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Short Report: Complications

The use of weighted health-related Quality of Life scores in people with diabetic macular oedema at baseline in a randomized clinical trial

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Abstract

Aims To examine the relationship between visual acuity in each eye and Quality of Life (QoL) outcomes in people with diabetic macular oedema.

Methods Cross sectional retrospective analysis of data collected at baseline in 289 people entered into a randomized clinical trial with diabetic macular oedema which investigated the safety and efficacy of a vascular endothelial growth factor inhibitor, pegaptanib sodium. At the baseline visit, visual acuity was measured through refraction and using retro-illuminated modified Early Treatment Diabetic Retinopathy Study Log MAR charts, and patient health-related QoL was determined using the European Quality of Life EQ–5D–3L and the Visual Functioning Questionnaire–25 (NEI–VFQ25). A regression analysis with QoL score from each vision-related domain as the dependent variable was fitted using linear and quadratic terms of the better and worse eye, age, gender, adjusted for number of concurrent conditions, ethnicity and level of diabetes control.

Results For all vision-related QoL domains from NEI–VFQ25 and EQ–5D–3L except ocular pain, both visual acuity in the better-seeing and the worse-seeing eye gave a significant increase in correlation coefficient over that obtained from clinical and demographic data. The NEI–VFQ25 correlation was most closely associated with a weighted visual acuity measure of 0.75 in the better and 0.25 in the worse eye or 0.60 in the better and 0.40 in the worse eye.

Conclusions We recommend that a weighted visual acuity measure from both eyes is considered in future diabetic macular oedema trials.

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Introduction

Diabetes is estimated to be increasing worldwide from 382 million in 2013 to 592 million in 2035 [1], and is a major cause of morbidity worldwide [2], with the incidence of diabetic retinopathy increasing in parallel. In people with diabetic retinopathy, the major cause of moderate vision loss is diabetic macular oedema, which can progress to cause increased visual impairment and eventual blindness, as defined by the World Health Authority definition of visual acuity (VA) $\leq$ 6/60 (log MAR $\geq$ 1.00) in the better-seeing eye [3].

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The health-related quality of life (HRQoL) of people with diabetic macular oedema is adversely affected at all stages of the disease [4,5]. Our current analysis was designed to use the baseline Quality of Life (QoL) EQ–5D–3L and NEI–VFQ 25 data and the VA data from a recent clinical trial [6] to determine the impact of the level of vision in the better- and worse-seeing eye on QoL, as a relative weighting between the vision in the two eyes as had previously been suggested in people with macular degeneration by Pleil *et al.* [7].

The European Quality of Life (EuroQol) Group EQ–5D–3L [8] is a generic instrument for describing and valuing health. It consists of two parts, the first having five domains from which the responses are combined using an algorithm to provide a single index value using MVH weights [9], for the health status of the individual; a score of 1 corresponds to perfect health, and a score of 0 corresponds to being dead. The second part of the tool is a visual analogue scale.

What's new?

- This study is the first to highlight the importance of using both eyes in assessing Quality of Life in diabetic macular oedema using a weighting between the better- and worse-seeing eyes.

The second questionnaire was the National Eye Institute-Visual Functioning Questionnaire 25(NEI–VFQ 25) [10]. It comprises 25 items to assess the difficulty of visual symptoms or day-to-day activities with 11 vision-related domains. All responses, apart from the general health question, are combined to provide a single composite score.

Methods

This retrospective analysis used baseline data from participants enrolled in the multicentre, Phase 2/3, randomized, sham-controlled, double-masked, 2-year, comparative trial (NCT 00605280) [11] in ophthalmology treatment centres in the USA, Canada, Australia, Europe, South America and India. Participants were ≥ 18 years of age with Type 1 or Type 2 diabetes and diabetic macular oedema involving the centre of the macula not associated with ischaemia. Participants were administered intravitreal injections of pegaptanib sodium 0.3 mg or sham injection every 6 weeks for up to 2 years. Details of inclusion and exclusion criteria, trial design and results can be obtained from the original publication of this trial [11].

Patient HRQoL was determined using the two separate instruments, the EQ–5D–3L and the NEI–VFQ 25 described above. Both instruments were administered to participants between the screening and baseline visit. In India, the two questionnaires were administered in the clinic by trained study personnel using paper-based versions which were faxed to the call centre for data entry onto the system. In all other centres, the questionnaires were administered in the participants' local language by trained interviewers at a call centre and data were entered directly into a database.

In the trial, baseline VA was measured through refraction and using retro-illuminated modified Early Treatment Diabetic Retinopathy Study (ETDRS) Log MAR charts. Distance VA was expressed as an ETDRS score (number of letters correctly read) ranging from 0 to 94, where higher ETDRS scores represented better vision.

