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Patient-reported outcomes and visual acuity after 12 months of anti-VEGF-treatment for sight-threatening diabetic macular edema in a real world setting

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ABSTRACT

Aims: To examine objective visual acuity measured with ETDRS, retinal thickness (OCT), patient reported outcome and describe levels of glycated hemoglobin and its association with the effects on visual acuity in patients treated with anti-VEGF for visual impairment due to diabetic macular edema (DME) during 12 months in a real world setting.

Methods: In this cross-sectional study, 58 patients (29 females and 29 males; mean age, 68 years) with type 1 and type 2 diabetes diagnosed with DME were included. Medical data and two questionnaires were collected; an eye-specific (NEI VFQ-25) and a generic health-related quality of life questionnaire (SF-36) were used.

Results: The total patient group had significantly improved visual acuity and reduced retinal thickness at 4 months and remains at 12 months follow up. Thirty patients had significantly improved visual acuity, and 27 patients had no improved visual acuity at 12 months. The patients with improved visual acuity had significantly improved scores for NEI VFQ-25 subscales including general health, general vision, near activities, distance activities, and composite score, but no significant changes in scores were found in the group without improvements in visual acuity.

Conclusions: Our study revealed that anti-VEGF treatment improved visual acuity and central retinal thickness as well as patient-reported outcome in real world 12 months after treatment start.

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1. Introduction

1.1. Diabetes and vision loss

Both type 1 and type 2 diabetes mellitus are major causes of vision loss [1]. Diabetic retinopathy (DRP) is a general term for vascular changes that occur in the retina that may become sight-threatening and require treatment [2]. Diabetic macular edema (DME) is a result of vascular changes close to the macula leading to swelling of the central retina in the macula and may induce vision loss [3–5]. Vision loss is the complication of diabetes [6] that affects the person's quality of life the most [7]. Almost every person with type 1 diabetes and more than half of the persons with type 2 diabetes develop some degree of diabetic retinopathy [8]. Many persons with diabetes do not have regular eye examinations, although it is known that early diagnosis and treatment of sight-threatening retinopathy reduce the risk of blindness [9]. In Sweden there is a screening program for diabetic retinopathy with fundus photography but the proportion of fundus examinations has decreased in recent years [10]. Early and regular screening for retinopathy is important in preventing retinopathy at an early stage [11].

1.2. Patient reported outcomes

In recent years, the relationship between patient-reported outcomes such as visual function and health-related quality of life has attracted attention worldwide [12,13]. It has been previously reported that visual impairment affects patient's reported outcomes [14–17]. Persons with diabetic retinopathy are more likely to have negative feelings about diabetes than persons without DRP [18]. These negative feelings may have negative effects on patient reported outcome [14,19]. Vision loss due to diabetes can also affect the person's perception of their ability to function independently [20]. Therefore, it is of outmost importance to target the early stages of DRP to inhibit its progression, to prevent the disease from reaching a level that has severe impact on a person's quality of life [21,22]. Persons with decreased visual acuity related to diabetic macular edema have rated their general health as relatively low [23], and have been associated with prior development of retinopathy and neuropathy, with decreased vision [24]. Overall, patient reported outcomes reflect the emotional impact of treatment and the impact of diabetes retinopathy on their quality of life [25].

1.3. Effect of treatment with anti-vascular endothelial growth factor (VEGF)

Anti-VEGF drugs have revolutionized the treatment of reduced vision due to DME [26,27]. Intravitreal treatment is generally initiated with monthly injections until visual acuity is stabilized. Additional treatment may be given depending on visual acuity and/or presence of macular edema on optical coherence tomography (OCT) [27]. Anti-VEGF treatment is capable of improving vision instead of merely stabilizing the condition [28,29]. Several studies have reported that ranibizumab improves patient-reported visual function [15,30–34], which can be stabilized for long periods of time [17].

Since 2011, intravitreal administration of anti-VEGF drugs for sight-threatening DME has been a part of routine clinical care in Sweden. We have previously reported baseline data from a cohort of patients [23]. To further examine objective visual acuity and patient-reported outcome measurements in a real world setting, meaning that data were collected in routine clinical care. It is also important to study this patient group over time. In this study, data from a 12 months follow up is reported in relation to baseline data.

