despite being cost-effective at a very high price, the hypothetical gene therapy for AD would still need to be priced considerably lower than other approved gene therapies on the market. Thus, a comprehensive pharmacoeconomic assessment remains critical in pricing innovative therapy and determining coverage for patients in need.

Keywords: Cost-effectiveness analysis, Markov model, Alzheimer's disease, gene therapy

Introduction

Alzheimer's disease (AD), a condition characterized by neurodegeneration causing significant cognitive decline, is a growing global concern. In the United States, it is estimated that 6.5 million people 65 and over are living with Alzheimer-related dementia in 2022, with projected healthcare expenditures shared by Medicare, Medicaid, and out-of-pocket payments of $321 billion.[1] However, such statistics fail to acknowledge the estimated $271.6 billion in costs associated with unpaid and informal caregiving by family and friends of people living with dementia.[1] Unfortunately, these numbers are only expected to continue increasing due to the aging population and improved life expectancy, especially in developed countries.[1]

Despite the considerable social and economic burdens associated with AD, treatment options for AD are limited, with five symptom-management therapies and one monoclonal antibody, aducanumab, as the only disease-modifying therapy.[1] Approved in 2021, aducanumab ended an almost two-decade drought of treatment approvals for AD; however, controversy surrounding the therapy's efficacy and cost since limited its utilization in practice.[2,3]

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Supported by rapid advancements in drug development, the quest for efficacious and safe treatments in AD continues by utilizing innovative approaches to produce protective effects against disease progression or reverse existing neural damage.

One potential solution is developing a gene therapy (GT) to prevent disease progression based on the proposed pathophysiology of AD. Studies reported that individuals carrying the e4 isoform of the apolipoprotein E (APOE) are at an increased risk of late-onset AD, while the e2 isoform is believed to be neuroprotective.[1] Thus, gene therapy delivering a copy of the APOE-e2 gene into the central nervous system may generate therapeutic benefits, especially in patients with only two copies of the APOE-e4 gene.[4] Such potential applications of GT in AD have been translated into human clinical trials, using a nonpathogenic viral capsid as the delivery vesicle.[4,5] Nonetheless, these specialty agents are not affordable for many patients. For instance, aducanumab was originally priced at $56,000 annually for an average patient and later reduced to $28,200.[3,6] The manufacturer claimed that this reduction was a result of the company's initiative to improve access to the agent and allow patients to receive the medication, prior to progressing to a point where clinical benefits are no longer attainable.[6] Despite the significant drop, the price remains much higher than the Institute of Clinical and Economic Review's (ICER) estimated benefit of $3,000-$8,400 per year for aducanumab, suggesting a 70-89% reduction compared to the newly listed price of $28,200 annually.[7] It is also worth noting

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that two gene therapy products approved in the U.S. with a similar mechanism of action, onasemnogene abeparvovec-xioi and voretigene neparvovec, are listed at $2.1 million per dose and $425,000 per eye, respectively.[8] Therefore, assessing the cost-effectiveness of novel therapies to justify their hefty price-tag has become increasingly important to both manufacturers and payers. The objective of this study is to estimate the monetary value of a hypothetical gene therapy for the treatment of AD, with varying efficacy and quality-adjusted life year (QALY) thresholds.

Methods

Model Overview

A cost-effectiveness analysis was performed in R[9] to determine the price of a hypothetical gene therapy that can delay disease progression in AD using simulated data. We constructed a Markov model under a health system perspective to follow two hypothetical cohorts with equal numbers of male and female patients, over a twenty-year horizon of annual cycles.[10] Two cohorts were included consisting of participants who are 65 and older with mild cognitive impairment (MCI) due to AD, resembling the typical population qualified for GT treatment in clinical trials and Medicare benefits.[5,11] Subjects received either standard of care or gene therapy with standard of care while transitioning through five states: MCI due to AD, mild AD, moderate AD, severe AD, and death, as illustrated in Supplementary Figure 1.[10] Subjects allocated to receive treatment only received GT once prior to entering the simulation, and treatment was anticipated to slow down the progression of dementia and delay transition into long term care (LTC). Additionally, the model assumed that treatment remained effective for patients with MCI, mild, and moderate AD but provided no benefits to patients once they were diagnosed with severe AD.

Simultaneously, subjects were placed in either the community or the LTC facility setting under the assumption that once subjects moved into assisted living, they were unable to return to the community setting.[10] Thus, this model was able to capture formal caregiving costs in a LTC facility while the valuation of informal caregiving in the community setting remained unaddressed. The model further simplified disease progression by preventing participants from advancing to another disease state as they transition from community to LTC.