Linear regression models with QoL score from each vision-related domain and with the EQ–5D index value as the dependent variables were fitted using linear and quadratic terms in the terms of the better and worse eye, age and gender, and were adjusted for number of concurrent conditions, ethnicity and level of diabetes control. Stepwise model selection procedures were used. All analyses were carried out using SAS v. 9.1.

Results

The countries of origin of the 326 participants were: USA (50), Canada (7), Australia (5), South America (10), India (27) and Europe (188), including Austria (9), Czech Republic (69), Denmark (4), France (33), Germany (26), UK (7), Italy (25), the Netherlands (3), Portugal (10) and Switzerland (2).

Of the 326 participants, 37 did not have a composite VFQ result, i.e. they did not complete every section of the VFQ 25, and hence results are available for 289 participants in this trial with diabetic macular oedema, 55% were male and 82% were Caucasian (see Table 1). The range of VA in the better-seeing eye was 35–94 letters, median interquartile (IQR) range 69 (62–77) letters. The range of VA in the worse-seeing eye was 0–70, 56 (46–63) letters. The correlation coefficient (r^2) between VA in the better and worse eyes was 0.57 ($P < 0.0001$).

The results of the regression analyses (Table 2) show that the proportion of variance in QoL scores explained by age group, gender, HbA_{1c} group and ethnicity, although statis-

Table 1 Characteristics of the study population

		N	%
Gender	Men	160	55.4
	Women	129	44.6
Ethnicity	Caucasian	237	82.0
	Asian	28	9.7
	Hispanic	13	4.5
	Black	7	2.4
	Other	4	1.4
Diabetes	Type 1	26	9.0
	Type 2	263	91.0
Smoker	No	20	6.9
	Yes	269	93.1
HbA1c	< 60 mmol/mol (< 7.6%)	135	46.7
	≥ 60 mmol/mol ≥ 7.6%)	154	53.3
Body Mass Index (weight (kg)/(height (m)^2)†		29.8 (5.5)	
Systolic blood pressure (mmHg)†		138 (14)	
Diastolic blood pressure (mmHg)†		78 (9)	
Visual acuity (ETDRS letters) in better eye*		69 (61–77)	
Visual acuity (ETDRS letters) in better eye†		69.1 (11.7)	
Visual acuity (ETDRS letters) in worse eye*		56 (46–63)	
Visual acuity (ETDRS letters) in worse eye†		52.4 (13.4)	
Number illnesses recorded*		4 (2–6)	

*Median (25th to 75th centiles); †Mean (SD).

Table 2 Regression analyses relating Quality of Life scores to vision

					Incremental r^2 beyond age group, gender, HbA_{1c} group, race									
	n	Mean score	SD	r^2 for fitting age group, gender, HbA_{1c} group, race	VA better eye		VA worse eye		0.75 VA better eye +0.25 VA worse eye		0.6 VA better eye +0.4 VA worse eye		0.5 VA better eye +0.5 VA worse eye	
General health	289	41.1	22.5	0.040	0.031	0.0027	0.019	0.0197	0.033	0.0018	0.032	0.0021	0.030	0.0027
General vision	289	54.3	17.8	0.017	0.137	< 0.0001	0.098	< 0.0001	0.152	< 0.0001	0.152	< 0.0001	0.148	< 0.0001
Ocular pain	289	78.8	22.9	0.061	0.002	0.4884	0.007	0.1469	0.003	0.3195	0.004	0.2479	0.005	0.2134
Near activities	289	57.9	23.7	0.029	0.158	< 0.0001	0.094	< 0.0001	0.169	< 0.0001	0.164	< 0.0001	0.157	< 0.0001
Distant activities	289	63.5	24.7	0.022	0.192	< 0.0001	0.109	< 0.0001	0.202	< 0.0001	0.195	< 0.0001	0.185	< 0.0001
Vision-specific														
Social functioning	289	79.3	23.2	0.052	0.128	< 0.0001	0.079	< 0.0001	0.138	< 0.0001	0.135	< 0.0001	0.129	< 0.0001
Mental health	289	55.9	28.3	0.089	0.098	< 0.0001	0.068	< 0.0001	0.109	< 0.0001	0.108	< 0.0001	0.105	< 0.0001
Role difficulties	289	54.4	28.3	0.059	0.080	< 0.0001	0.080	< 0.0001	0.097	< 0.0001	0.102	< 0.0001	0.102	< 0.0001
Dependency	289	68.4	31.3	0.109	0.094	< 0.0001	0.088	< 0.0001	0.113	< 0.0001	0.117	< 0.0001	0.117	< 0.0001
Driving	148	67.9	23.3	0.140	0.115	< 0.0001	0.070	0.0006	0.127	< 0.0001	0.127	< 0.0001	0.123	< 0.0001
Colour vision	287	86.2	21.9	0.024	0.022	0.0112	0.030	0.0032	0.030	0.0034	0.033	0.0021	0.034	0.0017
Peripheral vision	288	71.4	25.9	0.023	0.084	< 0.0001	0.095	< 0.0001	0.106	< 0.0001	0.114	< 0.0001	0.116	< 0.0001
Composite	289	66.2	19.2	0.060	0.160	< 0.0001	0.135	< 0.0001	0.186	< 0.0001	0.190	< 0.0001	0.188	< 0.0001
EQ5D	289	0.738	0.2	0.071	0.019	0.0160	0.033	0.0015	0.027	0.0038	0.032	0.0019	0.033	0.0014

