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Patient-reported and medical outcomes in patients treated for diabetic macular edema

A real-world longitudinal study

THERESE GRANSTRÖM



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Abstract

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Background Diabetes mellitus can lead to complications, when the complication affects the eyes it is called retinopathy. This can affect the macula and lead to severe loss of vision, diabetic macular edema (DME). This condition has traditionally been treated with laser. However, in 2011, anti-vascular endothelial growth factor (anti-VEGF) injections in the eye were approved as a treatment for diabetic macular edema, and started to be used in eye clinics.

Aim The overall aim of this thesis was to describe patient-reported outcomes and medical outcomes (PRO) in people treated for diabetic macular edema in a real-world setting in a long-time follow-up study in Sweden.

Methods Participants were enrolled at two eye clinics at two county hospitals in Sweden between 2012 and 2014. Patient-reported outcomes were measured using a vision-specific questionnaire, the 25-question National Eye Institute Visual Function Questionnaire (NEI-VFQ-25) and a generic questionnaire, the Short Form-36 Health Survey (SF-36). Completed questionnaires, medical data such as visual acuity (EDRS), macula swelling (OCT) and social background characteristics were collected before treatment start, at one-year and four-year follow up points. The data was analyzed, descriptive statistics developed and comparative analyses were performed. Interviews were performed before treatment start and were analyzed using qualitative content analysis.

Results A total of 59 participants were included at baseline. The mean age was 69 years, with an equal gender distribution. At baseline, the participants scored a low general health with the vision-specific questionnaire. In total, 21 participants were interviewed, and a theme emerged of 'being at a crossroads and a crucial phase in life with an uncertain outcome'. The participants expressed thoughts and concerns at different levels, including practical concerns about the treatment procedure and more existential thoughts about hope for improved visual acuity or fear of deterioration. The results at the one-year follow up showed that 30 patients had improved visual acuity and reported an improvement in several subscales in the NEI VFQ-25. The remaining 27 participants had no improvement in visual acuity or in the vision specific questionnaire. The four-year follow-up involved 37 people, and the result showed significant improvement in subjective near-vision activities and improved distance visual acuity.

Conclusion: Before treatment, the participants reported low general health and expressed concerns about the injection treatment and their vision. One year after treatment started, the results showed significant improvement in several NEI VFQ-25 subscales, decreased macula swelling and improved visual acuity. These positive results remained at the four-year follow-up point.

Keywords: Diabetes mellitus, Patient-reported outcomes, Retinopathy, Macular edema, Anti-VEGF treatment

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“Ju mer man tänker, ju mer inser man att det inte finns något enkelt svar” AA Milne

*Till min älskade familj
Beate, Aline och Dennis*

List of Articles

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

- I Granström, T., Forsman, H., Leksell, J., Jani, S., Modher Raghieb, A., & Granstam, E. (2015) Visual functioning and health-related quality of life in diabetic patients about to undergo anti-vascular endothelial growth factor treatment for sight-threatening macular edema. *Journal of Diabetes and Its Complications*, 29(8), 1183-1190.
<https://doi.org/10.1016/j.jdiacomp.2015.07.026>
- II Granström, T., Forsman, H., Brorsson, A. L., Granstam, E., & Leksell, J. (2018). Patients' experiences before starting anti-VEGF treatment for sight-threatening diabetic macular oedema: A qualitative interview study. *Nordic Journal of Nursing Research*, 38(1), 11-17.
<https://doi.org/10.1177/2057158517709409>
- III Granström, T., Forsman, H., Lindholm Olinder, A., Gkretsis, D., Eriksson, J. W., Granstam, E., & Leksell, J. (2016). Patient-reported outcomes and visual acuity after 12 months of anti-VEGF-treatment for sight-threatening diabetic macular edema in a real world setting. *Diabetes Research and Clinical Practice*, 121, 157-165.
<https://doi.org/10.1016/j.diabres.2016.09.015>
- IV Granstam, E., Rosenblad, A., Modher Raghieb, A., Granström, T., Eriksson, J. W., Lindholm Olinder, A., & Leksell, J. (2019). Long-term follow-up of anti-vascular endothelial growth factor treatment for diabetic macular oedema: a four-year real-world study. *Acta Ophthalmologica*, 0(0). doi: 10.1111/aos.14290

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Abbreviations

| | |
|------------|---|
| BMI | Body mass index |
| CRT | Central retinal thickness |
| DM | Diabetes mellitus |
| DME | Diabetic macular edema |
| DR | Diabetic retinopathy |
| ETDRS | Early Treatment Diabetic Retinopathy Study |
| GDM | Gestational diabetes mellitus |
| IFCC | International Federation of Clinical Chemistry |
| HbA1c | Glycated hemoglobin |
| HRQoL | Health-related quality of life |
| LADA | Latent autoimmune diabetes in adults |
| logMAR | Logarithm of the minimum angle of resolution |
| MODY | Maturity-onset diabetes of the young |
| NEI VFQ-25 | National Eye Institute Visual Function Questionnaire–25 |
| NDR | Swedish National Diabetes Register |
| OCT | Optical coherence tomography |
| PDR | Proliferative diabetic retinopathy |
| PRO | Patient-reported outcome |
| PRN | Pro re nata |
| PROM | Patient-reported outcome measure |
| QoL | Quality of life |
| RCT | Randomized controlled trial |
| RWE | Real-world evidence |
| SF-36 | Short Form 36 Health Survey |
| VA | Visual acuity |
| VEGF | Vascular endothelial growth factor |
| VRQoL | Vision-related quality of life |

Introduction

Many people have diabetes mellitus (DM), which can lead to diabetes complications. Complications that affect the eyes can lead to vision loss, which is a much feared outcome. This thesis describes real-world patient-reported and medical outcomes in a cohort of individuals, who began treatment with anti-vascular endothelial growth factor (VEGF) for diabetic macular edema (DME).

Patient-reported outcomes

Patient-reported outcomes (PRO) refers to a report by a person living with a disease regarding their health and quality of life (QoL) that is not interpreted by a caregiver or another person. Using PRO is an important way to include patients' perspectives, in addition to measurable medical data (Weldring & Smith, 2013).

Daily life is demanding and complex for patients with DM; therefore, it is important to let these patients describe their own experience of their daily life, their treatment, and the disease itself (Cappelleri et al., 2014; Deshpande et al., 2011; Fairclough, 2004). Living with DM means that individuals must maintain a balance between high and low blood sugar to avoid the risk of late diabetes complications and hypoglycemia.

Studies have shown that the risk of developing late complications can lead to health anxiety and fear, and the most feared complication is vision loss (Janzen Claude et al., 2014; Kuniss et al., 2019). Other studies have shown that people with DM can experience a general fear of late complications (Kuniss et al., 2019), fear of hypoglycemia (Martyn-Nemeth et al., 2016), and have an increased risk of depression (Gask et al., 2011).

To understand and meet the needs of these patients and to provide good diabetes care, use of PRO is very valuable. PRO can help health-care staff to improve their interaction with the patient (Snyder et al., 2013). One study showed that using PRO in clinical practice also has the potential to improve care for the patients and allows them to be involved in their own health care (Haugstvedt et al., 2019).

Quality of life

Quality of life (QoL) is one aspect of PRO (Rothman et al., 2007) and a treatment goal in diabetes care (Melmer & Laimer, 2016). The term QoL first appeared in the medical literature in the 1960s (Elkinton, 1966). There are many definitions of QoL (Felce & Perry, 1995) as it is multidimensional and includes subjective evaluation of both positive and negative aspects of life (WHOQOL Group, 1998). In research, it is important to be aware of this aspect of QoL and to clarify individuals' own interpretation of the concept (Post, 2014).

