AD Valorem: Alzheimer's Disease, Atopic Dermatitis, and Challenges for Value Assessment in Chronic Conditions

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BACKGROUND

- Chronic diseases, defined as conditions lasting 1 year or more that require regular medical attention or impair activities of daily living, affect more than half of adults in the United States (US) and are major drivers of healthcare costs.[1]
- Along with prevention efforts, pharmaceutical treatments are essential to managing the symptoms of and slowing the progression of many chronic conditions.[2,3]
- In an era of increased scrutiny on pharmaceutical pricing, cost-effectiveness modeling plays a key role in demonstrating the potential economic value of treatments and other health technologies.
- However, approaches to valuing and extrapolating treatment effects in cost-effectiveness models can differ between chronic, progressive conditions where slowing progression is critical to maintaining health (e.g., Alzheimer's disease [AlzDis], type 2 diabetes mellitus, age-related macular degeneration) and other chronic conditions where disease control and alleviation of symptoms to restore health is key (e.g., atopic dermatitis [ADerm], psoriasis, asthma, migraines).

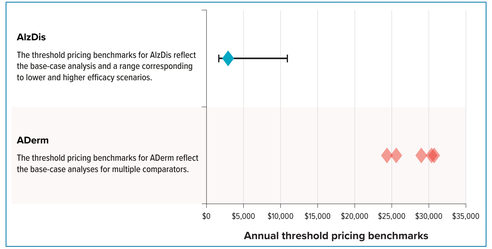
OBJECTIVE

- This study illustrates how disease characteristics and extrapolation assumptions used in cost-effectiveness modeling impact value assessments by contrasting recent economic evaluations in two distinct types of chronic conditions, AlzDis[4] and ADerm,[5] each with significant unmet need and economic burden.[6,7]

METHODS

- This review compared the modeling approaches and assumptions used in cost-effectiveness analyses for aducanumab in early AlzDis and for biologic therapies in moderate-to-severe ADerm conducted by the Institute for Clinical and Economic Review (ICER) in 2021.[4,5]
- To maximize comparability, we focused on analyses from a US third-party payer perspective. Emphasis was placed on comparing the following elements:
  - Baseline population characteristics
  - Modeling approaches
  - Treatment efficacy and long-term extrapolation assumptions
  - Treatment discontinuation assumptions
  - Health state utility values and the timing of quality-adjusted life-year (QALY) gains
  - Health state costs and the timing of cost offsets (i.e., non-treatment costs avoided)
- We also identified the threshold pricing benchmarks (i.e., economically justifiable prices) derived by ICER at a willingness to pay of $100,000 per QALY gained, which are independent of the actual prices of the treatments being assessed (Figure 1).

Figure 1. Threshold Pricing Benchmarks in Alzheimer's Disease and Atopic Dermatitis Derived by ICER



Note: Threshold pricing benchmarks were estimated at a willingness to pay of $100,000 per QALY gained.

RESULTS

- Our comparison of the base-case modeling approaches and assumptions in the AlzDis and ADerm cost-effectiveness analyses is presented in Table 1.
- The baseline population characteristics, nature of the health states, and applications of treatment effect in the two models reflected key differences between the two chronic conditions and the therapeutic window targeted by the new treatments being evaluated:
  - The ADerm population started treatment in a more severe state (baseline utility for nonresponders = 0.60) than the AlzDis population (baseline utilities for MCI due to AlzDis and mild AlzDis in community settings = 0.73 and 0.68, respectively).
  - The model structure for ADerm only allowed for patients' health status to improve relative to baseline (no movement to a worse health state allowed; utilities for responders = 0.80 to 0.88), while the model structure for AlzDis included progression to more severe states and to long-term care (utilities for severe AlzDis in community and long-term care settings = 0.37 and 0.31, respectively).
  - The difference in mean baseline age between the populations (ADerm = 36.5 years; AlzDis = 70 years) contributed primarily to higher competing mortality risks for AlzDis.
- We identified fundamental differences in the modeling assumptions around the extrapolation of treatment effect and treatment discontinuation over time:
  - The AlzDis treatment effect (reduction in progression estimated from pooled, placebo-controlled phase 3 clinical trials) was assumed to apply fully only for patients in the MCI due to AlzDis health state, to wane with progression (reduced by 50% in mild AlzDis), and to drop to 0% prior to stopping treatment (no efficacy in moderate AlzDis while treatment continued until severe AlzDis).
  - The ADerm treatment effect (proportions of patients achieving different levels of response from a network meta-analysis of placebo-controlled phase 3 trials) was assumed to persist indefinitely for responders remaining on treatment.
  - The models differed in their approaches to treatment discontinuation, with the trial-based discontinuation rates for ADerm applied annually over the time horizon and the within-trial discontinuation for AlzDis not extended to later years (i.e., patients remained on treatment until severe AlzDis). The discontinuation assumption for AlzDis resulted in ongoing aducanumab use in periods when the treatment effect was assumed to be reduced or eliminated, thus limiting the potential value of cost offsets due to delayed progression.
- As depicted in Figure 2, the interactions between disease severity at treatment initiation, the nature of the model health states, and the application of the treatment effects resulted in distinct patterns for the timing and magnitude of potential QALY gains and cost offsets associated with treatment:
  - In AlzDis, the potential QALY gains and cost offsets accrued indirectly by slowing progression and extending survival and thus occurred later in the time horizon and were more subject to discounting. The competing risks of mortality in the older AlzDis population also reduced the proportions of patients surviving long enough to realize these potential benefits.
  - In ADerm, the potential QALY gains and cost offsets accrued directly by achieving treatment response and thus occurred earlier in the time horizon and were less subject to discounting.
- The threshold pricing benchmarks, which were $1,650-$11,000/year for aducanumab in AlzDis (range reflecting uncertainty in aducanumab efficacy) and $24,400-$30,600/year for biologic therapies in ADerm (pricing benchmarks for scenarios reflecting efficacy uncertainty not available) (Figure 1), reflect in part the differences in the modeling approaches and assumptions related to treatment effect and discontinuation between AlzDis and ADerm.

