Quality of Life in Patients Suffering from Active Exudative Age-Related Macular Degeneration: The EQUADE Study

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Key Words

Quality of Life · Age-related macular degeneration ·
Ranibizumab · Anti-vascular endothelial growth factor

Abstract

Purpose: Age-related macular degeneration (AMD) is the main cause of visual loss in the elderly population. With the use of anti-vascular endothelial growth factor, the visual outcomes of exudative AMD patients have been improved. This study was aimed at assessing the quality of life (QoL) of exudative AMD patients treated with ranibizumab and at determining its drivers in a real-life setting. **Methods:** We performed a national, cross-sectional, observational survey based on questionnaires sent to members of French associations relative to AMD between December 2012 and March 2013. Patients suffering from exudative AMD with at least one intravitreal injection of ranibizumab within the last 6 months were included. Demographics, AMD characteristics, visual acuity (VA) and past and ongoing treatments were collected. The 25-item National Eye Institute Visual Function Questionnaire (NEI-VFQ-25) was self-administered. A multivariate model was used to identify QoL drivers. **Results:** 416 questionnaires fulfilled the complete crite-

ria for both QoL and cost analyses. The mean age of exudative AMD patients was 78.0 years and bilateral involvement was reported in 60.4%. The overall mean QoL score was 53.4. Mental health, driving and role difficulties were the most widely affected domains. After bivariate analyses, long-term illness status, worse VA and higher number of unpaid aids were associated with worse QoL, with odds ratios of 2.4, 5.2 and 11.6, respectively. The mean cost per year and per patient was 1,741 EUR. The main components of costs were aids and services and the purchase of visual equipment. **Conclusions:** The main predictors of QoL in exudative AMD patients treated with ranibizumab are VA outcomes, home healthcare and social services provided to the patients.

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Introduction

Age-related macular degeneration (AMD) is among the major causes of visual acuity (VA) loss in the elderly population [1]. Indeed, population estimates show that 25–30 million people suffer severe VA loss due to both exudative and atrophic forms of AMD [2].

Both types of AMD, the wet and the atrophic form, are characterized by central retina involvement resulting in VA loss with variable VA-decreasing profiles. Before the anti-vascular endothelial growth factor (anti-VEGF) era, the exudative form of AMD was the most severe because of its short-term poor visual prognosis due to the ingrowths of choroidal new vessels leading to exudation and bleeding into or beneath the neurosensory retina, whereas the dry form is classically characterized by a slower evolution following the apoptotic wave of the retinal pigment epithelium cell layer. Since 2006, the exudative form, in the majority of cases, benefits from anti-VEGF therapies, with VA improvement or stabilization in almost 90% of patients in the main clinical trials [3–5] and in real-life practice, with more mitigated VA outcomes depending on the treatment and follow-up protocols [6, 7]. While the prevalence of legal blindness following the diagnosis of exudative AMD has decreased with the use of anti-VEGF therapies [8, 9], both the treatment and follow-up of patients presently represent a major burden that is likely to have an impact on quality of life (QoL).

QoL in patients with AMD can be evaluated with QoL scales that allow comparisons between patients with similar or with different diseases. The 25-item National Eye Institute Visual Function Questionnaire (NEI-VFQ-25) is a 25-item generic, vision-related QoL instrument that has already been used with AMD [10, 11].

The aim of this study was to evaluate the QoL of exudative AMD patients recently treated with ranibizumab and to evaluate the cost of treatment borne by the patients themselves.

Patients and Methods

Study Design

This study was a national, cross-sectional, observational survey based on questionnaires sent by mail to members of either 'Association DMLA' or 'Retina France' between December 2012 and March 2013. A first pilot study was carried out between August and September 2012. This survey comprised five different fields collecting sociodemographic data, clinical data, data related to treatments for exudative AMD, data related to resources consumed and data related to QoL.

