Patients' preferences in treatment for neovascular age-related macular degeneration in clinical routine

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ABSTRACT

Purpose To assess the effect of ranibizumab treatment for neovascular age-related macular degeneration (nvAMD) on patients' preferences and vision-related quality of life (VRQoL) in a routine clinical setting.

Methods 55 treatment naïve patients were examined before and after the initial upload of three monthly injections of 0.5 mg ranibizumab. VRQoL was assessed using a Rasch-adjusted NEI-VFQ-25. Time trade-off (TTO), standard gamble, a visual analogue scale and the European Quality of Life Questionnaire (EQ-5D) were used to calculate utilities, and multiple logistic regression models were conducted to determine independent factors associated with utilities.

Results Mean±SD age was 75±7 years, and 40 patients (73%) were female. Mean±SD best-corrected visual acuity of the treated eye increased from 20/80 at baseline (logMAR 0.60±0.35) to 20/63 (logMAR 0.52±0.36; p=0.020) at follow-up after three injections. Utility score increases ranged from 2 utils (standard gamble anchored for death) up to 6.6 utils (EQ-5D German TTO, p=0.023) and visual functioning improved (Rasch adjusted composite NEI-VFQ score 50±21 to 54±21, p=0.042). Whether the worse or better eye was treated was not significantly associated with improvements in utility or VRQoL, whereas VA improvement in the treated eye was associated with an increase in utility (TTO, p=0.020).

Conclusions TTO performed best in this sample of elderly nvAMD patients undergoing anti-VEGF therapy. Better or worse eye treatment was not associated with a change in reported utilities or visual functioning in patients with newly diagnosed nvAMD. Directly elicited, vision-specific utilities gained with TTO seem to be sensitive to a change in vision status.

INTRODUCTION

A positive effect of ranibizumab treatment on patients' vision related quality of life (VRQoL) in neovascular (nv) age-related macular degeneration (AMD) has been reported in several studies.[1 2] One way to assess the impact of treatment on patients' QoL and, in particular, the satisfaction derived from a specific health outcome, is to assess utilities. Utility in a general sense refers to the preference an individual or society may have for any particular set of health outcomes. Utilities are a crucial measure for cost–benefit analyses and are used widely by policy planners for allocation of healthcare resources.[3] Commonly used tools to determine utilities in ophthalmology include the time trade-off method (TTO), standard gamble (SG) and the European Quality of Life Questionnaire (EQ-5D).[4] The different approaches have different limitations. TTO and SG are affected by time and duration effects, and SG by attitudes to risk as well as anchoring issues, while generic health-related QoL utilities, especially the EQ-5D, may not be sensitive to the specific effects of vision or vision impairment since they often do not contain vision-related content. Utility values and remaining life years are then used to calculate quality adjusted life years (QALYs), which are the basis of economic evaluations in healthcare.

When considering healthcare resource allocation for treatment of nvAMD, economic evaluations frequently differentiate between treatment of the first (worse) and second (better) eye, assuming a differential impact on patients' preferences (utilities) and QoL, and thus differing cost implications and cost–benefit ratios.[5] However, no data on patient reported preferences for anti-VEGF treatment of nvAMD assessed by standard utility instruments are currently available. Therefore, we investigated the effect of ranibizumab treatment for nvAMD on patients' preferences and VRQoL in a routine clinical setting using a range of utility methods, assessing their performance and appropriateness.

PATIENTS AND METHODS

Patients were recruited from the outpatient clinic at the Department of Ophthalmology, University of Munich, between September 2009 and March 2010. Approval was obtained from the Institutional Review Board of the University of Munich. All patients gave signed informed consent for study participation before enrolment and start of treatment. The study adhered to the tenets of the Declaration of Helsinki.