According to the World Health Organization, the definition of QoL is “an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns” (WHO, n.d.). In health care, it is important to understand the impact of different diseases and treatments on individuals' QoL, for health care personnel to identify patients with a higher risk of poor QoL (Arditi et al., 2019); thus, QoL is an important factor in medical and health research (Haraldstad et al., 2019). Vision loss caused by DM can place a high burden on the affected individual, which can lead them to experience a poorer QoL (Clarke et al., 2006; Trikkalinou et al., 2017). Therefore, the QoL in people affected by DM is an important perspective, as one treatment goal in DM is to maintain good patient QoL.

QoL in the context of a disease such as DM can be referred to as health-related quality of life (HRQoL), to distinguish this concept from other aspects of QoL. HRQoL focuses on the individual's experience of psychological well-being, physical capacity, and ability of social activities in relation to their perceived health. HRQoL is defined as the functional impact of a disease or its treatment (ISOQOL, 2016). To further clarify this, another concept known as vision-related quality of life (VRQoL) is a more specific term related to QoL from a visual perspective (Trento et al., 2019).

Patient-reported outcome measures

Patient-reported outcome measures (PROMs) are instruments, such as questionnaires, that are used to measure PRO (Weldring & Smith, 2013). PROMs give individuals an opportunity to express what's important for them and how they experience their situation (Øvretveit et al., 2017). In DM health care, the use of relevant PROMs is central to providing the individual with an opportunity to report their experiences related to the disease and treatments they receive (Reaney et al., 2014). In this project, it was important to use PROMs to allow participants to express their own experiences in their own way.

There are two types of instruments used to measure QoL and health status: generic and disease-specific instruments (Lohr & Zebrack, 2009; Øvretveit et al., 2017). Generic instruments are designed to be used across different diseases, conditions, and different population groups (Patrick & Deyo, 1989). Disease-specific instruments are designed to be sensitive to disease- and treatment-related changes (Wiebe et al., 2003).

The Short Form 36 Health Survey (SF-36) and EuroQol-5 Dimension (EQ5-D) are examples of generic PROMs. Generic questionnaires provide a single value or utility score for a given health state. Disease-specific PROMs are sensitive to disease- and treatment-related changes (Patrick & Deyo, 1989). Within the area of diabetes, several questionnaires have been developed (Chen et al., 2010; Sharma et al., 2005). Vision-specific PROMs have also been developed, for example, the Retinopathy Dependent Quality of Life and Vision Impairment Questionnaire (Brose & Bradley, 2010; Lamoureux et al., 2007) and National Eye Institute Visual Function Questionnaire–25 (NEI VFQ-25) (Mangione, 2000).

When planning a study, choosing the most relevant PROM should be given the same importance as choosing medical outcomes (McKenna, 2011), to best assess participants' experiences. It has been pointed out that in studies of visual impairment, it is important to use disease-specific questionnaires (Margolis et al., 2002; Massof & Rubin, 2001; Pesudovs et al., 2007; Rothman et al., 2007).

In this thesis, the author chose a vision-specific PROM, the NEI VFQ-25, which is a widely used questionnaire in studies of DME and vision loss (Bertelmann et al., 2016; Bressler et al., 2014). In addition, one generic PROM was used, the SF-36, which has been widely used in different areas. It is recommended to use a disease specific as well as a generic questionnaire in a research study (Machin & Fayers, 2016).

National Eye Institute Visual Function Questionnaire–25

The National eye institute visual function questionnaire- 25 (NEI VFQ-25) is a widely used PROM for measuring patient-reported visual function that has been previously used in studies of treatments for diabetic retinopathy (DR) (Gabrielian et al., 2010; Loftus et al., 2011; Mangione et al., 2001). The NEI VFQ-25 is recommended for use with various eye diseases and interventions (Mangione et al., 2001) as this PROM can detect even small changes in participants' experience of visual function (Kawashima et al., 2016; Klein et al., 2001; Trento et al., 2017). It has been shown that NEI VFQ-25 scores are strongly correlated with vision (Klein et al., 2001; Kowalski et al., 2012). Visual acuity (VA) is the most important factor related to decreased QoL, according to results of a 10-year follow-up study (Hirai et al., 2013). It is

important to increase understanding of the subjective disease burden of people affected by poor VA, to investigate the impact of factors influencing their NEI VFQ-25 scores (Bertelmann et al., 2016).

In some studies, the PROMs described measure HRQoL (Varma et al., 2006); in other studies, the PROMS used are a measure of VRQoL (Gabrielian et al., 2010; Okamoto et al., 2014; Papageorgiou et al., 2007), vision-related function (Bressler et al., 2014), and visual function (Mitchell, et al., 2013). There seems to be no not be a clear consensus on what is measured by the NEI VFQ-25. In this thesis, the author uses the term “visual function” according to the manual for the NEI VFQ-25 (Mangione et al., 2001).

Short Form 36 Health Survey

The Short form 36 health survey (SF-36) is a generic PROM used to measure HRQoL (Maruish, 2011). This instrument was constructed to measure health status in the Medical Outcomes Study. The SF-36 has been validated and translated into Swedish (Sullivan et al., 1995). The survey is designed for self-administration (Ware & Sherbourne, 1992). The SF-36 has been widely used in different areas, for example, in a study regarding glycemic control in relation to HRQoL (Svedbo Engström et al., 2019). It has been shown that people with severe DR have lower HRQoL (Jansson et al., 2018).

Diabetes mellitus

Diabetes mellitus (DM) is a metabolic disorder that is characterized by high levels of blood sugar. DM type 1 and type 2 are the most common, and additional types have been identified, for example, gestational diabetes mellitus (GDM), maturity-onset diabetes of the young (MODY), latent autoimmune diabetes in adults (LADA), or other specific types of diabetes owing to diseases in the pancreas or drug-induced diabetes. DM type 1 is likely owing to autoimmune destruction of beta cells, which leads to insulin deficiency. DM type 2 is characterized by abnormal resistance to the action of insulin and an inability by the body to produce sufficient insulin to overcome this resistance (Deshpande et al., 2008). Type 2 affects 90%–95% of all people with DM (ADA, 2019). The treatment goals for diabetes treatment are controlled blood glucose levels, reduced risk of complications, and maintaining a good QoL for the individual (Melmer & Laimer, 2016). People living with DM are at risk of developing diabetes complications; these individuals therefore face daily challenges in taking responsibility for their diet, exercise, and medication (Young-Hyman et al., 2016).

Around 163 million people worldwide are affected by DM. In Europe, the number is 59 million and in Sweden, over 521,000 people have been diagnosed with diabetes. It is estimated that around 190,000 people have undiagnosed DM (IDF, 2019).

Treatment and patient education to prevent diabetes complications

By addressing the risk factors most strongly associated with the onset of changes in blood vessels, diabetes complications can be delayed or prevented. Therefore, diabetes care should be focused on effective blood pressure and lipid-lowering therapy with statins (Socialstyrelsen, 2018). Patient education in self-care has a central role in caring for people with DM (Coppola et al., 2018). Furthermore, diabetes care should support people with DM to quit smoking and, if necessary, increase their physical activity. In addition, it is important to provide intensive blood glucose-lowering treatment in patients with type 1 diabetes, as well as newly discovered type 2 diabetes without known cardiovascular disease, to achieve the best possible glucose control. Weight reduction has a positive effect on the above risk factors. Obesity surgery can produce weight loss over a long period as well as improved glucose control. Therefore, after careful clinical assessment, health care providers should offer obesity surgery with structured follow-up to people with type 2 diabetes and severe obesity (body mass index (BMI) over 40 kg/m²). In the event of difficulties with controlling glucose and risk factors, surgery may also be considered with BMI of 35–40 kg/m² (Socialstyrelsen, 2018).