Aims:

- To evaluate objective visual acuity measured with ETDRS and retinal thickness using optical coherence tomography (OCT) at 4 and 12 months after treatment start.
- To evaluate patient-reported outcomes measurements, visual functioning (NEI VFQ-25), and health-related quality of life (SF-36).
- To describe the progress regarding levels of glycated hemoglobin (HbA1c) and its association with visual acuity (ETDRS).

2. Materials and methods

2.1. Subjects

This is a follow-up study where baseline data have been previously reported [23]. Participants were males and females over 18 years of age. All participants had visual impairment due to DME and received intravitreal treatment with ranibizumab (Lucentis®). Data collection started in May 2012 and was terminated in February 2015 at two county hospitals in Sweden.

2.2. Ethical considerations

This study was approved by the Regional Ethical Review Board of Uppsala, Sweden, and was conducted in accordance with the Declaration of Helsinki. All participants gave their written consent before study entry [23]. Participants were informed that they could terminate their participation at any time.

2.3. Clinical assessment

Visual acuity was measured using either the ETDRS letter chart (number of letters) at a distance of 2 m, or using the Snellen chart at 5 m. The ETDRS letter chart was used for eyes treated with anti-VEGF [2]. The initial eye examination included measurement of best-corrected visual acuity with the ETDRS or Snellen chart, slit-lamp examination of the anterior segment, intraocular pressure measurement, fundus

biomicroscopy, and measurement of retinal thickness by OCT (Topcon Corporation, Tokyo, Japan).

Glycated haemoglobin (HbA1c) are reported in derived NGSP units (%) followed by The International Federation of Clinical Chemistry (IFCC) reference method (mmol/mol).

Initially, the patients received three monthly injections. Thereafter they were examined once a month and received additional injections if required. When a steady state was reached in the eye, examinations were conducted less frequently. Additional intravitreal treatments were given at the physician's discretion in cases of unstable or reduced visual acuity and/or increased edema on OCT. Each eye was assessed individually and that the patient could receive treatment in the better-seeing eye, in the worse-seeing eye, or in both eyes. Five-letters improvement in visual acuity measured with ETDRS was considered as clinically significant, meaning that the improvement was perceptible to the patient.

All patients received two questionnaires, the National Eye Institute Visual Functioning Questionnaire 25 (NEI VFQ-25) and the Short Form -36 Health Survey (SF-36), at baseline, 4 and 12 months after treatment start. The questionnaires were sent to the patients by mail with a reply envelope attached. A reminder, which included a new questionnaire, was posted after 2–3 weeks if needed.

2.4. *Patient reported outcomes measurements*

The National Eye Institute Visual Functioning Questionnaire 25 (NEI VFQ-25) is a validated, eye-specific questionnaire that provides a subjective perception of one's own visual functioning [35] and has been used to assess visual functioning in several studies [15,32,36]. The questionnaire has been validated for Swedish-speaking persons [37] and consists of 25 questions divided into 11 vision-related subscales: general vision, ocular pain, near activities, distance activities, social functioning, mental health, role difficulties, dependency, driving, color vision, and peripheral vision. The questionnaire also includes a single item measuring general health and a composite score calculation [35,38].

The Short Form-36 Health Survey (SF-36) is a measure of health-related quality of life [39]. SF-36 measures eight parameters of health-related quality of life: physical function, role functioning (physical limitations), bodily pain, general health, vitality, social function, role functioning (emotional limitations), and mental health. The SF-36 has been validated and translated into Swedish [40].

2.5. *Data analyses*

SPSS, version 22 for Windows (SPSS, Chicago, IL, USA) was used for statistical analyses. The manual for NEI VFQ-25 was used in calculating the scale conversions, and calculations of subscale and composite scores [41]. Analyses were conducted with one treated eye per person and the worse-seeing eye was excluded when a person received anti-VEGF treatment in both eyes. Descriptive statistics were used for presenting patient demographics and characteristics. Linear regression analyses were used to examine which variable contributed most to visual acuity ETDRS scores. The *t*-test was used to examine differences in mean changes over time regarding objective measurements involving HbA1c, OCT, and ETDRS scores. A *t*-test was also used to identify changes in self-rated visual functioning (NEI VFQ-25) and self-reported health-related quality of life (SF-36). A value of $p < 0.05$ was considered statistically significant. The population was divided into two groups based on their change in ETDRS scores 12 months after the first anti-VEGF injection. One group of patients improved their ETDRS scores by more than five letters, which was considered clinically significant, and the other group which did not improve their ETDRS scores.