Patients and intervention

Only treatment naïve, newly diagnosed patients with nvAMD were included. The diagnosis of nvAMD was confirmed by fluorescein angiography. Patients received three monthly intravitreal injections of 0.5 mg ranibizumab. Participants underwent a full ophthalmological examination pre- and post-treatment, including best-corrected visual acuity (BCVA) using retro-illuminated logMAR ETDRS charts (Lighthouse International, New York, USA), fundus photography and optical coherence tomography. VRQoL and patients' preferences were recorded at baseline and follow-up after the third ranibizumab injection, in order to ensure that all patients underwent the same

treatment regime and that the treatment effect was likely to be at its maximum level possible.

Vision-related quality of life

The National Eye Institute Visual Function Questionnaire 25 Item (NEI-VFQ-25), a well evaluated tool available in German,[6] is one of the most widely used QoL scales in ophthalmology. In the current study, we performed Rasch analysis to assess the measurement properties of the German NEI-VFQ-25.

Psychometric validation of the German NEI-VFQ-25

In brief, Rasch analysis is a modern psychometric method that mathematically describes the interaction between respondents and test items. The Rasch model states that the probability of a correct response is a logistic function of the difference between person ability (person measure) and item difficulty (item measure), and applies a strict model which the pattern of participants' responses should satisfy. Raw ordinal scores are thus transformed into data that approximate interval-level measurement (expressed in log of the odds units, or logits). The specific methodology employed has been described in detail elsewhere.[7] We performed Rasch analysis using Winsteps software (V.3.68; Chicago, Illinois, USA).

Patient-reported preferences

Health state utilities depend on the individuals' relative preferences for different health states. The instruments used to assess the patients' preferences in this study included TTO, SG and the Euro-QoL (EQ-5D).[4]

Time trade-off

Within the TTO utility assessment, the respondents are asked to trade-off life for gains in health status. In ophthalmology the perfect health state is set at full visual function. The utility value is calculated as a ratio of the highest state of QoL equalling a utility value of 1.0, whereas the worst utility value is 0.[8]

TTO was conducted as follows. The first question to respondents was "How many years do you still expect to live?", followed by the second question "Assuming that there was a technology which restores you to full vision, what is the maximum number of remaining years of life you would be willing to give up if you could receive this technology and have normal vision in both eyes for the rest of your life?" Utilities were calculated as: (expected life years − years willing to trade off)/expected life years.

Standard gamble

A typical SG lottery asks a person to choose between experiencing a specific health state with certainty for the rest of their life and a lottery, usually described as a medical intervention, with two possible outcomes: an immediate return to perfect health with probability p or immediate death with probability (1−p). The probabilities of the two outcomes are repeatedly adjusted until the person indicates equal preferences between the certain health state and the lottery. The utility weight for the certain health state is equal to the individually adjusted probability p.

In our study, we performed two SG approaches which were anchored for two worst lottery outcome health states: death and blindness. Two anchor points were chosen as the readiness to take risks depends on the worst outcome.[9] The SG utilities were estimated using a computer-based preference assessment interview platform (X-trade).

EQ-5D and visual analogue scale

The EQ-5D is a generic multi-attribute utility instrument developed by the EuroQoL group,[10] comprising five dimensions—mobility, self-care, usual activities, pain/discomfort and anxiety/depression—and three severity levels. The EQ-5D also includes a visual analogue scale (VAS), which comprises a line with numbers between 0 (worst health-state) and 100 (best health-state). The raw data of the EQ-5D values were converted into utilities using the suggested conversion algorithms anchored for the VAS for a European (European VAS) and German (German VAS) collective and by TTO for a German collective (German TTO).

Statistical analyses

SPSS V.19.0 was used to analyse the data. Descriptive statistical analyses were performed to characterise the participants' socioodemographic, clinical, utility and VRQoL data, stratified by better or worse eye treated. Correlational analyses (bivariate and intraclass) were used to explore employed utility measures. Instruments were grouped into directly elicited, vision-specific utilities (TTO and SG, including different anchors), general utilities (different weights for the EQ-5D) and VRQoL estimates (VAS and Rasch scored NEI-VFQ-25). Fully-adjusted logistic regression models were conducted to determine the independent factors associated with patient-reported preferences (utilities) and VRQoL. Visual acuity was categorised into two categories: normal presenting vision in the better eye (<0.4 logMAR); and visual impairment and blindness (logMAR ≥0.4). All tests were considered to be statistically significant at an adjusted level of $p<0.05$.