When a change in diet and exercise habits do not produce a sufficiently large effect in type 2 diabetes, drugs are used to lower blood glucose levels. Metformin is the preferred initial glucose-lowering medication for most people with type 2 diabetes. Among these patients who have established cardiovascular complications, SGLT2 inhibitors or GLP-1 receptor agonists with proven cardiovascular benefit are recommended as part of glycemic management (Neal et al., 2017; Wanner et al., 2016).

Knowledge levels about DM and its complications have been found to be lower among affected individuals than the level expected by caregivers (Sabanayagam et al., 2016). This fact can lead to difficulties in communication, and the affected person may have difficulties understanding the impact a DM diagnosis could have on their daily life (Trento et al., 2019). These people require individual information as each person has their own needs regarding information and education (Kneck et al., 2014); it is therefore important that each patient accepts that they need information and education

to be able to manage their daily life (Fink et al., 2019). Group-based patient education led by those with both subject and pedagogical competence is recommended, to achieve the best possible treatment results (Socialstyrelsen, 2018).

Diabetes complications

DM can cause late complications, classified as microvascular and macrovascular complications. Microvascular complications can cause injury to the small vessels of the eye, kidneys, or the peripheral nerves. Microvascular complications include retinopathy of the eyes, neuropathy, or nephropathy (ADA, 2019; UKPDS Group, 1991). The pathological mechanisms involved in macrovascular disease include a process of atherosclerosis, which leads to narrowing of arterial walls throughout the body (Fowler, 2011); this in turn can lead to coronary heart disease, peripheral arterial disease, and stroke (Maric-Bilkan, 2017).

The Diabetes Control and Complications Trial began data collection at the beginning of the 1990s. Study findings showed that people affected by DM type 1 who received intensive insulin treatment did not develop late complications to the same extent as those who received standard treatment (DCCT/EDIC Research Group, 2015; Nathan, 2014). A 30-year follow-up showed that intensive insulin treatment could yield up to a 48% lower risk for DM-related eye complications (Nathan, 2014). The United Kingdom Prospective Diabetes Study showed that intensive glucose control in those with DM type 2 reduces the risk for microvascular complications, especially retinopathy (UKPDS Group, 1998).

It has been found that patients with diabetes type 2 have twice the risk for cardiovascular disease as that in people who do not have diabetes. Variables that affect this risk include smoking, albuminuria, blood pressure, low-density lipoprotein, and glycated hemoglobin (HbA1c) (Rawshani et al., 2018). Intensive glucose control has been shown to decrease the risk of cardiovascular events to a greater degree than standard therapy (Reaven et al., 2019) and also reduce the progression of diabetic retinopathy (ACCORD Study Group, 2010; Heller, 2009).

Diabetic retinopathy and macular edema

Diabetic retinopathy (DR) refers to microvascular complications affecting the eye (Cheung et al., 2010; Cheung & Wong, 2008; Coyne et al., 2004). There is increased risk for retinopathy with HbA1c levels 57–61 mmol/mol (Lind et al., 2019). DR is the most common complication arising from DM (Antonetti et al., 2012; Bandello et al., 2010; Cheung et al., 2010; Klein et al., 2010). DR

can lead to vision loss and more seriously, blindness (Bourne et al., 2014; Klein et al., 2008; Okamoto et al., 2014). Proliferative diabetic retinopathy (PDR) is the form of DR that can cause blindness and DME and can lead to visual impairment (Cheung et al., 2010). The international scale for grading of DR, which is diagnosed in the worse-seeing eye includes the following grades: mild, moderate, severe, and PDR (NDR, 2019).

DME may lead to retinal thickening. Swelling located at the central macula may have a negative effect on VA (Bandello et al., 2010; Lang, 2012). Epidemiologic studies have shown the effects of hyperglycemia, hypertension, and dyslipidemia on the incidence and progression of DME (Antonetti et al., 2012; Nathan, 2014; UKPDS Group, 1991).

To detect early signs of sight-threatening changes in the retina, it is important for patients with DM to undergo regular eye screening. If changes in the eye are detected at an early stage, treatment can help to limit subsequent vision loss (Olafsdottir et al., 2016; Tracey et al., 2016).

More than 21 million people worldwide are affected by DME and are at risk of vision loss (IDF, 2019). Given the incidence of DME, treatment that can prevent deterioration or that stabilizes or improves VA would be of substantial global benefit (Lee et al., 2015). Visual impairment caused by DME can often lead to reduced QoL and can have a negative impact on daily life (Mazhar et al., 2011). A qualitative study that described how participants experience living with DM and DME pointed out that personal and social losses affect people's ability to manage daily life, including managing DM; these findings highlight the importance of adequate information and support for these patients (Devenney & O'Neill, 2011).

Treatment for diabetic macular edema

Laser treatment

Laser treatment has been the standard treatment for DME since 1985. Laser treatment has been shown to reduce the risk of severe vision loss by stabilizing the VA (Keshav et al., 2008) or achieving a reduction in moderate vision loss by approximately 25%–50% (Early Treatment Diabetic Retinopathy Study (ETDRS), 1985; Keshav et al., 2008). However, relatively few patients experience significant improvement in VA after laser treatment and any improvement occurs slowly (Beck et al., 2009; Elman et al., 2010; ETDRS, 1985; Mitchell et al., 2011). Laser treatment is administered in an outpatient eye clinic, and no special preparations are required prior to treatment. The

procedure itself is performed under local anesthesia, and the patient can be discharged immediately afterwards. For many years, laser was the only treatment option available for DME; however, since 2011, another treatment, anti-VEGF injection treatment, has become available (Mitchell et al., 2011).

Anti-vascular endothelial growth factor treatment

In 2010, it was reported that repeated intravitreal administration of the anti-vascular endothelial growth factor (anti-VEGF) inhibitor ranibizumab reduced DME and improved VA (Massin et al., 2010). In subsequent years, several studies using ranibizumab or other anti-VEGF agents have reported similar findings (Brown et al., 2013; DRCRnet, 2015; Elman et al., 2010; Elman et al., 2012; Lang et al., 2013; Mitchell et al., 2011; Nguyen et al., 2012). Anti-VEGF treatment has been shown to improve VA in patients with DME (Bandello et al., 2012; Ollendorf et al., 2013; Stefanini et al., 2014). New guidelines for the treatment of DME recommend anti-VEGF treatment as a first choice (Schmidt-Erfurth et al., 2017). There are now several anti-VEGF drugs that have been approved for the treatment of macular edema owing to DME, including ranibizumab and aflibercept (Eylea, 2012; Lucentis, 2009). Intravitreal anti-VEGF is administered as an injection into the vitreous cavity of the eye. The injection is given under sterile conditions in an operating theater under topical local anesthesia. Treatment is most often initiated as three monthly injections followed by additional injections depending on VA and retinal edema as measured using optical coherence tomography (OCT).

Steroid implants

Steroid implants are a relatively new treatment regimen that now has a role in treatment for chronically persistent DME. Intravitreal treatment with glucocorticoids has been found to significantly decrease inflammatory processes; the treatment include an implant that releases corticosteroid into the vitreous for 6 months (Schmidt-Erfurth et al., 2017). It has been shown that only four to five injections over 3 years can significantly improve VA both statistically and clinically (Boyer et al., 2014).