Patients

The inclusion criteria were presence of active exudative AMD with at least one intravitreal injection of ranibizumab within the last 6 months. The exclusion criterion was ongoing participation in a clinical trial in ophthalmology. Since members of the Retina France association suffer from various retinal disorders (mainly inherited retinal dystrophies and AMD), identification of eligible

patients to this study was performed during a pre-screening phase organized by the association itself between October and December 2012. Participation of patients from the associations was voluntary and complete anonymity of participating patients in the survey was observed. The research adhered to the tenets of the Declaration of Helsinki.

Questionnaires

The questionnaires were sent by mail from the associations to all Association DMLA members or to those selected in the first pre-screening of the Retina France association. Data were directly collected from the questionnaires.

QoL Score and Other Criteria

The composite or global NEI-VFQ-25 score was the main evaluation criterion in this study [12]. This score is a simplified version of the NEI-VFQ-51 score (comprising 51 items) and allows for reliable evaluation of visual function and its impact on the QoL of patients suffering from ocular disorders [13].

Twelve subscale scores can be computed: general health (1 item), general vision (1 item), ocular pain (2 items), difficulty with near-vision activities (3 items), difficulty with distance-vision activities (3 items), limitation of social functioning due to vision (2 items), mental health problems due to vision (4 items), role limitations due to vision (2 items), dependency on others due to vision (3 items), driving difficulties (2 items), difficulty with color vision (1 item) and difficulty with peripheral vision (1 item). Each subscale score is converted to a score between 0 and 100, and higher scores indicate better vision-specific health-related QoL. An overall composite score can also be generated as the mean score of all items except for the general health item.

In order to assess the overall level of visual handicap, patients were classified into a composite criterion of corrected VA of both eyes defined by four categories of severity, as reported previously in a study of vision-related QoL in AMD [10]. Category 1 included patients with best eye VA (BEVA) ≥ 0.5 and worst eye VA (WEVA) ≥ 0.1 . Category 2 included patients with BEVA ≥ 0.5 and WEVA < 0.1 . Category 3 included patients with BEVA < 0.5 and WEVA ≥ 0.1 . Category 4 included patients with BEVA < 0.5 and WEVA < 0.1 . The value of the level of corrected VA of each eye reported by the patients was based on medical records obtained by their ophthalmologists.

The medico-economic burden of exudative AMD borne by the patients was also evaluated. Analysis included the annual cost of treatments (excluding costs defrayed by insurance), of nutritional supplementation, of transportations for treatment, of follow-up and reeducation as well as the net annual cost of aids and services for daily activities consecutive to AMD (purchase of visual aid equipment and material for environmental adaptation to the disease). Unpaid aides were defined as auxiliaries involved in daily life activities for which the patient reported that he/she received unpaid aid or assistance, including assistance for the daily life actions, support/assistance for household maintenance, assistance for communication or reading, assistance for administrative tasks, assistance for travels and outings and other types of assistance.

Statistical Analyses

Data analysis was performed by IMS Health with the SAS® System 9.2 software (SAS Institute, Cary, N.C., USA). Differences between subgroups were investigated through descriptive analysis,

Fig. 1. Detailed flow chart of patient selection.

especially in the preparatory phase dedicated to the creation of multivariate models. For qualitative or discrete variables, significant differences between subgroups were investigated using either the χ^2 test or the Fisher exact test. Analysis of stratified categorical data was performed with the Cochran-Mantel-Haenszel test. For analysis of quantitative variables, significant differences between

two subgroups were detected using Student's t test. The hypotheses of equality of variances and of normality had previously been confirmed by the F-test and the Shapiro-Wilk test. A non-parametric approach was adopted if these hypotheses were not verified, with the Wilcoxon or Mann-Whitney test used for comparison between two subgroups, and the Kruskal-Wallis test for comparison of

more than two subgroups. Analysis of variance was used if more than two subgroups were analyzed. Determinants of the altered health-related QoL in patients with exudative AMD were identified by multivariate regression model. As the distribution of composite QoL score (dependent variable) was highly non-normal (high kurtosis and heavy-tailed) and since no common data transformations (including log/inverse/square root/arc sinus transformations) had improved its normality, one option was to perform a discretization of our outcome into three levels based on percentiles of 33 and 66% and to run an ordered logistic regression such as a proportional odds model.