RESULTS

Clinical characteristics

A total of 55 patients with newly diagnosed and treatment naïve nvAMD participated in the study (table 1). Mean±SD age was 75±7 years, and 40 patients (73%) were female. The mean BCVA of the treated eye increased from 20/80 at baseline (logMAR 0.60±0.35) to 20/63 (logMAR 0.52±0.36; p=0.020) at follow-up after three injections (table 1). Mean BCVA of the fellow eye was 20/63 (logMAR 0.46±0.64) and did not change during the study period. VA significantly improved only in treated worse eyes (logMAR 0.69±0.35 to 0.57±0.38; p=0.013). Visual acuity in treated better seeing eyes remained stable (logMAR 0.43±0.31).

Utility scores increased for the whole sample pre- and post-treatment from 2 utils (SG anchored for death) up to 6.6 utils (EQ-5D German TTO). The only statistically significant utility value increase for the whole sample was found with the EQ-5D German TTO utilities and the VAS measurement (p=0.023 and p=0.001, respectively, table 1). There was no measurable change in utility scores over time within or between the worst or better eye treatment groups except for the VAS measurement which improved in patients whose worse eye was treated (p≤0.01; table 1).

Psychometric evaluation of the NEI-VFQ

After a number of revisions of the original scale, including collapsing response categories to three and splitting the multidimensional overall scale into two scales, a visual functioning and socioemotional well-being subscale, the visual functioning subscale of the NEI-VFQ-25, demonstrated good measurement characteristics as shown in table 2. Discriminant ability of the socioemotional scale could not be improved by further deletion

Table 1 Characteristics of the sample (n=55)

	Total sample n=55	Worse eye treated n=36	Better eye treated n=18	p Value§
Proportion				
Gender				
Male	15 (27.3%)	12 (33.3%)	3 (16.7%)	0.197†
Female	40 (72.7%)	24 (66.7%)	15 (83.3%)	
Age (years), mean±SD	75.5±6.9	75.6±7.0	75.2±7.0	0.837‡

	Total sample n=55		Worse eye treated n=36		Better eye treated n=18		p Value§	
	BL	FU	BL	FU	BL	FU	BL‡	FU‡
Treated eye VA (logMAR)								
Mean±SD	0.60±0.35	0.52±0.36	0.69±0.35	0.57±0.38	0.43±0.31	0.43±0.32		
p Value*	**0.020**		**0.013**		0.987		**0.011**	0.194
Other eye VA (logMAR)								
Mean±SD	0.46±0.64	0.47±0.61	0.19±0.15	0.22±0.20	1.01±0.86	0.96±0.83		
p Value*	0.630		**0.044**		0.280		**0.001**	**0.002**
Better eye VA (logMAR)								
Mean±SD	0.27±0.24	0.29±0.26	0.19±0.15	0.22±0.19	0.43±0.31	0.42±0.32		
p Value*	0.469		0.239		0.604		**0.004**	**0.006**
Standard gamble death								
Mean±SD	0.95±0.12	0.97±0.08	0.95±0.13	0.98±0.05	0.94±0.10	0.96±0.12		
p Value*	0.364		0.352		0.782		0.858	0.511
Standard gamble blindness								
Mean±SD	0.95±0.12	0.98±0.06	0.95±0.12	0.98±0.05	0.95±0.10	0.98±0.08		
p Value*		0.135		0.231		0.384	0.981	0.979
TTO								
Mean±SD	0.89±0.16	0.92±0.16	0.87±0.16	0.90±0.17	0.95±0.03	0.95±0.04		
p Value*	0.326		0.368		0.904		0.074	0.373
EQ-5D German TTO								
Mean±SD	0.79±0.26	0.86±0.20	0.80±0.27	0.87±0.20	0.78±0.25	0.83±0.22		
p Value*	**0.023**		0.067		0.245		0.763	0.534
Visual analogue scale								
Mean±SD	53.27±14.43	61.36±18.0	53.06±13.99	65.14±16.50	52.78±3.67	52.50±4.24		
p Value*	**0.001**		**<0.001**		0.945		0.947	**0.018**
NEI-VFQ visual functioning								
Mean±SD	50±21	54±21	51±19	56±18	44±24	48±24		
p Value*	**0.042**		0.086		0.390		0.286	0.177

