RTI (h)(s) Health Solutions

A Review of Vision-Related Utility Values and Their Suitability for Use in Cost-Effectiveness Models in Age-Related Macular Degeneration

William L Herring,[1] Justin Carrico,[1] Deirdre M Mladsi,[1] Renee Pierson,[2] Jennifer Lofland[2]

[1]RTI Health Solutions, Research Triangle Park, NC, United States; [2]Janssen Global Services, LLC, Horsham, PA, United States

OBJECTIVE

- To assess the suitability of visual acuity (VA)–based utilities used in wet age-related macular degeneration (AMD) for use in economic evaluations in dry AMD.

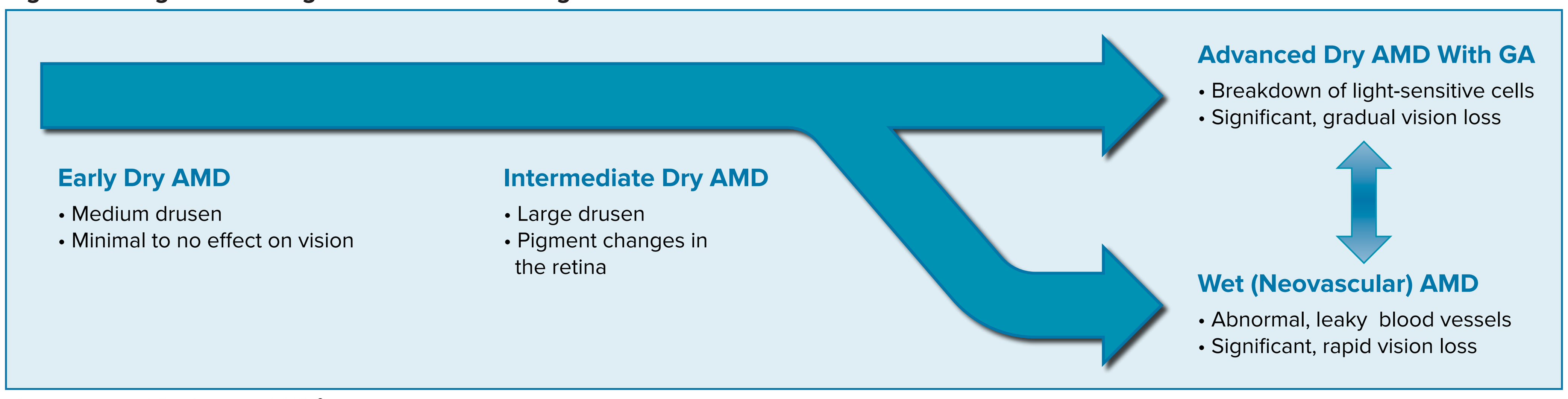
BACKGROUND

- AMD is a leading cause of vision loss that affects nearly 10% of the global population aged 50 years and older.[1]
- The risk of severe vision loss increases as AMD progresses, with advanced AMD characterized by the loss of macular tissue, known as advanced dry AMD with geographic atrophy (GA), or by the invasion of the retina by abnormal blood vessels, known as wet (also exudative or neovascular) AMD (Figure 1).[2]
- While therapies for wet AMD are well established, therapies in development for dry AMD would be without precedent.
- Economic evaluations of wet AMD therapies typically have relied on health states and utility values defined by VA, but the mechanisms of dry AMD can impair visual functioning without impairing VA.
  - The size, location, and pattern of GA growth are important in determining patients' VA and overall visual functioning.[4]
  - GA that is located near the foveal center presents a more immediate threat to patients' VA,[4] while growth not involving the foveal center can limit visual functioning without impairing VA.[5]

METHODS

- We reviewed two types of studies:
  - AMD utility studies, which were included in a published review of utilities in ophthalmology.[6]
  - Wet AMD economic modeling studies, which were included in a published review of cost-effectiveness (CE) models in AMD[7]; no published economic evaluations of dry AMD therapies were found.
- The selected studies were compared with two guideline-based visual impairment definitions[8,9] and the target populations for ongoing clinical trials in dry AMD.[10]
- The AMD utility studies were assessed to answer the following:
  - Were non-VA measures of visual functioning, such as contrast sensitivity (CS) or visual function questionnaire (VFQ-25) scores, considered?
  - Were patients with dry AMD included in the study population?
  - Did the study control for dry AMD severity?
- The wet AMD CE modeling studies were assessed to answer the following questions:
  - Were the health states defined by VA or by other measures of visual functioning?
  - What sources were used for the utility values?
  - If VA-based utility values were used, how did the VA ranges used in the model compare with the ranges in the relevant utility study?
- A crosswalk of VA utility levels (expressed as Snellen fractions and as Logarithm of the Minimum Angle of Resolution [LogMAR] values) was developed (Figure 2), with common definitions of visual impairment, ranges of VA levels used in published AMD utility analyses, and ranges of VA levels used to define health states in published wet AMD models.