Some items, e.g. driving have a response choice that indicates that the respondent does not perform the activity for reasons unrelated to vision. If a respondent selects this choice, the answer is treated as missing and an average of the remaining items is calculated. This is the reason for the reduced number in some domains.

tically significant, was not large (highest $r^2 = 0.14$ for driving).

Table 2 shows the relative contributions of the better- and worse-seeing eyes to the QoL scores, alone and in combination of better seeing/worse seeing 0.75/0.25, then 0.60/0.40 and the last being 0.50/0.50. These combinations were chosen with higher contributions in the better-seeing eye because r^2 values for the NEI–VFQ 25 in Table 2 show that the contribution of the worse eye is less than that of the better-seeing eye.

There was a relationship ($P = 0.016$) between EQ–5D–3L scores and VA in the better-seeing eye, for those with a VA in the better eye of < 60 letters, the median EQ–5D–3L score was 0.73 (0.59–0.81), and for those with a VA of ≥ 80 in the better-seeing eye, the median EQ–5D–3L score was 0.80 (0.69–0.94).

By using the QoL data, the current analysis did not show a strong correlation (levels of 0.027–0.033) with the EQ–5D–3L.

For the NEI–VFQ 25, there was no relationship between VA in either eye and ocular pain. There was a stronger correlation between visual loss and other QoL domains (e.g. distance 0.185–0.202 and near 0.157–0.169) and composite scores (0.186–0.19) using the NEI–VFQ 25. This links most closely to the visual loss in the better-seeing eye, but there is also a correlation with the worse-seeing eye. For all other vision-related QoL domains the VA in both the better and the worse eye gave a significant increase in r^2. Different combinations of VA in the better- and worse-seeing eyes show different effects on the QoL scores. For all but colour and peripheral vision, the increase was significantly larger for VA in the better than the worse-seeing eye.

For the three combinations of VA in the better- and worse-seeing eyes presented in Table 2, the incremental increase in r^2 was larger for combinations of VA in the better- and worse-seeing eyes than for either eye alone. The domains for which this was greatest were for the composite scores of peripheral vision, role difficulties and dependency.

Discussion

In 2002, Brown *et al.* [12] reported that visual loss caused a diminution in self-assessed quality of life but did not appear to be affected by the presence of co-morbidities. However, Davidov *et al.* [4] found that, as well as ocular disease levels of diabetic retinopathy, patient co-morbidities lead to significant impairment of both the physical and mental components of the HRQoL. A study of the impact of laser treatment [13] concluded that, after a pronounced reduction of quality-of-life impacts following the first laser treatment, there was an increasing negative impact as people move from first treatment to multiple treatments.

Previous studies [5,14] have demonstrated a correlation between lower QoL scores using the NEI–VFQ 25 and loss of vision in diabetic macular oedema and proliferative diabetic retinopathy.

This study does have some limitations:

1. The insensitivity of the EQ–5D for visual disorders is well established [15,16].
2. Furthermore, mapping NEI–VFQ 25 scores to EQ–5D utilities has been shown to provide low predictive power, suggesting an inability of the EQ–5D to discriminate vision-related activities [17].

However, the EQ–5D is an important tool that is used to determine cost-effectiveness for appraisals of new pathways and treatments by the National Institute for Health and Clinical Excellence (NICE) in England. We believe that, in such appraisals, data from both eyes should be used.

A recent review [18] found a stronger correlation between health state utility values (HSUVs) and better-seeing eye VA compared with worse-seeing eye VA. Our study has demonstrated that the VA in both eyes needs to be considered and is the first study to report a correlation between VA in the better- and worse-seeing eyes in diabetic macular oedema.

We would recommend that a weighted VA measure of 0.75 in the better and 0.25 in the worse eye, or 0.60 in the better and 0.40 in the worse eye is used in future diabetic macular oedema trials because this study has demonstrated that the most information can be provided by taking into account vision in both eyes when determining the effect on quality of life.

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Competing interests

JL and CS are employees of Pfizer. PS sat on the European Advisory Board for Pfizer in 2010–11 advising on Quality of Life studies. IS has no competing interests.

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