Effects of anti-VEGF treatment for diabetic macular edema

Patient-reported outcomes

As individuals treated with anti-VEGF for DME can experience different kinds of effects, for example, disease burden, anxiety, worry about blindness, or the responsibility for their daily life (Nefs & Pouwer, 2018), it is important to evaluate how these individuals experience their situation over time and to not only focus on medical outcomes.

In 2013, one of the first studies regarding patient-reported visual functioning among people treated with anti-VEGF for DME was performed. The results showed improvement in the NEI VFQ-25 composite score (Mitchell et al., 2013). It has been shown that patients treated with anti-VEGF injections have higher NEI VFQ-25 scores than those treated with sham injections (Bressler et al., 2014). Sub-scores for general health have been shown to be most affected when a person has an ocular disease that leads to vision loss (Bertelmann et al., 2016); in one study, NEI VFQ-25 scores increased from baseline to 6 months (Turkoglu et al., 2015). The NEI VFQ-25 has demonstrated the best ability to measure even small changes in a person's experience of visual function (Trento et al., 2017). Follow-up studies in a real-world setting cover a time span from 6 months to 2 years; as far as we know, there are no long-term follow-up studies.

Medical outcomes

Anti-VEGF injection treatment leads to improved VA, and it has been shown that repeated injections can reduce DME and improve VA (Massin et al., 2010). Anti-VEGF treatment has been shown to be more effective at improving VA in patients with DME than traditional laser treatment (Bandello et al., 2012; Ollendorf et al., 2013; Stefanini et al., 2014). The results of clinical trials have shown that VA was improved by approximately 10 ETDRS letters at 1 year after treatment (DRCRnet, 2015). After 2 years, the positive effects and improved VA remained (Cai & Bressler, 2017; Koc et al., 2018). After 3 years, the improvements were maintained when monthly injections were switched to pro re nata (PRN), as-needed dosing. One-third of participants experienced DR deterioration; therefore, careful monitoring is important in long-term management of patients with DR (Sun et al., 2018). One study reported that 25% of participants achieved improved VA and improved swelling in the macula (Blinder et al., 2017). Long-term results of clinical trials have shown that anti-VEGF treatment for DME is likely to

produce better improvement in vision after 5 years than other treatments (Bressler et al., 2016).

It has been indicated that the most important aspect in the final effect on VA is the patient's baseline best-corrected VA, and whether the patient has been previously treated is an important factor for a positive result (Plaza-Ramos et al., 2019). Positive effects in the best-corrected VA that are initially achieved have been shown to be sustained after 4 years using a PRN regimen; in addition, it has been pointed out that the number of injections is lower than reported in previous trials (Epstein, 2018). In the first year of treatment, the number of injections is higher than in the following years, when the mean number of injections declines (Hodzic-Hadzibegovic et al., 2018). Five-year follow-ups have shown VA stabilization of 62% in the treated eyes (Wecker et al., 2017) and favorable changes in DR severity (Bressler et al., 2018).

In recent years, it has become of interest to evaluate markers that can predict outcome when DME is treated using anti-VEGF injections (Campos et al., 2018). Retinal thickness and best-corrected VA have also been pointed out as important indicators in anti-VEGF treatment for DME (Sugimoto et al., 2019).

Rationale

Living with diabetes involves a risk of late complications. To avoid late complications, patients with DM have a large responsibility for their own health in their daily life, which can cause them to experience feeling burdened. One of the most feared complications is retinopathy, which can lead to vision loss and blindness. Since the 1950s, the traditional treatment for sight-threatening retinopathy has been laser treatment, but another treatment has become available: anti-VEGF injections. The results of previous large randomized controlled trials (RCTs) have shown that anti-VEGF treatment has a clinically positive effect on DME. This injection treatment has shown improvement in VA and a decrease in macular edema, and the positive results have remained in follow-up studies.

This thesis seeks to improve knowledge and understanding of how these individuals experience their VA and the treatment. In addition, an evaluation was conducted of the effect of anti-VEGF treatment on OCT and ETDRS in a real-world setting. This is important to increase knowledge and understanding for clinicians who treat these patients, so that they can provide their patients with the appropriate support, treatment, and information.

When the anti-VEGF treatment includes injections into the eye, which can be an unpleasant experience for the patient. In this thesis, emphasis was placed on measuring PRO in addition to medical results of the anti-VEGF treatment. To capture participants' experiences regarding VA and the injection treatment, two PROMs were used, one generic and one vision specific. In addition, interviews were conducted in which the respondents could relate their own experiences in their own words.

Aims

Overall aim

To describe patient-reported and medical outcomes in patients treated for DME with anti-VEGF injections in a real-world setting.

Specific aims

Study I - To describe patient-reported outcome (PRO), visual acuity (VA), and medical data for a selected group of Swedish patients just prior to receiving treatment with anti-vascular endothelial growth factor (VEGF) for diabetic macular edema (DME).

Study II - To qualitatively describe participants' thoughts and feelings about treatment, knowledge of the relationship between DM and visual impairment, and whether and how visual impairment affects daily life.

Study III - To examine objective visual acuity (VA) measured with ETDRS letter scores, retinal thickness (OCT), patient-reported outcome (PRO), and to describe levels of glycated hemoglobin (HbA1c) and its association with the effects on VA in patients treated with anti-VEGF for visual impairment, owing to diabetic macular edema (DME) over 12 months in a real-world setting.

Study IV - To evaluate visual acuity (VA) and central retinal thickness (CRT) using optical coherence tomography (OCT) during a 4-year period in patients treated for sight-threatening diabetic macular edema (DME) at two Swedish county hospitals. Additionally, to compare health-related quality of life (HRQoL) and subjective visual functioning before and after 4 years of treatment.

Methods

This thesis is a compilation thesis and includes four papers and a framework. The thesis is based on the author's licentiate thesis published in 2016 (Granström, 2016), which included two papers (Granström et al., 2015; Granström et al., 2016). In this doctoral thesis, two additional papers are included (Granström et al., 2018; Granstam et al., 2019). Therefore, there may be similarities between descriptions of the background, methods, results, and conclusions in the licentiate thesis and this doctoral thesis.

The first paper in this thesis describes quantitative data from baseline, including 59 participants. Sociodemographic characteristics and medical background data were collected, and participants completed two questionnaires, the NEI VFQ-25 and SF-36. The second paper presents qualitative data from interviews with 21 of a total 59 people included in the total study. The third paper in this thesis presents quantitative data from the 1-year follow-up. A total 58 participants were included; one participant dropped out after 4 months. The fourth paper presents quantitative data from the 4-year follow-up. A total 37 of the 59 participants from baseline were included in the 4-year follow-up. Nine participants died during the observation period, two declined participation in the follow-up, and 10 participants were lost to follow-up.

Setting and study design

The study in this thesis was a longitudinal, real-world, cohort study that followed a group of persons diagnosed with DME and started on anti-VEGF treatment at two eye-clinics in two county hospitals in Sweden from 2012 to 2014. Data were collected at baseline, 1 year, and 4 years (Table 1).