All predictive factors potentially related to an impairment of the QoL score and listed by clinicians were tested and analyzed. Univariate models for each independent variable were performed and a p value threshold of 5% was applied for selection of variables to be included in the multivariate model. A multicollinearity diagnostic was produced by linear regression analysis with the tolerance (values <0.6) and the variance inflation factor (values >2) for each selected independent variable. In case of multicollinearity, the practical aspects and importance of the variables were taken into account in order to make a decision on which variables to drop from the model. A backward selection procedure (threshold fixed at 0.2) was used to select the best model to fit the QoL loss as measured by the Akaike information criteria.

Results

Out of the 1,888 questionnaires mailed out, 611 (32.4%) were returned; 467 (24.7%) met the inclusion criteria and were fully completed for analyses. Among them, 416 met the complete criteria for both QoL and cost analyses. A detailed flow chart is presented in figure 1.

Sociodemographic Data and VA

The patients (mean age 78.0 years, 70.5% women) reported involvement of both eyes, with exudative AMD in 60.4%. The mean duration of exudative AMD was 7 and 2.3 years for the first and second eye, respectively. Other sociodemographic data describing the patients and the treatments are presented in table 1.

Among the patients with recorded VA for at least one eye (n = 352), 159 (34.0%) had VA <0.5 on both eyes, 23 (4.9%) had VA <0.1 on both eyes and 52 (11.1%) had VA ≥0.5 on both eyes. These data are presented in table 2. Among them, 142 (40.3%) were classified in category 1 while 119 (33.8%) were classified in category 4. More complete data are presented in table 3.

QoL Scores

The scores for composite NEI-VFQ-25 questionnaire per domain varied from 34.79 for driving to 75.94 for color vision. Mental health, driving and role difficulties were the most affected domains. Mental health, an item

Table 1. Sociodemographic characteristics of the cohort (n = 467)

Age, years (8 missing data)	78.0±7.5
Age at first diagnosis (29 missing data)	70.7±8.6
By age group	
<50 years	2 (0.4%)
50–59 years	5 (1.1%)
60–69 years	53 (11.5%)
70–79 years	189 (41.2%)
80–89 years	192 (41.8%)
≥90 years	18 (3.9%)
Women (10 missing data)	322 (70.5%)
Eye affected by exudative AMD	
Right eye only	99 (21.2%)
Left eye only	86 (18.4%)
Both eyes	282 (60.4%)
Other ocular disorders (no missing data)	
None	155 (33.2%)
Cataract (not yet operated)	88 (19.6%)
Cataract (operated)	186 (41.5%)
Glaucoma	43 (9.6%)
Others (not defined)	55 (12.3%)
Lifestyle (7 missing data)	
Alone	165 (35.9%)
In pairs	293 (63.7%)
In institution	2 (0.4%)
Area of residence (9 missing data)	
Rural (<3,000 inhabitants)	80 (17.5%)
Semi-rural (3,000–50,000 inhabitants)	171 (37.3%)
Urban (>50,000 inhabitants)	207 (45.2%)
Health coverage for AMD (19 missing data)	
Complete coverage by social security	281 (62.7%)
Other insurances	439 (96.5%)
Anti-VEGF treatments (49 missing data)	
Ranibizumab	558 (94.3%)
Bevacizumab	15 (2.5%)
Ranibizumab + bevacizumab	13 (2.2%)
Ranibizumab + pegaptanib	4 (0.7%)
Ranibizumab + bevacizumab + pegaptanib	1 (0.2%)
Pegaptanib	1 (0.2%)
Intravitreal injections within last year (n = 576)	4.72±2.72
Follow-up for 1 year (without induction phase)	3.57±1.97
Follow-up >1 year	5.15±2.81
Transportations for treatment/visit (19 missing data)	7.9±4.7
Distance, km	32.8±61.8

Figures are mean ± standard deviation or n (%).

considered in relation to vision, is analyzable through questions 3, 21, 22 and 25 of the self-administered QoL questionnaire NEI-VFQ-25. These results are detailed in table 4. The results for composite QoL NEI-VFQ-25 score per domain and per category are presented in figure 2.