3. Results

3.1. *Study subjects*

As previously described, we enrolled 59 patients in this study at baseline [23]. One person declined participation at the first follow-up at 4 months after the first injection. In total, 58 persons completed the study at the 1 year follow-up.

3.2. *Patient characteristics*

Table 1 shows characteristics of the total patient population. The patient sample was divided into two groups, 12 months after treatment start, involving persons with improved and unimproved visual acuity. The group without improved ETDRS was treated with insulin to a larger extent compared with the group with improvements in their visual acuity (not significant). In the group that showed an improvement in ETDRS scores, 24 persons received 5–10 injections, in the group without improvement, 16 persons received the same number of injections (ns) (Table 1).

3.3. *Visual acuity: ETDRS*

The visual acuity for the total patient sample was 65.0 letters (±12.1) at baseline, and showed a significant improvement after 4 months and remains at 12 months follow-up. The group with improved visual acuity showed a clinically significant change in mean ETDRS scores from baseline to the 12-month follow-up (Table 2).

3.4. *Retinal thickness: OCT*

The results showed a significant reduction for retinal thickness measured with OCT after 4 months and remains at 12 months follow up for the total patient sample population (Table 2).

3.5. *HbA1c*

The total patient sample as well as the two groups with improved and unimproved ETDRS showed no significant improvement in HbA1c levels. However, the HbA1c levels decreased from 8, 8% (73 mmol/mol) to 8.1% (65 mmol/mol) (not significant) in the group with no ETDRS improvement. The *t*-test showed that the group with unimproved ETDRS

Table 1 – Patient characteristics.

	Total patient sample ($n = 58$)[a] n	Improved ETDRS ($n = 30$) n	Unimproved ETDRS ($n = 27$) n
Female/Male	29/29	16/14	13/14
Age (mean, range)	68 (45–86)	69 (45–86)	68 (49–83)
Type of diabetes			
Type 1	5	2	3
Type 2	53	28	24
Diabetes treatment			
OAD (Oral antidiabetic agents)	14	8	6
Insulin	21	9	15
OAD and insulin	22	12	9
Number of visits (mean, range)	14 (10–19)	14 (11–19)	14 (10–19)
Number of injections (mean, range)	5 (1–10)	5 (3–10)	5 (2–8)
1–2	2	0	1
3–4	16	6	10
5–6	27	18	9
7–8	12	5	7
9–10	1	1	0
Laser treatments			
0	44	21	22
1	9	6	3
2	5	3	2
Visual impairment baseline			
Normal	26	11	14
Mild	23	13	10
Moderate/severe	6	4	2
Visual impairment at 12 months			
Normal	26	13	12
Mild	25	13	12
Moderate/severe	5	3	2

[a] One person was diagnosed with secondary neovascular glaucoma and vitreous hemorrhage and was excluded.

scores had significantly higher levels of HbA1c and significantly greater ETDRS scores at baseline than the group with improvements (Table 2).

Linear regression analyses showed that the changes in visual acuity ETDRS scores could be explained individually by HbA1c baseline ($r2 = 0.11$, $p = 0.08$) and HbA1c delta ($r2 = 0.13$, $p = 0.06$) and when they were combined ($r2 = 0.14$, $p = 0.013$).

3.6. *Patients with clinically reduced visual acuity at 12 months*

Of the patients with unimproved ETDRS values over time, eight persons had clinically reduced ($\geqslant$5 letters) their visual acuity (see Table 3). The mean age of these patients was 72.5 years (SD 5.4), and they had a mean number of 14 visits, with a mean number of 5 intravitreal injections.

Table 2 – Change from baseline to 12 months.