Table 1. Description of study designs, data-collection, samples, and analyses

| Study | Design | Data-collection | Sample | Analysis |
|-----------|------------------------------------|---|---|--|
| Study I | Quantitative cross-sectional study | Sociodemographic background characteristics NEI VFQ-25 and SF-36 questionnaires Data from medical records | Adults of either sex just prior to receiving anti VEGF -treatment for visual impairment due to DME. n=59 | Descriptive statistics analysis of variance (ANOVA) Spearman correlation Tukey's post hoc test |
| Study II | Qualitative descriptive study | Individual, semi-structured interviews Data from medical records | n=21 | Qualitative content analysis |
| Study III | Quantitative Cross-sectional study | SF-36 and NEI VFQ-25 questionnaires Data from medical records | n=58 | Descriptive statistics Linear regression t-test |
| Study IV | Quantitative cross-sectional study | SF-36 and NEI VFQ-25 questionnaires Data from medical records | n=37 | Pearson's χ^2 test Fisher's exact test Mann-Whitney U test Spearman's ρ Wilcoxon signed-rank test Logistic regression |

Participants

The criteria for inclusion were age over 18 years, no cognitive impairments, and the ability to speak and understand the Swedish language without an interpreter. Consecutive sampling was used by the responsible ophthalmologist at each eye clinic. When an ophthalmologist made the assessment that anti-VEGF treatment for DME was needed, the participant was offered treatment. If the person accepted the treatment, they were asked about whether they wished to participate in the study. Participants were informed about the study by the ophthalmologist at the clinic and received written and oral information. They were also informed that participation in the study was voluntary and not linked to their treatment. All participants signed a consent form to confirm their enrollment in the study.

Individuals diagnosed with DM in this study had several health care contacts. They visited a doctor at least once a year, or more often if there were problems or a change in treatment. At each visit, blood samples were taken and examinations performed to detect any complications. The patients also met with a diabetes nurse once a year to address control of blood glucose levels; if these were not within the reference levels, additional follow-ups were planned. Furthermore, participants underwent regular eye screening at the eye clinic.

Anti-VEGF treatment procedure

The anti-VEGF treatment started with three monthly injections. After the third injection, the patient was examined once a month. In conjunction with examination, the ophthalmologist decided whether the patient needed an additional injection or would return for an examination the following month. When a steady state was reached regarding macular edema, examinations were conducted less frequently.

Data collection procedure

Medical and sociodemographic background data

At baseline, data of both medical and sociodemographic background characteristics were collected. Social background data were collected in interviews with the patients. Medical data, including type of DM, HbA1c level, DM duration, treatment, and other medical treatments were obtained from electronic medical records; HbA1c data were obtained from the Swedish National Diabetes Register (NDR). The International Federation of Clinical Chemistry (IFCC) reference method has been adopted in Sweden; HbA1c values are reported according to the IFCC standard (mmol/mol) (Jeppsson et al., 2002; Lilja et al., 2013).

All participants underwent an eye examination after their inclusion in the study. VA was measured according to the Early Treatment Diabetic Retinopathy Study (ETDRS) letter chart at a distance of 2 meters or using a Snellen chart at 5 meters. ETDRS VA (number of letters) was measured in the eyes for which anti-VEGF treatment was planned. The ETDRS is a landmark study that defined the standardization of eye charts and VA testing, which led to the development of the ETDRS charts (ETDRS, 1985). Measurement of retinal thickness was performed using OCT (Topcon Corporation, Tokyo, Japan). Medical data for the 1-year and the 4-year follow-ups were collected from electronic medical records and eye examinations.

Interviews

A total of 21 respondents were interviewed. Interview respondents were consecutively included out of the total study population included at baseline. The ophthalmologist at each clinic asked patients if they would participate in an interview. The inclusion of participants for interviews continued until sufficient variation in the population could be observed in an overall overview.

The author of this thesis (TG) conducted the interviews and transcribed them after each interview occasion.

Participants were interviewed at the eye clinic before receiving their first anti-VEGF injection. The interview took place in a room at the eye clinic where the interviewer and participant had privacy. All interviews were conducted by the author (TG); participants had no relationship to the researcher before the interview.

The interviews were based on an interview guide and included open questions with themes. The focus was on the participants' experiences, thoughts, and feelings about the treatment, their perception about the connection or relationship between DM and visual impairment, and if and how visual impairment affected their daily life.

Examples of questions from the interviews are as follows: "What are your thoughts about the treatment you are going to receive?", "How does visual impairment affect you in your daily life?", and "Can you describe any connection between your diabetes and your vision problems?" The participants were asked to share their experiences and responses were followed up with probing questions (e.g., "What do you mean?", "Can you explain further?", "Can you give an example?") The interviews lasted between 10 and 40 minutes and were recorded and transcribed verbatim.

Patient-reported outcome measures

In our study, participants self-reported their visual function and QoL using two PROMs: the vision-specific NEI VFQ-25 and the generic SF-36. Participants completed the two questionnaires at three data collection points: at baseline, at the 1-year follow-up, and at the 4-year follow-up. At baseline, the questionnaires were distributed to participants at the eye clinic in conjunction with their being asked about participating in the study. At the 1-year follow-up, questionnaires were mailed to participants a couple of weeks before their visit to the eye clinic, together with instructions to complete the questionnaire at home and bring it to the eye clinic. The completed questionnaires were collected during the next planned appointment at the eye clinic. At the 4-year follow-up, questionnaires were completed in telephone interviews. First, an additional ethics review application was approved. A letter with information about the 4-year follow-up and a request for permission to call was mailed to all participants after the 1-year follow-up. Once participants had signed and returned their forms, they were called and the VFQ-25 and SF-36 questionnaires were completed in a telephone interview by a member of the research group. Around 50% of participants responded to the first letter, and the rest received a reminder on two further occasions.

Questionnaires

National Eye Institute Visual Function Questionnaire–25

The NEI VFQ-25 consists of 25 questions divided into 11 vision-related subscales, including 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 (Mangione et al., 1998; 2001).

Below is an example of a question in the NEI VFQ-25; the respondent chooses one answer.

**5. How much difficulty do you have reading ordinary print in a newspaper?
Would you say you have:**

1. *No difficulty at all*
2. *A little difficulty*
3. *Moderate difficulty*
4. *Extreme difficulty*
5. *Stopped doing this because of your eyesight*
6. *Stopped doing this for other reasons or not interested in doing this*

The subscale scores range from 0 to 100, where a higher score indicates better visual function (Mangione, 2000). The validity and reliability of the NEI VFQ-25 have been evaluated in previous studies (Mangione et al., 2001). Scale conversions are calculated and subscale scores, with 11 vision-related constructs plus the additional single-item general health score and a composite score, are determined according to the manual (Mangione, 2000). The questionnaire has been validated for Swedish-speaking patients (Eriksson, 2008).

Short Form-36 Health Survey

The SF-36 measures eight dimensions of HRQoL divided into two aspects, physical and mental health. The mental health part includes four scales: vitality (4 items), social functioning (2 items), role-emotional (3 items), and mental health (5 items). The physical health part includes four scales of physical functioning (10 items): role-physical (4 items), bodily pain (2 items), and general health (5 items) A self-reported health aspect is completed by respondents and is not included in the scoring process (Ware & Sherbourne, 1992). The subscale scores range from 0 to 100, where a high score indicates

a better health state. Scores represent the percentage of the total possible score achieved by respondents on a given scale (Maruish, 2011).

Below is an example of a question on the SF-36. The respondent chooses one response option for each part of the question.