Figure 1. Progression of Age-Related Macular Degeneration



Source: National Eye Institute (2015).[3]

RESULTS

- From the selected studies, our review found:
  - The utility studies looking at patients with AMD were conducted at least 10 years ago, with utilities most commonly used in published CE models coming from a TTO study conducted more than 15 years ago.[11]
  - Although the studies found that utility values generally decreased as VA worsened, the absolute utility values and the range of utility values across VA levels varied greatly across utility methodologies and studies.
    - Compared to other methodologies (SF-6D, VAS, HUI-3, and EQ-5D) and studies, the TTO utilities reported by Brown et al. (2000)[11] showed the greatest range between best (0.89 for ≥ 20/25) and worst (0.40 for < 20/400) (difference = 0.49).
    - TTO utilities reported in other studies had narrower ranges between best and worst (0.25 in Brown et al. [2002][12]; 0.17 in Aspinall et al. [2007][14]; and 0.13 in Espallargues et al. [2005][13]).
    - The HUI-3 utilities reported by Espallargues et al. (2005)[13] were lower than other methodologies at all VA levels, ranging from 0.50 for ≥ 20/40 to 0.27 for < 20/400].
    - The EQ-5D utilities reported by Espallargues et al. (2005)[13] were the only values not demonstrating consistent decline as VA worsened (0.70 for 20/50 to 20/80 and 0.75 for 20/100 to 20/400).
  - Each of the modeling studies considered used health states defined by VA ranges. The only CE study considering a non-VA measure of visual functioning was by Butt et al. (2014),[17] who compared a model structure based on CS levels with a traditional VA-based model structure.
- An overall lack of alignment in VA ranges was identified across the utility and CE modeling studies:
  - None of the VA ranges used in the utility studies or model structure health state definitions were fully aligned with guideline-based visual impairment definitions. For example, Espallargues et al. (2005)[13] defines a single utility value over a VA range from 20/100 to 20/400, a range that spans the WHO definitions for both moderate and severe visual impairment.[9]
  - Three of the five representative model structures applied VA-based utility values to health states defined with VA ranges that either did not match or could not be directly traced to VA ranges in the utility studies. For example, Javitt et al. (2008)[15] applied TTO utility values to VA health states based on Brown et al. (2000)[11] but defined the health states differently than did Brown et al. (2000)[11] (different thresholds were used between all states except for the threshold separating 20/160 and 20/200).
- Two wet AMD models used TTO utilities from studies not restricted to patients with AMD:
  - Stein et al. (2014)[18] used utilities from a study that included patients with other ophthalmic conditions.[21]
  - The CE analysis described in NICE (2012) used utilities from a study that simulated AMD health states in individuals drawn from the general population.[22]
- Only two of the utility studies considered non-VA measures of visual functioning.
  - Espallargues et al. (2005)[13] estimated TTO, VAS, SF-6D, HUI-3, and EQ-5D utility values for four levels of CS and for four levels of the Visual Function Index (VF-14), finding that utility values consistently decreased with worsening visual function across all methodologies except for the EQ-5D.
  - While Aspinall et al. (2007)[14] did not report specific utility values based on levels of visual functioning, better binocular CS was associated with higher TTO utility in their study.
- In the only analysis considering the interaction of VA and visual functioning, Espallargues et al. (2005)[13] found that TTO utility values decreased with worsening CS even after controlling for VA.
- While each of the utility studies included some patients with dry AMD, the analyses were of limited usefulness for economic evaluations of new therapies for dry AMD:
  - In the studies, the percentages of patients with dry AMD were either not reported or were low (16 of 72 [22%] with dry AMD only in Brown et al. [2000][11]).
  - Dry AMD severity levels (only considered in Aspinall et al. [2007][14]) were not aligned with dry AMD clinical trial populations, which are restricted to patients with GA (with or without subfoveal involvement) and no active or prior history of wet AMD.[10]
- In the only study looking at the effect of the type of AMD on utility, Aspinall et al. (2007)[14] found that the type of AMD (dry or wet) had no significant effect on TTO utility values. However, the number of patients with dry AMD in this study was not reported, and the definition of AMD severity did not differentiate between dry and wet AMD. These limitations prevent drawing definitive conclusions about the applicability of wet AMD utility values in patients with advanced dry AMD with GA.

CONCLUSIONS

- Substantial limitations and inconsistencies were observed in utility values for wet AMD, and key data gaps were identified related to dry AMD.
- Studies designed specifically for dry AMD that account for the features unique to advanced dry AMD with GA are needed to support economic evaluations of future dry AMD therapies.

