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Impact of Treatment Duration on the Potential Cost-Effectiveness of Disease-Modifying Therapies for the Treatment of Early Symptomatic Alzheimer's Disease

Malaz Boustani[1], Erin G. Doty[2], Louis P. Garrison Jr[3], Lee J. Smolen[4], Mark Belger[2], Timothy M. Klein[4], Daniel R. Murphy[4], Russel T. Burge[2], Joseph A. Johnston[2]

[1.] Indiana University, Indianapolis, IN; [2.] Eli Lilly and Company, Indianapolis, IN; [3.] University of Washington, Seattle, WA; [4.] Medical Decision Modeling Inc., Indianapolis, IN

BACKGROUND

- Amyloid-targeting monoclonal antibodies (mAbs), a novel class of disease-modifying therapies (DMTs) for Alzheimer's disease (AD), have demonstrated efficacy in clinical studies.[1-4]
  - With limited follow-up data from clinical studies, uncertainty exists around optimal treatment (Tx) duration with DMTs.
- In June 2021, US FDA granted accelerated approval for the first amyloid-targeting mAb, aducanumab, for the Tx of AD.[5]
- An economic analysis of aducanumab reported an incremental cost-effectiveness ratio (ICER) of $1.33 million per quality-adjusted life years (QALYs) gained vs. supportive care based on:
  - Lifetime incremental costs of $204,000.
  - Lifetime incremental gain of 0.154 QALYs.[6]
- Lilly's Phase 2 TRAILBLAZER-ALZ study of donanemab was the first study on AD DMT, to meet its pre-specified primary endpoint and demonstrate statistically significant slowing of cognitive and functional decline when used for a limited duration of time.
- Given the anticipated approval of additional DMTs for AD, we assessed the cost-effectiveness of hypothetical DMTs with different efficacy profiles and duration of use:
  - We speculate that cost-effectiveness will be sensitive to multiple factors, including drug cost, magnitude and duration of benefit, care partner impacts, Tx duration etc.
  - Quantifying the potential cost-effectiveness of DMTs under a range of assumptions will enhance the understanding of the potential value of DMTs with different attributes.

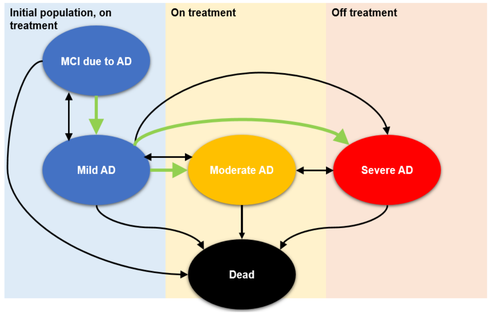
OBJECTIVE

To estimate the potential cost-effectiveness of hypothetical DMTs administered for different Tx durations in patients with early symptomatic AD:

- **Continuous Tx duration**
- **Fixed Tx duration**
- **Limited but variable Tx duration**

STUDY DESIGN

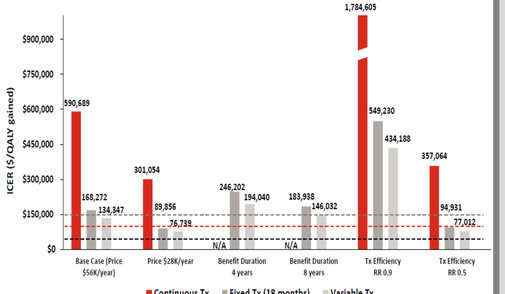
Fig. 1. AD Tx Model Flow Diagram



Abbreviations: MCI = mild cognitive impairment; AD=Alzheimer's disease
State transitions:
Disease progression under BSC
Disease progression impacted by DMT

KEY RESULT

Fig. 2. ICER for Base-case and Scenarios (DMT vs. BSC) – Payer Perspective



All values are incremental: DMT – BSC. Abbreviations: BSC=best supportive care; DMT=disease-modifying therapy; ICER=incremental cost-effectiveness ratio; QALY=quality-adjusted life years; RR=relative risk; Tx=treatment.
$50,000; $100,000; $150,000

Limitations

- With uncertainty about magnitude and duration of benefit of current AD DMTs under study, results should be viewed as exploratory and not representative of the cost-effectiveness of any DMT.
- Patient and care partner utilities obtained using generic health-related QoL measures do not adequately capture all relevant domains of interest in AD and likely underrepresent the impact of AD on patients and care partners.
- Accounting for one care partner as opposed to multiple care partners might lead to underestimation of the care partners costs and effects.
- Traditional cost-effectiveness models do not capture many additional elements of value generated by new treatments for AD.[16]
  - Elements of ISPOR's value flower framework (esp., insurance- and real-option values) are relevant for considering value of Tx for conditions like AD.[17]