		Total sample				Improved ETDRS				Unimproved ETDRS			
Variables		Mean	SD	t-value	p-value	Mean	SD	t-value	p-value	Mean	SD	t-value	p-value
HbA1c*	Baseline	8.3 (67)	16	1.312	0.195	8.0 (64)	14	0.054	0.958	8.8 (73)	18.4	1.710	0.103
	1 year	8.0 (64)	17			7.9 (63)	14			8.1 (65)	19.9		
OCT	Baseline	403	122	6.524	0.001	428	136	5.445	0.000	373	98	3.886	0.001
	1 year	282	83			276	68			289	99		
ETDRS	Baseline	65.0	12.1	−4.361	0.000	60.7	13.1	−9.973	0.000	69.9	8.8	1.727	0.096
	1 year	70.2	11.1			72.1	11.2			68.0	10.7		

SD, standard deviation; HbA1c, glycated hemoglobin; OCT, optical coherence tomography; ETDRS, visual acuity.
* HbA1c – NGSP (%), IFCC (mmol/mol).

Table 3 – Characteristics of patients with decreased visual acuity ($n = 8$).

Variables		Mean	SD	*t*-value	*p*-value
HbA1c*	Baseline	9.4 (79)	26	2.353	0.065
	1 year	7.0 (53)	4		
OCT	Baseline	390	141	2.061	0.078
	1 year	275	63		
ETDRS	Baseline	68.6	11.8	6.799	0.000
	1 year	59.5	12.7		

SD, standard deviation; HbA1c, glycated hemoglobin; OCT, optical coherence tomography; ETDRS, visual acuity.
* HbA1c – NGSP (%), IFCC (mmol/mol).

Compared with at start of treatment, five persons had a decrease of 5–9 letters in their ETDRS scores, two persons had a decrease of 10–14 letters, and one patient lost more than 15 letters at 12 months. The HbA1c levels showed a tendency to decrease from baseline to the 12 months follow-up in this group (see Table 3).

One person had decreased general condition nausea, vomiting, and difficulty breathing at the 4-month follow-up visit and was referred to the emergency room. This person had renal failure, asthma, and a previous pulmonary embolism that was assessed as not related to the anti-VEGF-treatment for macular edema. Another patient fell and contracted a subdural bleeding, which required surgery. This patient received several laser treatments in both eyes with no improvement in visual acuity during the study period.

Two other patients suffered from macular edema relapses that caused deterioration, and were instead treated with steroids. We could not identify any distinctive characteristic of the other patients that could explain the deterioration of their visual acuities.

3.7. *Patient-reported visual function: NEI VFQ-25*

The result from paired *t*-test showed a significant improvement from baseline to 4 months; general health ($p = 0.004$), general vision ($p = 0.001$), near activities ($p = 0.10$), mental health ($p = 0.013$) and composite score ($p = 0.020$), there were no significant improvement between 4 and a 12 months follow-up (Table 4).

Table 5 shows a significant improvement in the total patient population from baseline to 1 year for general health ($p = 0.002$), general vision ($p = 0.001$), near activities ($p = 0.015$), and distance activities ($p = 0.026$). Furthermore, when the cohort was divided into two groups based on ETDRS changes at 12 months, the group with improved ETDRS scores also showed significant improvements in general health ($p = 0.004$), general vision ($p = 0.000$), near activities ($p = 0.015$), and distance activities ($p = 0.008$). The group with no improvements in visual acuity showed no significant improvements in the NEI VFQ-25 subscales (Table 4). General vision ($p = 0.004$) was the only subscale that showed a significant difference in mean change between the groups.

3.8. *SF-36*

The SF-36 subscales showed no significant improvement (data not shown).

4. Discussion

This study shows the results from patients receiving anti-VEGF treatment for DME in an unselected population in a real-world setting at two eye clinics in Sweden. Approximately 50% of the patients improved their visual acuity after 4 months and remains at 12 months, which is consistent with other studies [15,33,42]. The general health measured with NEI VFQ-25 improved from baseline as seen in other studies [15,34], although there were low scores for baseline values [23].