Table 2. Distribution of VA among patients

Left-eye VA	Right-eye VA				
	<0.1	<0.5	≥0.5	unknown	total
<0.1	23 (4.9%)	56 (12.0%)	26 (5.6%)	6 (1.3%)	111 (23.8%)
<0.5	40 (8.6%)	40 (8.6%)	45 (9.6%)	10 (2.1%)	135 (28.9%)
≥0.5	25 (5.4%)	45 (9.6%)	52 (11.1%)	13 (2.8%)	135 (28.9%)
Unknown	7 (1.5%)	14 (3.0%)	11 (2.4%)	54 (11.6%)	86 (18.4%)
Total	95 (20.3%)	155 (33.2%)	134 (28.7%)	83 (17.8%)	467 (100%)

Table 3. Composite criteria of corrected VA

	With unclassified patients	Without unclassified patients
Category 1 BEVA ≥0.5 and WEVA ≥0.1	142 (30.4%)	142 (40.3%)
Category 2 BEVA ≥0.5 and WEVA <0.1	51 (10.9%)	51 (14.5%)
Category 3 BEVA <0.5 and WEVA ≥0.1	40 (8.6%)	40 (11.4%)
Category 4 BEVA <0.5 and WEVA <0.1	119 (25.5%)	119 (33.8%)
Not classified	115 (24.6%)	0 (0%)
Total	467 (100%)	352 (100%)

Modelization of the Composite QoL Score

A proportional odds model was used to determine factors associated with altered health-related QoL. Previously, three levels of QoL (low/medium/high) had been defined according to 33 and 66% percentiles as illustrated in table 5.

Potential independent variables used were symptom profile [disease duration, type of damage (unilateral vs. bilateral), VA criteria], other ocular disorders, use of medical treatments (treatment phase, anti-VEGF treatments, number of intravitreal injections within the last year), other treatments of AMD (photocoagulation, food supplements, rehabilitation sessions), socioeconomic or demographic characteristics (sex, age, area of residence, occupational status, health coverage for AMD), level of autonomy (lifestyle, use of personal vehicle) as well as aids and services (purchase of visual aid equipment, adjustment of the place of residence with specific facilities, aid of a paid/unpaid person, number of activities that require assistance).

Table 4. Composite QoL NEI-VFQ-25 score per field

Domains	Responses	Mean ± SD (range)
General health	461	44.58 ± 16.0 (4)
General vision	463	52.61 ± 17.0 (6)
Near-vision activities	465	48.95 ± 27.73 (5)
Distance-vision activities	467	53.47 ± 27.0 (7)
Peripheral vision	455	65.22 ± 27.17 (9)
Color vision	454	75.94 ± 27.1 (12)
Dependency	452	59.99 ± 30.48 (8)
Role difficulties	457	42.23 ± 29.35 (3)
Mental health	467	38.76 ± 24.97 (2)
Social functioning	462	71.48 ± 29.13 (10)
Driving	378	34.79 ± 34.76 (1)
Ocular pain	465	74.19 ± 23.3 (11)

SD = Standard deviation.

Table 5. Composite QoL NEI-VFQ-25 overall score

	QoL overall score
Responses used for the model	352 ^a
Mean ± SD	52.25 ± 21.27
Median (Q1–Q3)	51.52 (34.78–68.78)
Minimum, maximum	10.21, 96.35
Low QoL (0–38.7)	116 (33.0%)
Medium QoL (>38.7–62.1)	115 (32.7%)
High QoL (>62.1–100)	121 (34.4%)

^a Only patients with both an evaluable NEI-VFQ-25 overall score and VA criteria were used.