Emboldened values indicate statistical significance.
*Two-tailed paired t-test.
†Pearson's χ^2.
‡Independent samples two-tailed t-test.
§p Value refers to the difference in baseline and follow-up scores between the worse and better eye treatment groups.
EQ-5D, European Quality of Life Instrument, 5 dimensions; NEI-VFQ, National Eye Institute Visual Functioning Questionnaire; TTO, time trade-off; VA, visual acuity; VAS, visual analogue scale.

or inclusion of items. Thus the socioemotional scale was only used in the correlational analyses (table 3) but not in any of the regression models. The process is outlined in a previous Rasch analysis of the NEI-VFQ-25.[11] To facilitate the interpretation of the person measure scores, they were recalibrated from a negative–positive logit scale to range between 0 and 100 following Rasch analysis. Visual functioning improved from baseline to follow-up in the whole sample by 4.0 points on the transformed VFQ scale (50±21 to 54±21, p=0.042; table 1). As with the utility measures, no differences were found for visual functioning over time within or between the better and worse eye treatment groups.

Table 2 The fit parameters of the German NEI-VFQ 25 Item compared to the Rasch model

Parameters	Rasch model	NEI-VFQ-25 overall score	NEI-VFQ-25 Rasch guided subscales	
			Visual functioning	Socioemotional
Item no.		1–25	5–14	3, 17, 18, 20–24
Number of misfitting items	0	9	0	0
Person separation	>2.0	2.16	2.21	1.58
Person reliability	>0.8	0.82	0.83	0.71
Person mean	0	1.13	1.47	2.69
Principal components analysis (eigenvalue for first contrast)	<2.0	3.8	1.6	1.8
Variance by the first factor	>50%	49.6%	53.5%	68.1%

Table 3 Correlations of utility measures and visual acuity at baseline (bivariate Pearson's correlation coefficients)

	ETDRS letters	SG death	SG blindness	TTO	EQ-5D European VAS	EQ-5D German TTO	EQ-5D German VAS	VAS	PM VF	PM SEW
ETDRS letters baseline										
CC	1	0.288*	0.295*	0.046	−0.092	−0.042	−0.120	0.091	0.065	0.066
p		0.045	0.039	0.748	0.521	0.771	0.402	0.526	0.651	0.648
SG death										
CC		1	0.825†	0.312*	0.099	0.046	0.102	0.360†	0.471†	0.446†
p			0.000	0.023	0.482	0.741	0.469	0.008	0.000	0.001
SG blindness										
CC			1	0.466†	0.160	0.081	0.134	0.349*	0.341*	0.343*
p				0.000	0.252	0.563	0.340	0.010	0.013	0.012
TTO										
CC				1	0.074	0.024	0.047	0.048	0.031	0.031
p					0.593	0.862	0.731	0.728	0.823	0.821
EQ-5D European VAS										
CC					1	0.927†	0.975†	0.196	0.177	0.083
p						0.000	0.000	0.153	0.197	0.546
EQ-5D German TTO										
CC						1	0.934†	0.226	0.081	0.048
p							0.000	0.097	0.558	0.728
EQ-5D German VAS										
CC							1	0.217	0.181	0.113
p								0.111	0.186	0.410
VAS										
CC								1	0.490†	0.298*
p									0.000	0.027
PM VF										
CC									1	0.394†
p										0.003
PM SEW										
CC										1
p										

*Correlation is significant at the 0.05 level (2-tailed).
†Correlation is significant at the 0.01 level (2-tailed).
CC, correlation coefficient; SG, standard gamble; TTO, time trade-off; VAS, visual analogue scale; VF, visual function.