The total sample population had significantly improved ETDRS scores and OCT results. When the study sample was divided into two groups, one group with improved visual acuity and the other group with no improvements in visual acuity, some differences were found between the groups. Visual acuity in the group with improved ETDRS scores measured a lower scores at baseline which can indicate the treatment outcome result as shown in the present study in line with earlier results [15,17]. The group with improved visual acuity comprised a larger percentage of patients with five to six

Table 4 – NEI-VFQ-25 at baseline, 4 months and 12 months.

Subgroup VFQ-25	Baseline (mean, SD)	4 month (mean, SD)	12 month (mean, SD)
General health	36.70 (22.02)	47.16 (23.01)	47.81 (21.88)
General vision	61.18 (18.94)	67.36 (14.36)	67.84 (15.01)
Ocular pain	84.72 (20.70)	87.50 (16.59)	88.73 (17.11)
Near activities	66.36 (21.41)	71.55 (18.73)	72.92 (20.76)
Distance activities	73.46 (24.94)	77.21 (23.58)	79.55 (21.59)
Social functioning	87.26 (19.99)	89.25 (17.50)	89.62 (18.63)
Mental health	76.50 (21.31)	83.58 (14.25)	81.64 (17.86)
Role difficulties	79.40 (23.18)	80.36 (22.24)	78.01 (21.85)
Dependency	93.43 (18.86)	93.37 (15.02)	90.87 (21.47)
Driving	74.66 (35.17)	75.00 (33.00)	75.68 (35.10)
Color vision	91.62 (19.05)	86.74 (23.48)	92.46 (16.69)
Peripheral vision	76.82 (24.18)	80.10 (21.03)	79.92 (24.90)
Composite score	78.30 (16.75)	81.04 (15.01)	81.17 (15.91)

Table 5 – Change in NEI VFQ-25, baseline to 1 year.

		Total sample				Improved ETDRS				Unimproved ETDRS			
Subscales VFQ-25		Mean	SD	*t*-value	*p*-value	Mean	SD	*t*-value	*p*-value	Mean	SD	*t*-value	*p*-value
General health	*Baseline*	36.70	22.02	−3.359	.002	37.50	24.45	−3.186	.004	36.36	20.01	−1.547	.137
	1 year	46.81	21.88			51.04	18.77			43.18	24.62		
General vision	Baseline	61.18	18.94	−3.485	.001	57.69	19.04	−4.573	.000	65.83	18.16	−.327	.747
	1 year	67.84	15.01			69.23	14.12			66.67	16.33		
Ocular pain	Baseline	84.72	20.70	−1.801	.077	80.36	23.92	−1.548	.133	90.50	15.00	−.609	.548
	1 year	88.89	17.11			85.27	20.43			92.50	11.97		
Near activities	Baseline	66.36	21.41	−2.517	.015	63.39	18.75	−2.596	.015	69.67	24.40	−.868	.394
	1 year	72.92	20.76			71.88	20.24			73.33	21.78		
Distance activities	Baseline	73.46	24.94	−2.299	.026	72.47	23.61	−2.849	.008	74.00	27.14	−1.033	.312
	1 year	79.55	21.59			79.76	21.48			79.17	22.57		
Social functioning	Baseline	87.26	19.99	−1.347	.184	86.57	17.99	−1.140	.265	87.50	22.53	−.749	.461
	1 year	89.62	18.63			89.35	16.52			89.50	21.25		
Mental health	Baseline	76.50	21.31	−1,906	.062	76.12	22.31	−1.573	.127	78.00	20.26	−.784	.440
	1 year	81.64	17.86			82.89	16.72			80.50	19.63		
Role difficulties	Baseline	79.40	23.18	.643	.523	79.91	22.40	1.045	.305	79.00	24.93	.161	.873
	1 year	78.01	21.85			76.79	19.75			78.50	24.35		
Dependency	Baseline	93.43	18.62	.818	.417	97.22	6.54	1.028	.314	89.58	26.15	.285	.779
	1 year	90,87	21.47			92.90	20.11			88.19	23.43		
Driving	Baseline	74.66	35.17	−.269	.789	75.69	36.25	−.186	.855	72.92	35.94	−.294	.772
	1 year	75.68	35.10			77.08	33.55			73.61	38.32		
Color vision	Baseline	91.62	19.05	−.299	.766	92.59	13.54	−.700	.490	90.24	24.11	.046	.964
	1 year	92.46	16.69			94.44	12.66			90.00	20.41		
Peripheral vision	Baseline	76.92	24.18	−1.087	.282	75.93	26.39	−1.546	.134	78.13	2250	−.259	.798
	1 year	79.92	24.90			80.56	23.34			79.42	2752		
Composite score	Baseline	78.30	16.75	−2.115	.039	77.27	15.74	−2.400	.024	79.57	18.37	−.516	.611
	1 year	81.17	15.91			81.32	15.10			80.71	17.33		