CONCLUSIONS

- **The cost-effectiveness of hypothetical AD DMTs were highly sensitive to duration of Tx, therapy cost, Tx efficacy in slowing AD progression, and duration of Tx benefit.**
- **Efficacious ADs DMTs used for limited duration or until amyloid plaque clearance have potential to deliver value consistent with accepted cost-effectiveness thresholds.**

Methods

Study Design

Model Framework (Fig. 1)

- Markov state-transition simulation model with life-time horizon, based in part on Institute for Clinical and Economic Review model for aducanumab.[6]
- Annual discounting of costs and outcomes: 3%
- Perspective: Healthcare system (Payer) and Modified Societal.
- Comparator: Best supportive care (BSC).

Model Assumptions and Inputs

- In accordance with the previous model for aducanumab,[6] except as noted below and in **Table 1.**
- **Clinical Inputs**
  - *Relative risk (RR) of AD progression (base case): 0.70 for progression from MCI, and 0.70 for progression from mild AD dementia, based on expected efficacy from amyloid-targeting therapies.*
- **Tx Duration Scenarios**
  - *Continuous Tx until progression to severe AD dementia, with Tx benefit until progression to moderate AD dementia and only while on Tx.*
  - *Fixed Tx duration of 18 months (mo.) or until progression to severe AD dementia, with continuing Tx benefit until progression to severe AD dementia.*
  - *Limited but variable Tx duration (max 18 mo.), with continuing Tx benefit until progression to severe AD dementia.*
    - *40% discontinue at 6 mo. due to amyloid clearance, rest continuing for 18 mo. (or until progression to severe AD dementia).*
    - *Patients incurred $4,000 for diagnostic test at 6 mo. to assess amyloid clearance.*
- The modified societal perspective also included patient productivity costs and, for care partners, their medical costs, productivity costs, and disutilities.

Scenarios and One-way Sensitivity Analysis (OWSA)

- **Payer perspective**: evaluated impact of Tx efficacy (RR: 0.7 [base-case], 0.9, and 0.5), duration of Tx benefit (until severe AD dementia [base-case], 4- and 8- years [yrs]), and Tx cost ($56,000 [base-case] and $28,000 [scenario]).
- In OWSA, model inputs were varied by ±20% or within fixed limits one at a time.

Table 1. Key Model Inputs

Model Input	Value	Perspective		Source
		Payer	Modified Societal	
Clinical Inputs				
RR, hypothetical DMT+BSC vs. BSC alone				
Progression from MCI	0.7	X	X	Assumption
Progression from Mild AD dementia	0.7	X	X	Assumption
Progression from Moderate AD dementia	1.0	X	X	Assumption
Annual transition probabilities to LTC				
MCI due to AD	2.40%	X	X	Calculated
Mild AD dementia	3.80%	X	X	Neumann et al., 1999[7]
Moderate AD dementia	11.00%	X	X	
Severe AD dementia	25.90%	X	X	
RR of death by health state				
MCI due to AD	1.82	X	X	Andersen et al., 2010[8]
Mild AD dementia	2.92	X	X	
Moderate AD dementia	3.85	X	X	
Severe AD dementia	9.52	X	X	
Probability of Tx discontinuation due to ARIA	10%	X	X	FDA AdComm Briefing Document[9]
Utility Inputs				
Patient disutilities, community setting				
MCI due to AD	-0.17	X	X	Neumann et al., 1999[10]
Mild AD dementia	-0.22	X	X	Neumann et al., 1999[7, 10]
Moderate AD dementia	-0.36	X	X	
Severe AD dementia	-0.53	X	X	
Patient disutilities, LTC setting				
MCI due to AD	-0.17	X	X	Assumption
Mild AD dementia	-0.19	X	X	Neumann et al., 1999[7, 10]

Table 1. Key Model Inputs (contd.)

Model Input	Value	Perspective		Source
		Payer	Modified Societal	
Moderate AD dementia	-0.42	X	X	Neumann et al., 1999[7, 10]
Severe AD dementia	-0.59	X	X	
Care partner disutilities, community setting and LTC setting				
MCI due to AD	-0.03		X	Neumann et al., 1999[10]
Mild AD dementia	-0.05		X	Neumann et al., 1999 & Mesterton et al., 2010[7, 11]
Moderate AD dementia	-0.08		X	
Severe AD dementia	-0.10		X	
Cost Inputs				
Hypothetical DMT annual cost	$56,000	X	X	Assumption
Annual direct medical cost	$8,840	X	X	Leibson et al., 2015[12]
Direct medical multiplier costs				
MCI due to AD	1.12	X	X	Leibson et al., 2015[12]
Mild AD dementia	1.56	X	X	
Moderate AD dementia	1.93	X	X	
Severe AD dementia	1.93	X	X	
LTC cost per month	$7,186	X	X	Administration on Aging[13]
Care partner direct medical costs per mo.				
MCI due to AD	$447		X	Robinson et al., 2020[14]
Mild AD dementia	$938		X	Assumption based on Robinson et al., 2020 & Mesterton et al., 2010[11, 14]
Moderate AD dementia	$1,501		X	
Severe AD dementia	$1,876		X	
Brain MRI cost per scan	$255.33	X	X	CMS physician fee schedule[15]