Figure 2. Comparison of Visual Acuity Utility Values and Health State Definitions

Visual Acuity															
Snellen fraction[a]	≥ 20/20	20/25	20/32	20/40	20/50	20/63	20/80	20/100	20/125	20/160	20/200	20/250	20/320	20/400	< 20/400
LogMAR[a]	≤ 0.0	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0	1.1	1.2	1.3	> 1.3
Definitions (Better-Seeing Eye)															
AAO (2016)[8]	No Visual Impairment			Visual Impairment							Legal Blindness				
WHO (2016)[9]	No or Mild Visual Impairment						Moderate Visual Impairment					Severe Visual Impairment			Blindness
AMD-Specific Utility Studies (via Poku et al., 2013[6])															
Better-Seeing Eye Studies															
Brown et al. (2000)[11]	(B1) TTO: 0.89 SG: 0.96		(B2) TTO: 0.81 SG: 0.88			(B3) TTO: 0.57 SG: 0.69			—	—	(B4) TTO: 0.52 SG: 0.71				(B5) TTO: 0.40 SG: 0.55
Brown et al. (2002)[12]	TTO: 0.84		TTO: 0.80		TTO: 0.71				—	—	TTO: 0.59				
Espallargues et al. (2005)[13]	(E1) TTO: 0.73 VAS: 0.71 HUI-3: 0.50 SF-6D: 0.70 EQ-5D: 0.75				(E2) TTO: 0.67 VAS: 0.63 HUI-3: 0.38 SF-6D: 0.67 EQ-5D: 0.70			(E3) TTO: 0.64 VAS: 0.66 HUI-3: 0.36 SF-6D: 0.65 EQ-5D: 0.75							(E4) TTO: 0.60 VAS: 0.63 HUI-3: 0.27 SF-6D: 0.65 EQ-5D: 0.71
Binocular Studies															
Aspinall et al. (2007)[14]	TTO: 0.93		TTO: 0.86		TTO: 0.74				—	—	TTO: 0.68				TTO: 0.76
Health States in Selected Wet AMD Models (via Schmier and Hulme-Lowe, 2016[7])															
Studies using TTO utilities (B1–B5 above) from Brown et al., 2000[11]															
Javitt et al. (2008)[15] (among others)	(B1)			(B2)			(B3)				(B4)			(B5)	
Patel et al. (2012)[16] (among others)	—		(B2)			(B3)			—	—	(B4)				—
Studies using SF-6D utilities (E1–E4 above) from Espallargues et al., 2005[13]															
Butt et al. (2014)[17]	(E1)				(E2)			(E3)							(E4)
Studies using TTO utilities from other sources															
Stein et al. (2014)[18,b]	0.92	0.84			0.76			0.66			0.61				
NICE (2012)[19,c]	0.86					NR			NR		NR				0.50

AAO = American Academy of Ophthalmologists; EQ-5D: EuroQol five dimensions questionnaire; HUI-3 = Health Utilities Index Mark III; NICE = National Institute for Health and Care Excellence; NR = not reported; SG = standard gamble; TTO = time trade-off; VAS = visual analog scale; WHO = World Health Organization.

[a] Snellen fraction and logMAR VA levels, as well as their equivalencies, were taken from Digital Imaging and Communications in Medicine (2013).[20]

[b] TTO utilities were derived from Brown et al. (2003),[21] a non-AMD-specific study that reported utilities for specific VA levels rather than VA ranges.

[c] TTO utilities were derived from Czoski-Murray et al. (2009).[22] This study used simulated AMD health states in the general population and reported the relationship between VA and utilities using a regression analysis.