SD, standard deviation.

injections, and there were fewer patients receiving insulin treatments. Before the anti-VEGF treatment started, this patient group had lower HbA_{1c} levels and ETDRS scores but a higher degree of retinal thickness.

Linear regression analyses showed that variations in visual acuity could be correlated with the levels of HbA1c and change in HbA1c after anti-VEGF treatment. This is consistent with a consensus document regarding appropriate management of diabetic macular edema by an expert panel [43]. In a study with a smaller patient population, similar results to our study were reported, although the patients had higher HbA1c levels at baseline [44]. It is noteworthy, that both studies reflect real world conditions. In contrast, post hoc analysis from the RIDE/RISE study [15,45] reported that HbA1c levels at baseline did not affect the treatment outcomes. In these large clinical studies, a good glycemic control is an inclusion criterion. While in real life studies, the included patients can suffer from poorly controlled diabetes and high level of HbA1c. We found the greatest decrease in HbA1c levels at 1 year follow-up in the group of eight subjects that experienced worsening of ETDRS. Taken together, the findings may indicate that a high initial HbA1c followed by a rapid drop may be associated with a risk for less beneficial outcomes of anti-VEGF treatment. It is important to further examine the factors that can affect the outcome of treatment [46], such as glycemic control, visual acuity, degree of macular edema [47] or blood pressure control.

The cohort in this study exhibited low general health before starting the anti VEGF-treatment [23], lower than in other studies [15,32,34]. Knowing that these patients demonstrated low general health is important as it can enable the health care system to develop and provide relevant support and information. An important point is that regular eye screening in Sweden has decreased during the last year [10]. The cause of the decline is unknown. It is well known that regular eye examinations/screening are essential for detecting eye complications at an early stage, when the condition can be monitored and treated to preserve vision. This study emphasizes the importance of regular eye screening to identify and treat vision-threatening complications and maintain a good health-related quality of life.

After one year, the patients who improved their visual acuity also improved the score for several key subscales of the NEI VFQ-25 which is in line with other [17]. These patients experienced an improved general health, better visual acuity and found it easier to observe objects at near and far distances. It can be assumed that this is useful for patients in their everyday life. In contrast, the patients in present study did not improve the composite score which has been demonstrated in another study [15].

Within the group of patients with no improvements in visual acuity, we identified eight persons with decreased visual acuity. This group of patients had a higher mean age, higher HbA1c levels, and slightly higher OCT at baseline compared with the rest of the group with unimproved ETDRS. There was a decrease in HbA1c levels in these patients, although it was not significant. Previous studies have reported that a rapid decrease in HbA1c levels can cause damage [48], and can affect subsequent anti-VEGF treatment [44]. Although the number of patients was small and it was not possible to reach significant conclusions, it is nonetheless important to mention that additional studies are needed regarding this patient group. A closer cooperation between the ophthalmologists and the diabetes physician could be beneficial, for example to optimize HbA1c levels in a controlled and individualized manner before starting anti-VEGF treatment for DME.

The result of the SF-36 survey showed that none of the subscales showed significant improvements at any time. These observations emphasize the importance of using disease-specific measurements for this patient group [49].

Regarding limitations of this study, it comprised a relatively small sample size. It is however important to emphasize that this patient group received anti-VEGF treatment for DME in a real-world setting in Sweden, where it is a common treatment option.

In conclusion, findings in this real-world study of long-term outcomes of anti-VEGF-treatment showed that the patient-reported outcome significantly improved in the total patient population. The results also indicate the role of HbA1c at baseline and the treatment effects in ETDRS scores. However, additional studies are needed to address the long-term effects of these parameters on DME.

Conflict of interest

None.

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