The relation of reported utilities

All vision-specific utilities, namely the SG anchored for death and blindness and the TTO, were highly correlated using Pearson's correlation coefficient (table 3) and intraclass correlation ($r>0.5$; $p<0.001$ for all). All three measures showed similar ceiling effects, but only SG measures were correlated to VA, VAS and person measures (visual functioning and socioemotional well-being, table 3). As the SG anchor for blindness cannot be used to calculate QALYs, we only used the SG anchored for death for subsequent analyses.

The three different weightings for the EQ-5D data were highly correlated with each other; however, they correlated to no other clinical measures. Ceiling effects were present but less marked than for SG and TTO. In subsequent analyses, only the German TTO weighting was used.

The Rasch guided person measures for the visual functioning and socioemotional well-being subscales of the NEI-VFQ-25 and the EQ-5D based VAS rating were all inter-correlated and correlated to both SG ratings, but were not correlated with other clinical measures (table 3).

The impact of treatment on patients' preferences

We created binary variables for all utility scores at follow-up, categorising the change into improvement (including stable scores, difference to baseline ≥ 0) and worsening (difference to baseline <0). Logistic regression models were used to examine the association between an improvement in patient reported preferences and ranibizumab treatment for nvAMD. An improvement of vision in the treated eye was significantly associated with an improvement in the TTO score ($p=0.020$; table 4). However, whether the better or worse eye was treated was not significantly associated with any of the utility measures. Age was significantly associated with reported differences in SG anchored for death ($p=0.010$) and the EQ-5D German TTO ($p=0.038$; table 4). An improvement in visual functioning as measured with the NEI-VFQ-25 subscale was significantly associated with an improvement in reported scores for SG anchored for death ($p=0.025$).

DISCUSSION

In this sample, ranibizumab treatment for nvAMD led to an improvement in visual acuity of the treated eye, patient reported visual functioning and utilities as measured with TTO and the EQ-5D anchored for German TTO. In multivariate analyses, better or worse eye treatment was not significantly associated with any utility measures, whereas an improvement of vision in the treated eye was significantly associated with increased TTO utilities. SG utilities (both anchors) were highly concordant but were not responsive to treatment in this sample. This has important implications for economic evaluations of ophthalmic interventions as it suggests that vision-specific, directly elicited utilities collected with TTO may be most sensitive to a change in vision status. Generally, responsiveness of utility instruments to change over time, that is after an intervention, remains a challenge to be addressed.

Table 4 Binary logistic regression models for change ('better or stable' vs 'worse') in reported utility scores

	Standard gamble death		EQ-5D German TTO		TTO		VAS	
	OR (95% CI)	p Value	OR (95% CI)	p Value	OR (95% CI)	p Value	OR (95% CI)	p Value
Age	**1.27 (1.06 to 1.52)**	**0.010**	**1.13 (1.01 to 1.27)**	**0.038**	1.06 (0.94 to 1.20)	0.350	0.98 (0.88 to 1.08)	0.659
Gender	1.63 (0.25 to 10.69)	0.612	0.19 (0.03 to 1.31)	0.091	0.25 (0.05 to 1.34)	0.105	0.35 (0.08 to 1.63)	0.183
Better eye treated	2.59 (0.21 to 31.65)	0.456	1.97 (0.31 to 12.42)	0.468	0.06 (<0.01 to 1.05)	0.054	4.70 (0.83 to 26.47)	0.079
VA improvement (treated eye)	3.89 (0.46 to 32.72)	0.212	3.88 (0.69 to 21.90)	0.124	**0.08 (0.01 to 0.67)**	**0.020**	0.43 (0.07 to 2.56)	0.355
VI status change	7.92 (0.62 to 101.77)	0.112	1.05 (0.16 to 6.88)	0.957	9.08 (0.79 to 103.94)	0.076	0.72 (0.11 to 4.58)	0.731
Improvement in visual functioning	**9.98 (1.33 to 74.77)**	**0.025**	0.49 (0.12 to 1.96)	0.313	2.88 (0.55 to 15.17)	0.212	3.67 (0.87 to 15.55)	0.078

Emboldened values indicate statistical significance.
TTO, time trade-off; VA, visual acuity; VAS, visual analogue scale; VI, visual impairment.