REFERENCES

1. Wong WL, Su X, Li X, Cheung CM, Klein R, Cheng CY, et al. Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: a systematic review and meta-analysis. Lancet Glob Health. 2014 Feb;2(2):e106-16.
2. Bowes Rickman C, Farsiu S, Toth CA, Klingeborn M. Dry age-related macular degeneration: mechanisms, therapeutic targets, and imaging. Invest Ophthalmol Vis Sci. 2013 Dec 13;54(14):ORSF68-80.
3. National Eye Institute. Facts About Age-Related Macular Degeneration. September 2015. Available at: https://nei.nih.gov/health/maculardegen/armd_facts. Accessed March 24, 2017.
4. Brader HS, Ying GS, Martin ER, Maguire MG. Characteristics of incident geographic atrophy in the complications of age-related macular degeneration prevention trial. Ophthalmology. 2013;120:1871-9.
5. Sunness JS, Rubin GS, Zuckerbrod A, Applegate CA. Foveal-sparing scotomas in advanced dry age-related macular degeneration. J Vis Impair Blind. 2008 Oct 1;102(10):600-10.
6. Poku E, Brazier J, Carlton J, Ferreira A. Health state utilities in patients with diabetic retinopathy, diabetic macular oedema and age-related macular degeneration: a systematic review. BMC ophthalmology. 2013 Dec 4;13(1):74.
7. Schmier JK, Hulme-Lowe CK. Cost-effectiveness models in age-related macular degeneration: issues and challenges. Pharmacoeconomics. 2016 Mar;34(3):259-72.
8. American Academy of Ophthalmology. US Eye Disease Statistics. Available at: http://www.aao.org/eye-disease-statistics. Accessed March 24, 2017.
9. World Health Organization (WHO). Change the definition of blindness. ICD Update and Revision Platform. Available at: http://www.who.int/blindness/Change%20the%20Definition%20of%20Blindness.pdf?ua=1. Accessed March 24, 2017.
10. ClinicalTrials.gov. NCT02895815, NCT02288559. Available at: https://clinicaltrials.gov/ct2/results?term=geographic+atrophy&Search=Search. Accessed March 28, 2017.
11. Brown GC, Sharma S, Brown MM, Kistler J. Utility values and age-related macular degeneration. Arch Ophthalmol. 2000;118:47-51.
12. Brown MM, Brown GC, Sharma S, Landy J, Bakal J. Quality of life with visual acuity loss from diabetic retinopathy and age-related macular degeneration. Arch Ophthalmol. 2002;120(4):481-4.
13. Espallargues M, Czoski-Murray CJ, Bansback NJ, Carlton J, Lewis GM, Hughes LA, et al. The impact of age-related macular degeneration on health status utility values. Invest Ophthalmol Vis Sci. 2005;46(11):4016-23.
14. Aspinall PA, Hill AR, Dhillon B, Nelson P, Lumsden C, Farini-Hudson E, et al. Quality of life and relative importance: a comparison of time trade-off and conjoint analysis methods in patients with age-related macular degeneration. Br J Ophthalmol. 2007 Jun;91(6):766-72.
15. Javitt JC, Zlateva GP, Earnshaw SR, Pleil AM, Graham CN, Brogan AJ, et al. Cost-effectiveness model for neovascular age-related macular degeneration: comparing early and late treatment with pegaptanib sodium based on visual acuity. Value Health. 2008 Jul-Aug;11(4):563-74.
16. Patel JJ, Mendes MA, Bounthavong M, Christopher ML, Boggie D, Morreale AP. Cost-utility analysis of bevacizumab versus ranibizumab in neovascular age-related macular degeneration using a Markov model. J Eval Clin Pract. 2012 Apr;18(2):247-55.
17. Butt T, Patel PJ, Tufail A, Rubin GS. Modelling cost effectiveness in neovascular age-related macular degeneration: the impact of using contrast sensitivity vs. visual acuity. Appl Health Econ Health Policy. 2014;12(3):289-97.
18. Stein JD, Newman-Casey PA, Mrinalini T, Lee PP, Hutton DW. Cost-effectiveness of bevacizumab and ranibizumab for newly diagnosed neovascular macular degeneration (An American Ophthalmological Society Thesis). Trans Am Ophthalmol Soc. 2014;111:56-69.
19. National Institute for Health and Care Excellence. Ranibizumab and pegaptanib for the treatment of age-related macular degeneration: technology appraisal guidance. May 2012. Available at: https://www.nice.org.uk/guidance/ta155/. Accessed March 31, 2017.
20. Digital Imaging and Communications in Medicine. RR Ophthalmic Refractive Reports Use Cases (Informative): Reference Tables for Equivalent Visual Acuity Notations. National Electrical Manufacturers Association. 2013. Available at: http://dicom.nema.org/dicom/2013/output/chtml/part17/sect_RR.2.html. Accessed March 31, 2017.
21. Brown MM, Brown GC, Sharma S, Landy J. Health care economic analyses and value-based medicine. Surv Opthalmol. 2003 Apr 30;48(2):204-23.
22. Czoski-Murray C, Carlton J, Brazier J, Young T, Papo NL, Kang HK. Valuing condition-specific health states using simulation contact lenses. Value Health. 2009 Jul 1;12(5):793-9.

CONTACT INFORMATION

Will Herring, PhD
Director, Health Economics

RTI Health Solutions
200 Park Offices Drive
Research Triangle Park, NC 27709

Phone: +1.919.541.6423
Fax: +1.919.514.7222
E-mail: wherring@rti.org

Presented at: ISPOR 2017 International Meeting, May 20-24, 2017, Boston, MA, United States