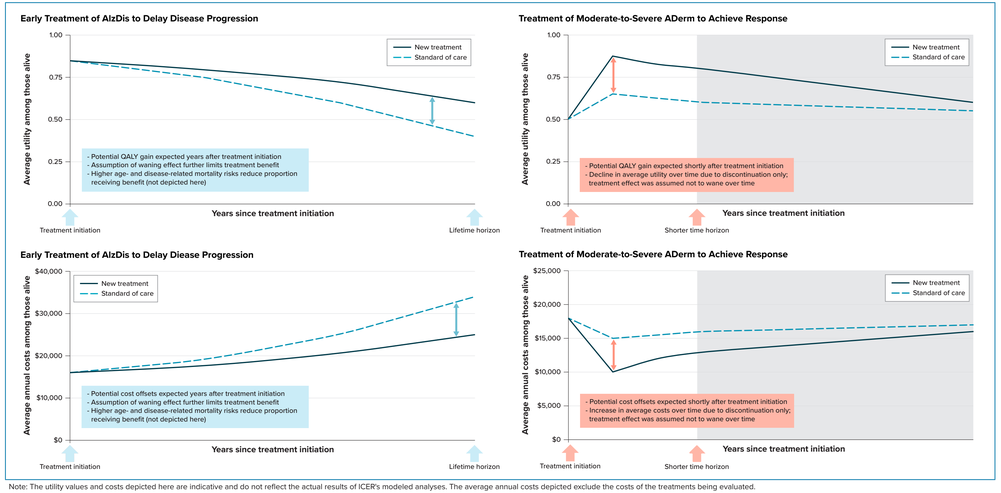
Table 1. Comparison of Base-Case Modeling Approaches and Assumptions

Characteristic	AlzDis[4]	ADerm[5]
Population at baseline	• MCI due to AlzDis (55%) and mild AlzDis (45%) • Mean age = 70 years • Female = 52%	• Adults with moderate (54.1%) to severe (45.9%) ADerm • Mean age = 36.5 years • Female = 43.7%
Comparators	• Aducanumab vs. SOC	• mAbs and JAK inhibitors vs. SOC
Modeling approach and health states	• Markov-based structure • MCI due to AlzDis and mild, moderate, and severe AlzDis in community and long-term care settings	• Markov-based structure • Response to treatment based on percentage improvements in EASI
Time horizon	• Lifetime	• 5 years
Cost and health outcomes discount rate	• 3% per year	• 3% per year
Treatment efficacy and data source	• HR for progression from MCI due to AlzDis based on CDR-SB scores over 78 weeks • Estimated from 2 pooled, placebo-controlled phase 3 clinical trials	• Proportions with 50%, 75%, and 90% improvements in EASI over 12-16 weeks • Estimated from an NMA of 15 placebo-controlled phase 2 or phase 3 clinical trials
Treatment effect extrapolation and discontinuation	• HR for progression cut by 50% and 100% for progression from mild and moderate AlzDis, respectively • AE-related discontinuation within trial only; treatment otherwise stopped at severe AlzDis	• Response category maintained while patients remain on treatment • Annual discontinuation rate resulting in loss of response
Disease progression	• Natural history transition probabilities among severity levels • Transition probabilities to long-term care increasing with severity	• Not included in the model
Mortality	• RRs vs. general population age-related mortality increasing from 1.82 to 9.52 with AlzDis severity • Indirect effect of treatment due to slowing progression	• Assumed no effect of ADerm or treatment
Health state utility values[a]	• MCI due to AlzDis = 0.73 in the community (0.73 in long-term care) • Mild AlzDis = 0.68 (0.71) • Moderate AlzDis = 0.54 (0.48) • Severe AlzDis = 0.37 (0.31)	• Nonresponders = 0.60 • EASI 50 = 0.80 • EASI 75 = 0.85 • EASI 90 = 0.88
Health state costs	• Direct medical costs increasing with severity (specific values not reported) • Direct nonmedical costs of $86,232 per year (long-term care setting only)	• Direct medical costs from $8,596 (EASI 90) to $18,589 (nonresponders) per year