Model Assumptions

Simulated costs fluctuated depending on disease state and care setting. For all subjects, costs of general medical care were calculated using annual per capita spending for Medicare beneficiaries in 2014 adjusted by disease state multipliers.[7,12] Meanwhile, for LTC-dwelling subjects, care expenditures also included the average yearly cost associated with an LTC stay.[7] Further details on these costs including associated assumptions are described in the ICER analysis of aducanumab.[7] All costs of care were adjusted to 2022 dollars using the consumer price index inflation rate, and a 3% annual discount rate was applied.[13] Utility estimates were extracted from the ICER report, which were derived based on disease severity, age, and care setting.[7] Finalized values included as key parameter inputs for costs, utility, and transitional probabilities between care settings and their sources are available from the author upon request. Mortality rates were computed using age and gender-specific all-cause mortality in the U.S. in 2019 and relative risk in mortality based on disease state.[7,14]

In the base-case analysis, GT was expected to produce a 30% risk reduction in disease progression and delayed entrance into LTC. This value was rather conservative compared to other cost-effectiveness analyses focused on GT. This conservative assumption was dictated by the fact that GT is typically developed for monogenic conditions (e.g., hemophilia A, sickle cell disease, and spinal muscular atrophy) justifying a high success rate.[15] On the contrary, genetics is only considered one of the major risk factors predisposing a subject to an AD diagnosis; thus, the clinical benefits of GT in the treatment of AD may be more unpredictable.[15] Our approach is consistent with previous studies investigating the cost-effectiveness of a disease-modifying therapy in AD that have utilized a more conservative approximation of efficacy.[10,16]

We performed a sensitivity analysis to examine the relationship between drug prices and certain key parameters. For instance, we increased the effectiveness to 50% and recalculated the drug price at three different willingness-to-pay (WTP) thresholds: $50,000/QALY, $100,000/QALY, and $150,000/QALY, with the last being the typical WTP in the US.[16]

Results

Under the assumption that treatment is 30% effective, GT was predicted to generate 6.07 QALYs compared to 5.29 QALYs in the SOC group, corresponding to $406,559 and $430,554 in cost of care, respectively. Therefore, GT had lower costs and improved QALYs when compared to SOC. Based on the simulation, GT was expected to lengthen life expectancy by 1.0 years (10.2 years for the treatment cohort and 9.2 for the control cohort) and prolong a subject's residence in the MCI, mild, and moderate AD states (Figure 1). Meanwhile, GT produced lower overall mortality and decreased mortality in the LTC setting (Supplementary Figures 2 and 3). The LTC setting had a noticeably higher number of residents in severe AD and increased mortality compared to other disease states throughout the 20 cycles. This phenomenon was anticipated, as patients are more likely to move to the LTC setting when their condition worsens and associated mortality rates increase. Despite assuming that the transitional probability from severe AD to death is not affected by drug administration, the LTC setting still experienced a lower number of severe AD years and deaths after 20 years in the treatment arm (746 years and 286 deaths) compared to standard of care (1,230 years and 395

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deaths). Interestingly, a higher overall mortality in the treatment arm was observed in the community setting after 20 cycles (662 subjects and 585 subjects for the treatment and control cohort, respectively.

Table 1 presents the cost-effective prices at varying willingness-to-pay thresholds and relative risk reduction post-treatment. As willingness-to-pay (WTP) thresholds rose, the cost-effective prices also grew proportionately. The cost-effective price increased from $63,039 at the $50,000/QALY threshold to $141,126 at the $150,000/QALY threshold. Our sensitivity analysis that increased the drug's effectiveness to 50% resulted in cost-effective prices that were nearly twice as high at each WTP threshold (e.g., $260,902 at the $150,000/QALY).

Discussion

We found improved QALYs and reduced AD severity with GT, which offers cost-effectiveness at $141,126 assuming 30% effectiveness at $150,000/QALY under the health system perspective. Nonetheless, such prediction still places GT for AD patients at a much more modest price range compared to other commercialized GTs currently on the market. Two gene therapy products approved in the U.S. based on a similar mechanism of action, onasemnogene abeparvovec-xioi and voretigene neparvovec, are listed at $2.1 million per dose and $425,000 per eye, respectively.[8] Overpricing is a common practice in the pharmaceutical and biotechnology industry in the U.S., allowing for up to approximately 40% in rebates for pharmacy benefit managers from drug manufacturers.[17] However, even with generous rebate offers, the modeled cost-effective price remains considerably lower than other approved products.