The observed p level (0.4432) of the score test did not lead to rejection of the proportional odds assumption. Globally the model was significant with $R^2 = 0.5811$, and 58.1% of the variation of the QoL score variable was explained by the factors included in the model. The likeli-

Fig. 2. Composite QoL NEI-VFQ-25 score per domain and per category.

hood ratio χ^2 test was 294.98 for 11 degrees of freedom ($p < 0.0001$).

Several factors and situations were identified as risk factors increasing the probability of a high QoL loss. These included disease duration ($p = 0.0286$, odds ratio [OR] = 1.06 per year), having long-term illness status ($p = 0.0007$, OR = 2.44), having worse VA (category 4, $p < 0.0001$, OR = 5.24) or intermediate VA (category 3, $p = 0.0017$, OR = 3.76) compared to the best acuity level (category 1), having purchased visual aid equipment ($p = 0.0181$, OR = 1.88), having specific facilities at home ($p = 0.0329$, OR = 4.03) and having a higher number of unpaid aids ($p < 0.0001$, OR = 11.57). In contrast, driving was identified as a significant protecting factor ($p < 0.0001$, OR = 0.21). These data are detailed in table 6.

Medico-Economic Evaluation of the Costs Borne by the Patients

Patients reported a need for transportation to their appointments for intravitreal injections in 100% or for med-

ical examination in 97.9% of cases, and 277 out of 467 patients (59.3%) required assistance as a consequence of AMD. The use of different resources is detailed in figure 3.

The mean cost of exudative AMD per year and per patient was 1,741 EUR (standard deviation 3,397 EUR), the main components of the cost being aids and services as well as the purchase of visual equipment. These cost items are detailed in table 7.

Discussion

Since the beginning of the anti-VEGF era, few studies have focused on exudative AMD patients recently treated with ranibizumab and attempted to evaluate the QoL and cost borne by the patients themselves in order to cope with this disease. In the EQUADE study, the response rate to the questionnaires was relatively high, with 32.4% of return and 24.7% of inclusion criteria met ($n = 467$ for QoL score validated). The main risk factors associated

Fig. 3. Use of different resources.

Table 6. Factors associated with modification of QoL in multivariate analyses

Parameter/effects	OR	p value of the parameters estimate	Wald confidence interval (95%)	
			lower bound	upper bound
Long-term illness status (yes vs. no)	2.44	0.0007	1.46	4.08
Duration after diagnosis (per year)	1.06	0.0286	1.01	1.12
VA criteria ¹				
Category 2 vs. category 1	0.82	0.5949	0.38	1.73
Category 3 vs. category 1	3.76	0.0017	1.65	8.61
Category 4 vs. category 1	5.24	<0.0001	2.63	10.45
Driving (yes vs. no)	0.21	<0.0001	0.12	0.39
Aids and services				
Paid (yes vs. no)	2.02	0.0246	1.09	3.74
Unpaid (1 or 2 vs. none)	3.61	<0.0001	2.03	6.43
Unpaid (≥3 vs. none)	11.57	<0.0001	5.61	23.86
Visual equipments (yes vs. no)	1.88	0.0181	1.11	3.17
Specific facilities at home (yes vs. no)	4.03	0.0329	1.12	14.519

¹ VA = Composite criterion of corrected VA of both eyes.

Table 7. Net annual cost per item borne by the patients

Items	Mean $\pm$ SD (% of total cost)	Range
Dietary supplements	150 $\pm$ 188 (8.6)	0–1,137
Transportation for intravitreal injections	168 $\pm$ 398 (9.6)	0–3,600
Transportation for medical examination	140 $\pm$ 343 (8.0)	0–3,480
Transportation for reeducation	4 $\pm$ 34 (0.2)	0–560
Paid aids and services	710 $\pm$ 2,684 (40.8)	0–41,340
Purchasing of equipment	524 $\pm$ 1,480 (30.1)	0–18,297
Specific facilities at home	45 $\pm$ 405 (2.6)	0–7,000
Total net cost for patients	1,741 $\pm$ 3,397 (100)	0–43,176

Costs are in EUR.