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

- a) Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports
- b) Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling or playing
- c) Lifting or carrying groceries
- d) Climbing several flights of stairs
- e) Climbing one flight of stairs

- 1. No, not limited at all*
- 2. Yes, limited a little bit*
- 3. Yes, limited a lot*

The SF-36 questionnaire has been validated and translated into Swedish (Sullivan et al., 1995) and is designed for self-administration (Ware & Sherbourne, 1992). Validation has shown the empirical robustness of the scales and underlying health dimensions of the SF-36 (Persson et al., 1998). A license to use the SF-36 was applied for and granted (Optuminsight Life Sciences, Inc., Johnston, RI, USA; license no: QM045614). Scores on the SF-36 and eight dimensions were calculated and were obtained from the licensed software program (Maruish, 2011).

Analyses

All statistical analyses were performed in IBM SPSS Statistics 24/25 (IBM Corp., Armonk, NY, USA). *P*-values < 0.05 were considered statistically significant.

Study I

Descriptive statistics were used to present patient demographics and characteristics. Mean scores, standard deviation (SD), and range were calculated for the subscales in the SF-36, NEI VFQ-25, ETDRS, and OCT. The degree of DR was categorized based on the eye most affected by DME as mild, moderate, severe, or proliferative (Wilkinson et al., 2003).

Visual impairment was categorized into three groups based on the patient's better-seeing eye: normal vision, logarithm of minimum angle of resolution (logMAR) ≤ 0.10 ; mild visual impairment, logMAR 0.20–0.50; moderate/severe visual impairment, logMAR ≥ 0.60 .

The patient groups from the two eye clinics were equivalent regarding sociodemographic and medical characteristics; thus, the patients were handled as one single cohort. Analyses were conducted on one treated eye per patient; the eye with the worst VA was excluded in cases where the patient received anti-VEGF treatment in both eyes.

The cohort was divided into subgroups according to visual impairment, degree of retinopathy, and whether treatment was planned for the better- or worse-seeing eye. Analysis of variance (ANOVA) was then performed to examine whether there were any differences between the subgroups in relation to the NEI VFQ-25 and SF-36. To examine differences between subgroups regarding visual impairment and the treated eye in relation to the NEI VFQ-25 subscales, Tukey's post hoc test was used.

Study II

The qualitative content analysis used in this study was based on the method described by Graneheim & Lundman (2004). Qualitative content analysis is relevant for analyzing interview data (Krippendorff, 2013).

First, recorded material from the interviews was reviewed repeatedly. Then, the interviews were transcribed verbatim by the same person (TG). The next step was to read the interview transcripts several times. This was done to obtain an overall, holistic view of the material and an overall impression of the content, to identify content in the material that was related to the aim of the study.

The analysis process continued with identifying meaning units in the text and then the condensing meaning units. In this phase, emphasis was placed on the description closest to the text. The analysis continued with interpretation of the underlying meaning in the condensed meaning units. When this was formulated, subcategories were identified; the last step was to identify a theme (Table 2).

Table 2. Analysis process, examples of citations, meaning units and subcategories.

| Subcategory | Visual impairment in everyday life | Hope and last chance | Thoughts about the anti-VEGF treatment |
|--------------|--|--|--|
| Meaning Unit | Difficult to see people and not recognize them until they are close | Shocked but thought there was a chance to get better | Can you move normally and are there any restrictions afterwards |
| Quotation | "... so it's so difficult ... and then it gets more difficult when you are outdoors ... because sometimes I don't recognize people I meet- ... not until they are quite close" | "I was a little shocked at first and thought oh ... But then I thought if this is something that can make me see better of course I want to try ... it is a chance to get better .." | "Can I move as usual after the injection ... or is there any restrictions, such as taking it easy ... or something like that .." |

During the analysis process, discussions were continuously held by the research group. The analysis process also involved reflection by moving back and forth between the transcribed interviews, meaning units, codes, subcategories, and categories. Manifest analysis was performed using an inductive approach leading to categories and subcategories, and the underlying meaning of the categories was expressed as a latent theme.

Study III

A paired *t*-test was used to determine whether there were any changes over time in self-reported visual function (NEI VFQ-25) and self-reported HRQoL (SF-36), HbA1c levels, OCT, and ETDRS.

In the first step, the total cohort was analyzed. In the next step, the cohort was divided into two subgroups, one with patients who had improved VA and another group with those who had no improvement in VA. An improvement of ≥ 5 ETDRS letters was considered clinically significant (Klein et al., 2001). Analyses were conducted for one treated eye per patient, as described in study I.

Study IV

Logistic regression analysis was used to examine VA and OCT from baseline to 4 years. An increased score of ≥ 5 letters was considered an improvement in ETDRS VA and a reduction of $\geq 10\%$ μm was considered an improvement in CRT on OCT.

The results are presented as odds ratios (ORs) with accompanying 95% confidence intervals (CIs). Descriptive statistics and categorical data are presented as frequencies and percentages (n, %), means (m) and standard deviations (SD). Comparisons between two independent groups were performed using Pearson's χ^2 test or Fisher's exact test for categorical data; the Mann–Whitney *U* test was used for ordinal, discrete, and

continuous data. Spearman's rank correlation was used for correlation analyses. Comparisons between two dependent groups were performed using the Wilcoxon signed-rank test for ordinal, discrete and continuous data.

Improvements in VA and CRT from baseline to 4 years were examined using logistic regression analysis; an increased ETDRS score of ≥ 5 letters was considered an improvement in VA.

Ethical considerations

Ethical approval for the study in this thesis was obtained from the regional ethics committee in Uppsala, 211/264 (papers I, II, and III) and amendment 211/262/2 (paper IV). The study was conducted in accordance with the tenets of the Declaration of Helsinki (WMA, 2016).

All participants gave their informed consent by signing a consent form. All included persons received written and oral information about the study and its purpose. Participants were informed that they could terminate their participation in the study at any time. The fact that the study was voluntary was emphasized in the information provided to participants, as well as the fact that non-participation would not affect the standard of care that participants received. Information about contact details for the responsible individuals in the study was included.

When reporting the results of the study, it was important that results from a specific participant were not traceable, so the data were given a code number and the code key was kept in a safe location at the eye clinic. The questionnaires were labeled with the code numbers. Because the included participants are a vulnerable group and may experience thoughts and feelings after the interviews, they were informed that they could contact the interviewer or their consulting ophthalmologist for further discussion, if needed.

Results

PRO data and medical data from baseline are presented in **study I** and results from interviews at baseline are described in **study II**. The 1-year follow-up data of PRO and the medical results are described in **study III** and the 4-year follow-up data of PRO and medical results are described in **study IV**. Characteristics of the participants are presented in Table 3, and results from the PROM questionnaire NEI VFQ-25 in **studies I–IV** are presented in Table 4.