[a] Caregiver utilities were not considered in base-case analyses conducted from a third-party payer perspective.

AE = adverse event; CDR-SB = Clinical Dementia Rating = Sum of Boxes; EASI = Eczema Area and Severity Index; HR = hazard ratio; JAK = Janus kinase; mAb = monoclonal antibody; MCI = mild cognitive impairment; NMA = network meta-analysis; RR = relative risk; SOC = standard of care.

Figure 2. Timing of Potential QALY Gains and Cost Offsets for Treatments for Alzheimer's Disease and Atopic Dermatitis



Note: The utility values and costs depicted here are indicative and do not reflect the actual results of ICER's modeled analyses. The average annual costs depicted exclude the costs of the treatments being evaluated.

CONCLUSIONS

- There are fundamental differences between chronic conditions in the pattern of disease progression, the objective of new treatments in development (e.g., slowing progression to maintain health vs. alleviating symptoms to restore health), and the resulting timing of the therapeutic window in the disease course.
- These differences impact the approaches and assumptions used in cost-effectiveness models for new treatments for chronic conditions, particularly around the nature of the health states, the application and extrapolation over time of the treatment effect, and treatment discontinuation.
- As a result, value assessment frameworks relying on traditional cost-effectiveness analyses[8,9] may inequitably value treatments for chronic progressive conditions provided early in the course of the disease, in which case potential benefits may accrue long after treatment initiation.
- Such conditions merit inclusion in ongoing discussions on updates to cost-effectiveness modeling guidelines[10] and on augmented and/or risk-adjusted cost-effectiveness analysis.[11,12]

REFERENCES

1. US CDC. About chronic diseases. 2022. https://www.cdc.gov/chronicdisease/about/index.htm.
2. WHO. Preventing chronic diseases: a vital investment. 2005. https://apps.who.int/iris/bitstream/handle/10665/43314/9241563001_eng.pdf.
3. RAND. Multiple chronic conditions in the United States. 2017. https://www.rand.org/content/dam/rand/pubs/tools/TL200/TL221/RAND_TL221.pdf.
4. ICER. Aducanumab for Alzheimer's disease: effectiveness and value: final evidence report and meeting summary. August 5, 2021. https://icer.org/wp-content/uploads/2020/10/ICER_ALZ_Final_Report_080521.pdf.
5. ICER. JAK inhibitors and monoclonal antibodies for the treatment of atopic dermatitis: effectiveness and value: final evidence report. August 17, 2021. https://icer.org/wp-content/uploads/2020/12/Atopic-Dermatitis_Final-Evidence-Report_081721.pdf.
6. Adamson AS. The economics burden of atopic dermatitis. Adv Exp Med Biol. 2017;1027:79-92. doi: 10.1007/978-3-319-64804-0_8.
7. Wong W. Economic burden of Alzheimer disease and managed care considerations. Am J Manag Care. 2020 Aug;26(8 Suppl):S177-S183. doi: 10.37765/ajmc.2020.88482.
8. Sanders GD, Neumann PJ, Basu A, Brock DW, Feeny D, Krahn M, 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(10):1093-103.
9. ICER. Value assessment framework. 2020. Updated February 3, 2022. https://icer.org/wp-content/uploads/2020/11/ICER_2020_2023_VAF_02032022.pdf.
10. O'Mahony JF, Paulden M, McCabe C. NICE's discounting review: clear thinking on rational revision meets obstacle of industrial interests. Pharmacoeconomics. 2021;39(2):139-46. doi: 10.1007/s40273-020-00990-8.
11. Lakdawalla DN, Doshi JA, Garrison LP Jr, Phelps CE, Basu A, Danzon PM. Defining elements of value in health care-a health economics approach: an ISPOR Special Task Force Report [3]. Value Health. 2018 Feb;21(2):131-139. doi: 10.1016/j.jval.2017.12.007.
12. Lakdawalla DN, Phelps CE. Health technology assessment with diminishing returns to health: the Generalized Risk-Adjusted Cost-Effectiveness (GRACE) approach. Value Health. 2021 Feb;24(2):244-249. doi: 10.1016/j.jval.2020.10.003. Epub 2021 Jan 12.

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