Use of utility instruments comes with a range of inherent challenges. Whether utility measures are sensitive to changes in health status over a short period of time is debatable.[12] Similarly, anchoring them for perfect vision—blindness rather than perfect health or death—is controversial[9] as utility measures tend to produce lower utilities when anchored for blindness rather than death, which makes comparability across different illnesses and interventions difficult.[9] Indeed, SG anchored for blindness was not associated with any of the assessed factors in our study. This, coupled with the high concordance of both measures, suggests that anchoring for death is appropriate as this yields universally comparable results. Another issue concerns obtaining utilities from an elderly sample with a short remaining life span and low willingness to trade any of it for an intervention. This is reflected in our study where most utility values were associated with age. The VAS, as a magnitude estimate of health, or in this case VRQoL, was highly correlated to the NEI-VFQ-25 person measures, but not with other utility measures. Thus we would not recommend it to be used as the sole utility measure in any research scenario.

Better or worse eye treatment was not associated with improvements in utilities in our study. This may have implications for cost-effectiveness analyses which often assume a differential impact of better or worse eye treatment on utilities. Utility values used for economic evaluation in ophthalmology, in particular in the field of AMD, are often deduced using approximations from clinical data (eg, visual acuity) rather than from directly collected utilities.[13] Utilities directly derived from patients are very likely to differ from utility values inferred from visual acuity, as patients' preferences are vastly different even at the same level of visual acuity.

Vision functioning improved in our sample by four points, which is similar to the minimal clinically important difference for the non-Rasch adjusted NEI-VFQ-25 (3—4 points in the composite score).[14] The observed increase in visual functioning was similar regardless of whether the better or worse eye was treated, which corresponds to findings reported from the ANCHOR and MARINA studies.[2]

Strengths of our study include the use of a standard VRQoL instrument and a large array of utility tools to assess ranibizumab treatment effects in nvAMD, which has not been performed previously. Moreover, the use of three different population value sets to calculate the EQ-5D utilities is also important, especially given the varying findings in our study. Further strengths include the use of Rasch analysis to assess the psychometric properties of the German NEI-VFQ-25, and to produce interval-level measurements of visual functioning. Such a psychometric evaluation has not been done for the German version of the NEI-VFQ-25 to date. Our study setting in daily clinical routine better reflects actual treatment conditions and outcomes than highly standardised phase III clinical trials. The main limitation of our study is the small sample size, and uneven size of the subgroups for better and worse eye treatment, which may have diminished our ability to reveal significant associations and ensure that the associations we did find were not due to chance alone. Indeed, the wide CIs present for some of our data imply poor precision, and future trials are required to replicate the findings in a larger sample population. Another limitation is the short follow-up time; however, empirical evidence suggests that the largest treatment effect, if any, is to be expected at 3 months, and then either maintained or lost over the subsequent months. Indeed, other large randomised studies have shown similar increases in NEI-VFQ-25 visual functioning score at 3 months to that found in our study.[1 2]

In conclusion, ranibizumab treatment for nvAMD leads to improvements in visual acuity, patient reported visual functioning and patient preferences, as elicited by TTO. Non vision-specific utility measures, or SG anchored for blindness, did not detect a change over time. Better or worse eye treatment was not associated with any of the patient reported utilities assessed, suggesting that gain in utility from better and worse eye treatment may be similar and that differential allocation of resources in cost-effectiveness analyses may not be warranted.

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