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CLINICAL INVESTIGATION

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Influence of photodynamic therapy for age related macular degeneration upon subjective vision related quality of life

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Abstract *Background:* Photodynamic therapy (PDT) has been used in the treatment of choroidal neovascularisation secondary to age-related macular degeneration (AMD). This study prospectively investigated patients' subjective change in visual function following PDT as treatment for AMD. *Methods:* Eighty-two consecutive patients receiving PDT in Tasmania, Australia, between May and November 2003 were recruited. In conjunction with a comprehensive clinical examination, the Visual Function-14 (VF-14) questionnaire was administered. Final follow-up occurred between February and March 2005. The VF-14 was scored by traditional summary scoring and by Rasch analysis. *Results:* Five of the 82 (6.1%) subjects recruited were excluded from analysis. PDT was performed on average 5.7±2.6 times per patient. Raw VF-14 scores tended towards being significantly lower at follow-up than at baseline (67.6±27.2 against 64.5±27.7; P=0.052), and did significantly deteriorate using a collapsed Rasch analysis (P=0.0102). Following treatment, 38 (47.5%) eyes had lost three or more Snellen lines of best-corrected visual acuity. *Conclusion:* Patients undergoing PDT typically report reasonable visual function. In parallel with visual acuity, self-reported visual function may deteriorate slightly after PDT for AMD, but not as much as reported in untreated AMD.

Keywords Choroidal neovascularisation · Visual disability · Rasch analysis · Visual function · Verteporfin

Introduction

In the western world, age-related macular degeneration (AMD), a degenerative disease of the macula, is the most common cause of severe vision loss in elderly people [4, 10, 34]. The hallmark of advanced or advancing age-related macular degeneration is sub-retinal or choroidal neovascularisation (CNV). Although CNV may occur throughout the fundus, macular CNV tends to be most detrimental on visual function [17]. CNV can be classified according to its position (subfoveal, juxtafoveal, or extrafoveal) and its angiographic appearance (predominantly classic, minimally classic, or occult with no classic)[12].

Currently, therapeutic options for CNV are limited. However, recently photodynamic therapy (PDT) with verteporfin (Visudyne; Novartis Pharmaceuticals, North Ryde, NSW, Australia), has been approved for use in Australia [9]. PDT has been shown to inhibit the progression of CNV, whilst preserving non-degenerative tissue [24, 26]. In large randomized controlled trials, PDT reduced the absolute risk of losing three or more Snellen lines of visual acuity, in eyes which had predominantly classic CNV [7, 8, 32]. The

results from these studies have been reproduced in smaller cross-sectional investigations [5, 9, 31]. For patients who exhibit occult and no classic, or minimally classic lesions, lesion size has been shown to be an important predictor in the magnitude of treatment benefit [6].

Whilst PDT may hold the CNV lesions at bay, as with all new therapies clinicians must ensure that patients' visual function is also maintained. Using a decision analysis model, Sharma et al. suggested that there was a small but significant gain in quality-adjusted life years conferred through PDT [27]. In a global quality of life outcome of PDT study, self-reported reading ability was the subscale which best differentiated between patients who felt their function was worse and those who thought it was better [13]. Further to this, self-reported visual function can deteriorate despite PDT [3]. This study was established to prospectively measure the subjective visual function of patients who were undergoing PDT as treatment for AMD.

Material and methods

Patient recruitment

A prospective longitudinal design was adopted. Eighty-two consecutive patients with AMD, undergoing PDT in Tasmania, Australia, between May and November 2003 were recruited. The mean±SD age of the cohort was 78.2± 8.0 years. In total, 58 (70.7%) females were enrolled. Patients with ocular comorbidities were not excluded.

In accordance with the declaration of Helsinki and subsequent revisions, each patient provided informed consent prior to participation. Approval for this study was obtained from the Southern Tasmania Health and Medical Human Research ethics committee.

Outcome measures

At baseline and each subsequent review, patients underwent a comprehensive clinical review, which included measurement of Snellen best-corrected visual acuity (BCVA); and a dilated fundus examination. Each participant was reviewed as part of routine clinical practice.

Fluorescein angiography was performed upon recruitment and again at the time of follow-up. Photographs were taken using a Canon CF-60UV fundus camera (Canon Japan). The grading of subjects' fundus lesions was based on angiographic findings, and was performed by investigators (J.E.K., V.S.J.) blinded to the subjects' visual function. In addition to the position and appearance, the size and greatest linear dimension of each CNV lesion was recorded. Measurements were performed using the OCUlab image management system (Perkin Elmer UK, http://www.digital-healthcare.com). PDT was performed according to a standard protocol, which has been described previously.[32] All adverse events related to the therapy were recorded.