SD = Standard deviation.

with decreased QoL were worse VA (category 4), long-term illness status and a higher number of unpaid aids and specific facilities at home. The global QoL score was 53.4, with major variations depending on domains, from 75.9 for color vision to 38.8 for mental health and 34.8 for driving. Our results are similar to those of a multicenter cross-sectional study aimed at analyzing the impact of BEVA and WEVA on QoL [11]. Indeed, the mean NEI-VFQ-25 global score in this study was 52.6, and the scores for color vision and mental health were 77.2 and 41.4, respectively. On the other hand, the mean global NEI-VFQ-25 score was lower in a previous study published in 2007 conducted in different departments of ophthalmology in different European countries, with the QoL score varying from 44.4 to 56.5 [14]. However, 100% of the patients included in this study had bilateral exudative AMD, which was not the case for the EQUADE study, in which both eyes were more often than not involved (60.4%).

As expected from VA outcomes, several anti-VEGF treatments such as pegaptanib, ranibizumab or aflibercept have demonstrated significant improvements in the composite QoL score on the NEI-VFQ-25, reflecting overall improvement in the respondents' visual health and related functional capacities [5, 15–17]. However, these results were obtained in multicenter randomized clinical trials with fixed regimens of treatment and may be biased by the profile, recruitment and follow-up of patients during the trials. Indeed, compared with the treatment paradigms validated by clinical trials, patients with exudative AMD receive fewer anti-VEGF injections and benefit from less frequent monitoring in real-life clinical practice.

We acknowledge some limitations of this study. The survey was conducted among members of associations and may not completely reflect the population of exudative AMD patients. Indeed, patients belonging to an association are often better informed and supported compared to other patients with similar disease profiles. However, 70% of the patients participating in this survey were women and the mean age was 78.0 years, which is consistent with the epidemiology of the disease [18–20]. Furthermore, the mean number of injections (4.7 during the last year) and follow-up visits ($n = 8$) reported in the EQUADE study were also consistent with two previously conducted real-life studies on exudative AMD patients [6, 21]. Considering VA, 75.4% of the patients included in this study were able to self-report VA for at least one eye, which is a relatively high percentage. Moreover, the level of confidence in these data may be high because they were based on medical records obtained by the patients from their ophthalmologists.

In terms of costs, the EQUADE study did not analyze the societal expenses related to exudative AMD, but rather evaluated the burden of expenses borne by the patients. In fact, this study underscored the relatively high level of annual personal expenses incurred by patients with exudative AMD, the main part of which consisted in paid aids (41%) and the acquisition of visual equipment (30%). Furthermore, paid and unpaid services appear to have a major impact on QoL, a factor likely to be explained by the level of dependency, which is correlated to the use of these services. However, these costs are lower than reported in other previous studies. Before the anti-VEGF era, in 2004, the average total costs related to actively treated exudative AMD patients were 3,714 EUR, two thirds medical and one third non-medical, with a slight increase corresponding to AMD severity [22]. In another study, the average annual societal costs in France per bilateral exudative AMD patient treated were estimated at 7,349 EUR [23]. Societal costs included direct vision-related medical costs (e.g. treatment of AMD and vision-related equipment), direct non-vision-related medical costs (e.g. medication) and direct non-medical-related costs (e.g. home healthcare and social services). However, the EQUADE study did not include the societal cost of anti-VEGF treatment and direct non-vision-related medical costs.

In conclusion, the main current predictors of QoL in exudative AMD patients treated with ranibizumab are VA outcomes, home healthcare and social services. As a result, VA preservation represents a major issue for the patients involved.

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