Table 3. Characteristics of the participants in studies I-IV

| | Study I | Study II | Study III | Study IV |
|----------------------------------|---------------|-----------------|---------------|---------------|
| Variable | | | | |
| Number | 59 | 21 | 58 | 37 |
| Sex, male/female | 30/29 | 10/11 | 29/29 | 21/16 |
| Type of diabetes (type 1/type 2) | 5/54 | | 5/53 | 4/33 |
| Blood pressure | 151/82 | | | |
| | (Mean ± SD) | (Median, Range) | (Mean ± SD) | (Mean ± SD) |
| Age, years | 68.5 (± 10.0) | 69 (49-86) | 68 (45-86) * | 68.7 (± 8.3) |
| HbA1c (mmol/mol) | 68 (± 16) | 66 (44-84) | 64 (± 17) | 64.5 (± 13.3) |
| ETDRS (letter score) | 63.9 (± 13.2) | 67 (36-84) | 70.2 (± 11.1) | 67.8 (± 15.9) |
| OCT (µm) | 396 (± 129) | 358 (258-648) | 282 (± 83) | 279 (± 103) |
| Diabetes duration | 17 (±10) | | | 16.6 (±11) |

* (Mean, Range)

Table 4. National Eye Institute Visual Function Questionnaire–25 (NEI VFQ-25) at baseline, 1 year, and 4 years

| Subscales | Baseline (n=59) | 1 year (n=58) | 4 years (n=37) |
|--------------------------|------------------|------------------|------------------|
| NEI VFQ-25 questionnaire | Mean (\pm SD) | Mean (\pm SD) | Mean (\pm SD) |
| General health | 35.65 (22.04) | 47.81 (21.88) | 43.9 (27.3) |
| General vision | 60.71 (18.28) | 67.84 (15.01) | 62.7 (23.2) |
| Ocular pain | 84.21 (20.80) | 88.73 (17.11) | 90.5 (17.0) |
| Near activities | 66.23 (21.56) | 72.92 (20.76) | 72.1 (28.4) |
| Distance activities | 73.54 (24.62) | 79.55 (21.59) | 77.6 (25.6) |
| Social functioning | 87.50 (19.66) | 89.62 (18.63) | 85.5 (21.8) |
| Mental health | 76.54 (20.87) | 81.64 (17.86) | 80.1 (22.9) |
| Role difficulties | 78.07 (25.14) | 78.01 (21.85) | 79.1 (29.8) |
| Dependency | 93.48 (18.12) | 90.87 (21.47) | 87.6 (27.7) |
| Driving | 72.02 (37.02) | 75.68 (35.10) | 64.7 (39.3) |
| Color vision | 91.18 (19.41) | 92.46 (16.69) | 88.7 (26.2) |
| Peripheral vision | 77.68 (21.16) | 79.92 (24.90) | 83.8 (25.8) |
| Composite score | 78.12 (16.72) | 81.17 (15.91) | 79.5 (20.3) |

Study I

In study I, data were collected at baseline before participants initiated anti-VEGF treatment for DME. A total of 59 participants were enrolled in the study; participant characteristics are shown in Table 1. Mean age was 68.5 years and the sample was equally distributed regarding sex. Fifty-six percent of patients had completed elementary school, 61% were cohabitating, and 66% were retired. Type 2 DM was the most common DM type, and approximately 70% of patients had two or more DM-related complications. At baseline, 23 participants had insulin treatment, 14 tablet treatment, and the remaining 22 participants had both insulin and tablet treatment.

Vision-related baseline data showed that 25% of patients had proliferative DR and 25% had severe DR. In 61% of patients, treatment was planned for the worse-seeing eye; nearly 70% had received previous laser treatment. Mean VA measured using ETDRS letters was 63.9 (\pm 13.2) and the mean OCT was 396 (\pm 129) μ m.

The results of the NEI VFQ-25 showed the lowest score for general health (mean 35.65 \pm 22.04) and the highest for dependency (mean 93.48 \pm 18.12). For the SF-36, respondents had the lowest scores on the subscale of general

health (mean 56.55 ± 22.14) and the highest on the subscale of role-emotional (mean 88.73 ± 22.32) (Table 5).

Table 5. Short Form (36) Health Survey (SF-36) scores at baseline

| Subscales | Mean | SD |
|----------------------|-------|-------|
| Physical functioning | 67.42 | 27.15 |
| Role physical | 71.30 | 34.10 |
| Bodily pain | 70.16 | 29.55 |
| General Health | 56.55 | 22.14 |
| Vitality | 61.40 | 20.46 |
| Social functioning | 84.15 | 22.80 |
| Role emotional | 88.73 | 22.32 |
| Mental health | 77.45 | 17.11 |

Study II

In study II, participants were interviewed at baseline before they initiated anti-VEGF treatment for DME. A total of 21 patients were interviewed, 11 women and 10 men, with ages between 49 and 86 years.

The results from the interviews yielded an overall theme: *to be at a crossroads and a crucial phase in life, with an uncertain outcome*. The overall theme was based on two categories and six subcategories (Table 6).

Table 6. Theme, categories, and subcategories

| Theme | To be at a crossroads and a crucial phase in life with an uncertain outcome. | | | |
|---------------|--|---|------------------------------------|--|
| Categories | Perplexity before the treatment | Perception about diabetes and visual impairment | Experience of visual impairment | Experience of visual impairment in everyday life |
| Subcategories | Concern about the injections | Awareness about the relationship between diabetes and visual impairment | Experience of disease progression | Dealing with everyday life |
| | Hope and gratitude before treatment | Unawareness about the relationship between diabetes and visual impairment | Fear of deterioration or blindness | Feeling limitations in daily life |
| | Thoughts about the treatment procedure | | | |
| | A feeling of a last chance | | | |

Perplexity before treatment

Thoughts about anti-VEGF treatment

Before the first injection, many of the participants expressed concern, uncertainty, or anxiety; some even used the word “scared” to describe their mood. They expressed eagerness to start the treatment and to be able to finish it as quickly as possible. Some participants had been offered anti-VEGF treatment before but had declined as the thought of the injections was frightening.

. . . It’s really hard knowing that someone will do this to my eyes . . . I must say I find it very, very hard . . . and I notice that I have been very, very tense the last few days . . . (F8)

Most participants had never heard about the injection treatment for DME and thought that laser treatment was the only option. When participants were offered anti-VEGF treatment, some initially hesitated to receive the treatment because it involved injections into the eye. At the same time, they were thankful that there was another type of available treatment. Worries about the treatment were expressed, for example, whether it hurt, whether you can see the needle, how many injections are needed. The participants had various experiences regarding information about the treatment. Some patients felt safe and calm and others felt insecure and worried about the injections.

Hope and a last chance

The participants felt hope that they might experience improved VA after treatment and were thankful that there was a treatment available in addition to traditional laser treatment. They expressed caution and stated that they would be satisfied if their VA was stabilized and deterioration could be stopped at the current level or at least not worsen.

I don’t think it will get worse . . . I am sure of that . . . and if I am lucky and it gets better, so be it . . . and if it stabilizes . . . it will be good too . . . so I am positive . . . (F6)

Participants expressed the hope to be able to maintain their current abilities, such as driving and reading. They also experienced this treatment as a last chance to stabilize or improve their VA.

Perception about diabetes and visual impairment

Relationship between diabetes and visual impairment

The participants showed a balance between awareness and unawareness regarding the relationship between diabetes and visual impairment. Many

participants did not understand the association between diabetes and visual impairment or that diabetes could lead to late complications.

I did not understand what it was . . . but I saw some pictures and I could see a dark spot, but I didn't understand what it was . . . (M2)

Experience of disease progression

Several experiences of the situation of having DME were expressed in the interviews. Some participants noticed a sudden decrease in VA. For other participants, visual impairment developed slowly over time and they noticed a small difference over time.

Well, when I noticed . . . this . . . something was not right . . . it was not like this before . . . I was able to do crosswords without glasses. . . but suddenly now I could not . . . it was just blurry . . . (F10)

Fear of deterioration or blindness

The fear of becoming blind occupied many participants' thoughts. A feeling of being handicapped if their VA deteriorated further was expressed, and participants also expressed concern about the future. Participants who were still gainfully employed had thoughts about how visual impairment would affect their work.

I don't want to lose my vision, which is my worst fear . . . (F6)

Visual impairment in everyday life

Participants had varying degrees of visual impairment and experienced daily life in different ways. Generally, participants could manage their daily lives when they were in their own homes, but some were dependent on someone else for help.