At the time of inclusion into the study, patient's self-reported visual function was assessed. The Visual Function Index (VF-14) was utilised to assess visual function [29]. The VF-14 is a standardised vision-related quality of life instrument, which has been validated for the measurement of functional visual status of patients [1, 16]. Questions relate specifically to visual activities of daily living and are graded on a five-category Likert scale. The response scores range from 0 to 4 and reflect, respectively, no difficulty; a little difficulty; a moderate amount of difficulty; a great deal of difficulty; or totally unable to perform [29]. The questionnaire was administered by interview upon recruitment, then again between February and March 2005. The primary outcome for this study was the change in visual function. The total VF-14 score was calculated by two methods, traditional summary scoring where raw scores are summed and were calculated as a percentage of total possible function, and by Rasch analysis. Total VF-14 scores, calculated by either method, ranges from 0 to 100 where a score of 100 implies perfect visual function [29].

Subject stratification and data analysis

Rasch analysis is an iterative probabilistic approach to calibrating person ability and item difficulty on the same unidimensional underlying construct. Rasch analysis was performed using Facets version 3.57,[15], which calculates the Andrich rating scale version of Rasch model estimates using joint maximum likelihood estimation [2]. The Rasch model does not assume values for response categories (e.g. 1,2,3…), but does assume that all categories are on the same underlying latent variable. Categories which were underutilized or disordered were collapsed into adjacent categories.[14] The category "a great deal of difficulty" overlaps with "unable to do the activity" and "a little" overlaps with "a moderate amount".

The Rasch model gives the probability of selecting a particular response category in terms of the interaction between "response severity" and subject measure through an iterative logistic process. The resulting response scale calibrations and person measures are expressed in log-odd units (natural logarithm of an odds ratio), or logits, positioned along a hierarchical scale with logits of greater magnitude representing increasing visual impairment. By definition, this scale is linear. The scale was converted to a 0–100 unit format to be comparable with the traditional summary scoring of the VF-14. Patient measures used for the analysis were taken directly from the Facets output. Since the use of a rating scale may vary from one time to another, the Wolfe and Chiu approach for determining a common frame of reference was used to disentangle change in scale use from true changes in person measures [37].

Table 1 The change in visual function following PDT. *n* number of applicable participants; *SD* standard deviation; *NS* not statistically significant

Visual function measures	Baseline			Follow-up			*P*-value for change*
	n	Mean	± SD	n	Mean	± SD	
Reading small print	77	2.0	±1.6	77	2.2	±1.5	0.053 (NS)
Reading newspaper or book	77	2.0	±1.5	77	2.1	±1.6	0.279 (NS)
Reading large print books	77	0.8	±1.3	77	0.9	±1.3	0.463 (NS)
Recognising people in close proximity	77	0.8	±1.2	77	0.9	±1.3	0.009
Seeing steps/kerbs	77	0.5	±0.8	77	0.6	±0.8	0.130 (NS)
Reading street signs	77	1.1	±1.4	76	1.2	±1.4	0.212 (NS)
Doing fine handwork	68	2.0	±1.8	65	2.2	±1.7	0.420 (NS)
Filling forms or cheques	75	1.5	±1.7	74	1.4	±1.6	0.786 (NS)
Indoor hobbies	50	1.3	±1.7	48	1.3	±1.6	0.502 (NS)
Outdoor hobbies	42	0.8	±1.4	40	1.2	±1.6	0.258 (NS)
Cooking	71	0.5	±0.9	74	0.6	±0.9	0.437 (NS)
Watching television	77	0.9	±1.1	77	1.1	±1.1	0.381 (NS)
Total VF-14 score	77	67.6	±27.2	77	64.5	±27.7	0.052 (NS)
Total Rasch Scaled	77	56.5	±24.9	77	52.6	±25.1	0.010

*Performed using the Wilcoxon signed-rank test

Although baseline and post-treatment data were analysed separately, common rating scale calibrations were determined by analyzing baseline and post-treatment data together. Analysis of the change in visual function over time was performed using the Wilcoxon signed-rank test with Intercooled Stata 7.0 for Windows (Stata Corporation, USA). Subjects were stratified by their pre-therapy BCVA. Their eye primary undergoing treatment was grouped according to those which had a BCVA better than 20/200, or equal to or worse than 20/200. The eye receiving PDT at the time of inclusion into this study was deemed to be the primary eye undergoing therapy. In a separate analysis, subjects were grouped according to their pre-treatment lesion size (either ≤4 disc areas or >4 disc areas) and type of CNV lesion. The Chi-squared and Mantel-Haenszel analyses were used for categorical variables.