Another issue concerning reimbursement for novel therapies in the U.S. is the concept of a concentrated upfront payment for a once-in-a-lifetime treatment with little clinical experience.[18] The U.S. payer structure is constructed on a fee-for-service schedule, and insured individuals are allowed to switch among plans annually during the enrollment periods or after a qualifying life event, making it difficult to recognize the long-term benefits of a one-time curative or preventative treatment.[18] As an effort to facilitate gene therapy uptake by clinicians and insurance plans, modified approaches to the reimbursement process have been proposed. One possible solution is to apply an outcome-based reimbursement plan, meaning that payment is released to manufacturers as the patient meets expected clinical endpoints at specified time points.[19,20] Another recommendation is to offer bonuses linked to clinical benefits, including avoidance of side effects, avoidance of complications, and sustained efficacy over a prolonged period of time.[19] Drug companies have also launched programs allowing payment in installments for innovative therapy, which do not require assessment of outcomes.[20]

On the other hand, insurance plans may doubt the extrapolated efficacy from clinical trial data to a broader patient population, given that typical participants in gene therapy trials are qualified by sponsors based on several inclusion and exclusion criteria.[21] The external validity of clinical trials therefore may be jeopardized if those criteria fail to reflect the general population being treated. For instance, while the FDA endorses excluding individuals with increased likelihood of immunogenic reactions to investigational gene-based agents, restricting participation of individuals with multiple comorbidities may limit a drug candidate's translation into clinical practice, considering the fact that AD typically affects older adults with several health conditions.[22-24] AD is often considered a multifactorial and polygenic condition;[15,25,26] although genetics play a significant role in disease courses, fixing one defective gene or adding a protective gene do not necessarily guarantee clinically relevant and significant benefits, leading to worsened predictability and poor application in clinical practice.[15,25,26] Given the great expense coupled with high uncertainty, reimbursement for such treatments will remain a concern for both private and government-funded payers.

Limitations

First, the model may have failed to capture the multidimensional nature of AD and caregiving in AD, as a patient's cognition, function, and behavior can fluctuate despite remaining in the same classification of disease severity.[5,10] Such fluctuations in a patient's condition can cause noticeable variability in caregiving needs and spending on healthcare services. Another limitation of this model was that the costs related to pre-administration screening to determine treatment eligibility were not included. Since GT is expensive, extensive effort is warranted to ensure that patients who are likely to receive optimal benefits are given access to the treatment. Third, costs associated with post-administration monitoring and treatment due to adverse reactions such as immunologic events were not addressed. Such expenditures are particularly relevant if payers are interested in adopting the efficacy-based reimbursement structure. Overall, it should be anticipated that incorporation of costs of screening, monitoring, and treatment-emergent adverse effects may decrease the cost-effectiveness price of the hypothetical treatment. Finally, there are concerns regarding the mathematical validity of QALY as a utility estimate and the use of an assumption-based modeling framework to provide economic evaluation of novel therapeutics.[27] While our analysis conformed to the common methodology currently utilized in cost-effectiveness analyses, we acknowledge the importance of challenging the limitations of typical approaches to health technology assessment, including the identification and estimation of key parameters and future prediction solely based on past observations. Original and innovative approaches in health technology assessment are needed to address these shortcomings and they deserve increased attention from researchers and key decision makers.

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Conclusion

Our findings suggest that a hypothetical one-time gene therapy administration against AD will be cost-effective at $141,126 under the health system perspective assuming 30% effectiveness and $150,000 WTP threshold. This valuation remains significantly lower compared to existing gene therapies on the market even after considering the typical rebate rate of 40% from manufacturers to payers. In addition, introduction of a gene therapy into an insurance formulary results in several challenges including concentrated upfront payment, limited clinical experience, and high uncertainty in predicting long-term benefits, demanding close collaboration among stakeholders and implementation of innovative reimbursement structures.

Disclaimer: The statements, opinions, and data contained in all publications are those of the author(s).

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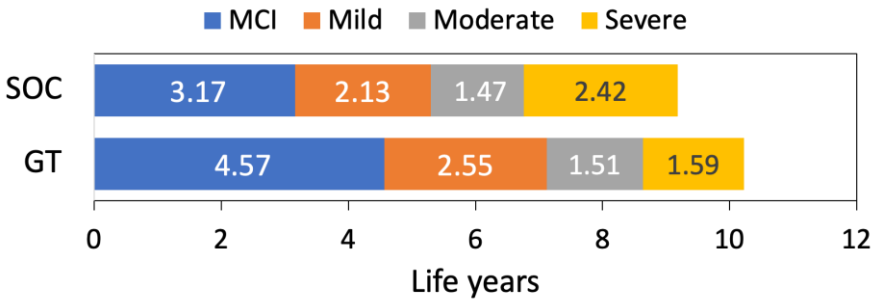

Figure 1. Average time spent in each disease state by cohort. GT led to longer life expectancy (10.22 years versus 9.18 years) and longer time spent in MCI, mild, and moderate AD.
AD: Alzheimer's disease; GT: gene therapy; MCI: mild cognitive impairment due to Alzheimer's Disease; SOC: standard of care.

Threshold ($/QALY)	30% effectiveness (RR = 0.70)	50% effectiveness (RR = 0.50)
$50,000	$63,039	$114,420
$100,000	$102,082	$189,661
$150,000	$141,126	$260,902

Table 1. Maximum cost-effective GT price by willingness-to-pay (WTP) threshold and treatment effectiveness. QALY = Quality-adjusted life year; RR = relative risk; $ = U.S. dollars.

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