Abbreviations: AD=Alzheimer's disease; ARIA=amyloid-related imaging abnormality; BSC=best supportive care; DMT=disease-modifying therapy; LTC=long-term care; mo.=month; MCI=mild cognitive impairment; RR=Relative risk.

Incremental ICER (Payer Perspective)

- ICER ($/QALY gained for DMT) was $590,689 for continuous Tx, $168,272 for fixed Tx, and $134,347 for limited but variable Tx (**Fig. 2**).
  - **Fig. 2** also presents ICERs for key scenario analyses.
- **Table 2** presents the costs and QALYs gained from payer perspective.

Fig. 3 Y axis: the range presents the Low and High values.
Abbreviations: AD=Alzheimer's disease; Com=community; ICER=incremental cost-effectiveness ratio; LTC=long-term care; MCI=mild cognitive impairment; QALY=quality-adjusted life years; RR=Relative risk ; Tx=treatment.

Base Case (Payer Perspective)

Table 2. Base-Case Findings (DMT vs. BSC)

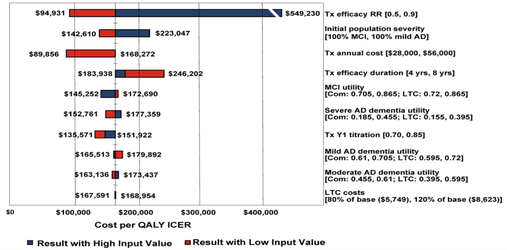
	Continuous Tx	Fixed Tx	Variable Tx
Total Costs	**$275,076**	**$78,397**	**$62,591**
Tx Costs	$269,758	$73,067	$53,678
LTC Costs	$1,577	$1,587	$1,587
Patient Direct Medical Costs	$3,741	$3,743	$7,326
Total QALYs	**0.466**	**0.466**	**0.466**
Life Years	0.462	0.462	0.462
ICER ($/QALY gained)	**$590,689**	**$168,272**	**$134,347**

All values are incremental: DMT – BSC. Abbreviations: BSC=best supportive care; DMT=disease-modifying therapy; ICER=incremental cost-effectiveness ratio; LTC=long-term care; QALY=quality-adjusted life year; Tx=treatment.

OWSA – Fixed Tx Duration (Payer Perspective)

- ICER was most sensitive to: Tx efficacy; initial population severity; Tx annual cost; and Tx efficacy duration (**Fig. 3**).

Fig. 3. Factors Affecting ICER - Fixed Tx (Base ICER - $168,272)



- Major factors impacting ICER – Payer Perspective:
  - Continuous Tx: Tx efficacy and Tx annual cost.
  - Variable Tx: Tx efficacy, initial population severity, Tx annual cost, and duration of Tx efficacy.
  - Tornados not shown for Continuous Tx and Variable Tx.

Base Case (Modified Societal Perspective)

Table 3. Base-Case Findings (DMT vs. BSC)

	Continuous Tx	Fixed Tx	Variable Tx
Total Costs*	**$261,049**	**$64,368**	**$48,562**
Care partner Medical Costs	($2,351)	($2,352)	($2,352)
Patient Productivity Costs	$214	$214	$214
Care partner Productivity Costs	($11,889)	($11,891)	($11,891)
Total QALYs**	**0.473**	**0.473**	**0.473**
Patient QALYs	0.466	0.466	0.466
Care partner QALYs gained	-0.007	-0.007	-0.007
ICER ($/QALY gained)	**$552,188**	**$136,096**	**$102,678**

All values are incremental: DMT – BSC. Abbreviations: BSC=best supportive care; DMT=disease-modifying therapy; ICER=incremental cost-effectiveness ratio; QALY=quality-adjusted life year; Tx=treatment.
**** Includes Tx costs, LTC costs and patient direct medical costs – same as Payer Perspective.***
***** Includes Incremental QALYs – same as Payer Perspective***

- ICER ($/QALY gained for DMT) was $552,188, $136,096, and $102,678 for continuous Tx, fixed Tx, and variable Tx, respectively **(Table 3).**
- Tx costs, LTC costs, patient direct medical costs, and incremental QALYs were identical for modified societal- and payer-perspectives **(Table 2)**.

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