Results

A total of 82 consecutive patients undergoing PDT were recruited. There was a relatively low attrition rate (6%). During the study period, two subjects declined further therapy and were excluded from subsequent analysis; two patients died (unrelated to therapy); and one was lost to follow-up. The mean follow-up time was 536±25 days.

At the time of recruitment, the mean visual function score was 70.2±26.1 (range 12.5–100). Reading small print and performing fine handiwork was the reported as being the most difficult tasks to perform (Table 1). The median BCVA at the time of recruitment was 20/100 and 20/40, in the primarily treated eye and the contralateral eye, respectively. Three subjects undertook PDT bilaterally at the time of inclusion into this study. Subjects' baseline ocular comorbidities are displayed in Table 2.

At baseline, 64 (83.1%) study eyes were found to have predominantly classic CNV lesions, 11 (14.3%) had occult with no classic lesions and two (2.6%) had minimally classic lesions. Thirty-four (44.2%) eyes were found to have subfoveal lesions, six (7.8%) had juxtafoveal, two (2.5%) had extrafoveal lesions and 35 (45.5%) had CNV lesions encroaching all regions. Twenty-eight (36.4%) eyes from different subjects had CNV lesions which were greater than 4 times their optic disc area.

Table 2 Subject's baseline ocular comorbidities. *n* number of eyes; *AMD* age-related macular degeneration; *NS* nuclear sclerotic cataract; *BRVO* branch retinal vein occlusion; *VH* vitreous haemorrhage; *RPED* retinal pigmented epithelium defect

	Treated eye		Contralateral eye	
	n	(%)	*n*	(%)
AMD	69	(86.3)	26	(35.1)
AMD (atrophic)	–	–	9	(12.7)
AMD+NS	4	(5.0)	4	(5.4)
AMD+glaucoma	4	(5.0)	2	(2.7)
NS	–	–	8	(10.8)
AMD+BRVO	3	(3.7)	–	–
AMD+VH	–	–	1	(1.4)
Band shaped keratopathy	–	–	1	(1.4)
RPED	–	–	1	(1.4)
Macular sparing retinal detachment	–	–	1	(1.4)
Nil	–	–	21	(28.4)
Total	80	(100)	74	(100)

PDT was performed on average 5.7±2.6 times per patient. Following enrolment in this study, 16 (20.7%) subjects went on to have PDT in their contralateral eye. During the study period, 24 (31.2%) subjects remained free of signs of AMD in one eye. Infusion related back pain was reported on four occasions, two different patients reported transient photopsia and one subject became nauseated during the verteporfin infusion.

Thirty-five (44.5%) subjects reported the same or an improvement in raw VF-14 scores. However, the mean VF-14 score, at the time of follow-up, were statistically significantly lower than at baseline (P=0.025). As displayed in Table 1, the sole raw score item which statistically significantly deteriorated was the ability to recognise people in close proximity. There was also a trend at the time of follow-up for more people to report difficulty in reading small print.

During the study period, 16 subjects went on to have PDT in their contralateral eye. Fifteen of these subjects reported a worse total VF-14 score at the time of follow-up (OR; 21.6, 95% CI: 2.7–933.7). Of the 24 subjects who remained free of AMD in one eye, 15 (62.5%) reported having either the same or an improvement in visual function at follow-up. The VF-14 scores remained the same or improved in only 20 (37.7%) of the subjects who had bilateral AMD (OR; 2.75, 95% CI: 0.91–8.48).

At follow-up, the median BCVA was 20/200 and 20/60, in the primarily treated eye and the contralateral eye, respectively. Forty (51.9%) subjects presented with an initial VA and final VA better than 20/60 in their best eye. Following treatment, 38 (47.5%) eyes had lost three or more Snellen lines of BCVA. The change in BCVA following PDT is depicted in Fig. 1.

Lesion size (being either ≤4 disc areas or >4 disc areas) at baseline did not significantly influence the change in visual function scores (OR for reduction in VF-14 scores; 1.62, 95% CI: 0.49–5.65) or the change in BCVA (OR for reduction in BCVA; 1.79, 95% CI: 0.47–8.42). Similarly, the baseline CNV lesion type (predominantly classic against all other types) did not significantly influence visual function scores (OR for reduction in VF-14 scores; 1.78, 95% CI: 0.44–7.73) or the change in BCVA (OR for reduction in BCVA; 0.65, 95% CI: 0.10–2.97).

At the commencement of the study, 30 people drove a car, whilst 23 people had stopped driving because of their vision, of whom 12 had done so within the preceding 6 months. During the study period five people ceased driving due to their sight.

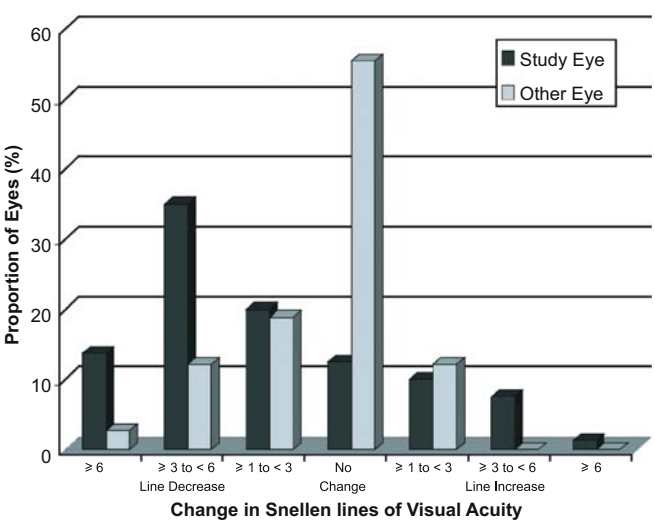

Fig. 1 The change in Snellen BCVA following PDT

Discussion

AMD is a common cause for significant loss of visual function. This study supports the earlier work of Armbrecht et al. that visual function does mildly deteriorate despite PDT [3]. However, this finding only reach statistical significance using Rasch analysis [14]. This approach resolves the discontinuities inherent in summary scoring where all items are assumed to be of equal difficulty. Rasch analysis can provide an appropriate calibration for each item [23]. Rasch analysis has been applied widely to patient-centred outcomes in ophthalmology including the VF-14 [33, 35] and outcome measures for refractive surgery [22] and low vision rehabilitation [30]. The use of Rasch analysis in measuring health outcomes has suggested improved validity in item inclusion, precision of measurement and more efficient instruments [21, 35]. Our results illustrate that Rasch analysis removed some measurement noise in the raw data, which was chiefly due to disordering of response category usage. Analysing the VF-14 results by both summary and Rasch scoring provides a good example of the problems of scale discontinuity with summary scoring and the advantages of improved measurement precision of Rasch analysis. Rasch analysis should be used for analyzing patient-centered outcome measurements wherever possible.

With a larger cohort and a longer follow-up period, we do not corroborate the finding that patients predominantly lose their distance vision. Although we found a trend towards people reporting more difficulty in reading small print at the time of follow-up, the ability to recognise people in close proximity was the sole item which had statistically significantly deteriorated on raw score.

Given the positive findings on the efficacy of PDT from previous studies,[7, 8, 32] a pathologically matched control group was unavailable. Nonetheless, inferences can be made. Without PDT, most affected eyes will have poor central vision (with a visual acuity worse than 20/200) within 2 years [28]. The VF-14 has previously revealed that participants with vision impairment are more likely to report difficulty in performing all items [36]. Other questionnaires, such as the NEIVFQ25, include other domains

of quality of life, and while these may be important, we were specifically interested in visual function. Although not necessarily directly comparable, other studies that have measured visual function using the VF-14 in AMD have shown poorer raw scores for patients with severe or late AMD (62 for unilateral and bilateral combined and 35 for bilateral cases;[25] and 64 for unilateral cases [18]).

Compared with previous investigations, a greater proportion of eyes in this study deteriorated in BCVA following PDT [5, 9, 31]. Approximately 48% of eyes had lost three or more Snellen lines of BCVA following PDT. Such a finding may reflect the heterogeneous nature of our study group and the fact that subjects were not excluded if they had ocular comorbidities.

The small number of eyes in the not-predominantly classic lesion groups limited investigation into the influence of lesion type. Further to this, the finding that subjects who required PDT bilaterally reported deterioration in overall visual function may be due to a confounding effect or Simpson's paradox. Further prospective investigation, with thorough AMD risk factor assessment, is required.

By the year 2030, it has been predicted that the rates of visual impairment in people aged over 50 years will have doubled [11]. Given that AMD is likely to contribute significantly to this morbidity[19, 20], novel validated therapies are clearly required. The change in subjective visual function reported in this study will serve as a useful benchmark for future comparison of rates of vision loss for newer therapies.

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