Participants reported different ways they could adapt and compensate in their everyday lives. Some had been forced to quit hobbies and activities, and now had lower expectations of their VA over time. Many participants experienced a feeling of limitation in their daily life. One problem was not being able to see the faces of people who they met when they were out, which could be embarrassing.

So it is hard . . . and it is harder when you are outside . . . because sometimes I don't recognize people . . . when you meet them . . . until they are right up close . . . only then, I can see who it is and then I maybe don't have time to say hello . . . (M6)

Study III

In study III, data were collected 1 year after participants initiated their anti-VEGF treatment for DME. A total 57 participants completed the 1-year follow-up; patient characteristics are shown in Table 3.

The total cohort showed significant improvement on the NEI VFQ-25 subscales of general health, general vision, near activities, distance activities, and composite score. When we divided the cohort into patients with improved VA and those with no improvement in VA, we noted that the change in VFQ-25 scores had occurred in the group of patients with improved VA, who improved significantly for the subscales general health, general vision, near activities, and distance activities. This was in contrast to the group who experienced no improvement in VA; those patients had no improvement in NEI VFQ-25 scores (Table 7). For the SF-36, there was no significant change in any of the subgroups.

Table 7. National Eye Institute Visual Function Questionnaire–25 (NEI VFQ-25) subscale scores at 1-year follow-up

| Subscales VFQ-25 | | Total patient sample n = 58 | | | Improved ETDRS n = 30 | | | Non Improved ETDRS n=27 | | |
|---------------------|----------|--------------------------------|-------|---------|--------------------------|-------|---------|----------------------------|-------|---------|
| | | Mean | SD | P-value | Mean | SD | P-value | Mean | SD | p-value |
| General Health | Baseline | 36.70 | 22.02 | .002 | 37.50 | 24.45 | .004 | 36.36 | 20.01 | .137 |
| | 1 year | 46.81 | 21.88 | | 51.04 | 18.77 | | 43.18 | 24.62 | |
| General Vision | Baseline | 61.18 | 18.94 | .001 | 57.69 | 19.04 | .000 | 65.83 | 18.16 | .747 |
| | 1 year | 67.84 | 15.01 | | 69.23 | 14.12 | | 66.67 | 16.33 | |
| Ocular Pain | Baseline | 84.72 | 20.70 | .077 | 80.36 | 23.92 | .133 | 90.50 | 15.00 | .548 |
| | 1 year | 88.89 | 17.11 | | 85.27 | 20.43 | | 92.50 | 11.97 | |
| Near Activities | Baseline | 66.36 | 21.41 | .015 | 63.39 | 18.75 | .015 | 69.67 | 24.40 | .394 |
| | 1 year | 72.92 | 20.76 | | 71.88 | 20.24 | | 73.33 | 21.78 | |
| Distance Activities | Baseline | 73.46 | 24.94 | .026 | 72.47 | 23.61 | .008 | 74.00 | 27.14 | .312 |
| | 1 year | 79.55 | 21.59 | | 79.76 | 21.48 | | 79.17 | 22.57 | |
| Social Functioning | Baseline | 87.26 | 19.99 | .184 | 86.57 | 17.99 | .265 | 87.50 | 22.53 | .461 |
| | 1 year | 89.62 | 18.63 | | 89.35 | 16.52 | | 89.50 | 21.25 | |
| Mental Health | Baseline | 76.50 | 21.31 | .062 | 76.12 | 22.31 | .127 | 78.00 | 20.26 | .440 |
| | 1 year | 81.64 | 17.86 | | 82.89 | 16.72 | | 80.50 | 19.63 | |
| Role Difficulties | Baseline | 79.40 | 23.18 | .523 | 79.91 | 22.40 | .305 | 79.00 | 24.93 | .873 |
| | 1 year | 78.01 | 21.85 | | 76.79 | 19.75 | | 78.50 | 24.35 | |
| Dependency | Baseline | 93.43 | 18.62 | .417 | 97.22 | 6.54 | .314 | 89.58 | 26.15 | .779 |
| | 1 year | 90.87 | 21.47 | | 92.90 | 20.11 | | 88.19 | 23.43 | |
| Driving | Baseline | 74.66 | 35.17 | .789 | 75.69 | 36.25 | .855 | 72.92 | 35.94 | .772 |
| | 1 year | 75.68 | 35.10 | | 77.08 | 33.55 | | 73.61 | 38.32 | |
| Color Vision | Baseline | 91.62 | 19.05 | .766 | 92.59 | 13.54 | .490 | 90.24 | 24.11 | .964 |
| | 1 year | 92.46 | 16.69 | | 94.44 | 12.66 | | 90.00 | 20.41 | |
| Peripheral Vision | Baseline | 76.92 | 24.18 | .282 | 75.93 | 26.39 | .134 | 78.13 | 2250 | .798 |
| | 1 year | 79.92 | 24.90 | | 80.56 | 23.34 | | 79.42 | 2752 | |
| Composite Score | Baseline | 78.30 | 16.75 | .039 | 77.27 | 15.74 | .024 | 79.57 | 18.37 | .611 |
| | 1 year | 81.17 | 15.91 | | 81.32 | 15.10 | | 80.71 | 17.33 | |

The results for the total cohort showed a significant improvement in VA and a significant decrease in retinal swelling. Out of the total cohort 30 patients had improved their ETDRS scores by > 5 letters; 27 patients had not improved their ETDRS score (Table 8). The distribution regarding number of injections was unequal, although the medians were comparable. In the group with no improvement in VA, a larger proportion had insulin treatment; the median number of injections during the study period was five. At 1-year follow-up, the two subgroups had similar VA, although the mean improvement was 12

ETDRS letters for the group with improved VA, and the mean decrease was 2 letters for patients without improved VA.

Table 8. Changes from baseline to 12 months.

| Variables | | Total sample | | Improved ETDRS | | Unimproved ETDRS | |
|-----------------------|----------|--------------|------|----------------|------|------------------|------|
| | | Mean | SD | Mean | SD | Mean | SD |
| HbA1c (mmol/mol) | Baseline | 67 | 16 | 64 | 14 | 73 | 18 |
| | 1 year | 64 | 17 | 63 | 14 | 65 | 20 |
| OCT (μm) | Baseline | 403 | 122 | 428 | 136 | 373 | 98 |
| | 1 year | 282 | 83 | 276 | 68 | 289 | 99 |
| ETDRS (letter score) | Baseline | 65.0 | 12.1 | 60.7 | 13.1 | 69.9 | 8.8 |
| | 1 year | 70.2 | 11.1 | 72.1 | 11.2 | 68.0 | 10.7 |

Among those with no improvement, eight patients showed a significant reduction in their VA (≥ 5 ETDRS letters). What distinguished these patients from the others was that they had a higher mean age and the largest increase in HbA1c levels, although this was not statistically significant.

In the eight patients with decreased VA, HbA1c was $79 (\pm 26)$ mmol/mol at baseline and $53 (\pm 4)$ mmol/mol at 1-year follow-up, which can be considered a sharp decline. Central macular swelling in these patients was $390 (\pm 141)$ μm at baseline and declined to $275 (\pm 63)$ μm at 1-year follow-up. Objectively measured VA was $68.6 (\pm 11.8)$ ETDRS letters at baseline and $59.5 (\pm 12.7)$ ETDRS letters after 1 year.

Study IV

In study IV, data were collected 4 years after participants initiated anti-VEGF treatment for DME. A total of 37 persons completed the 4-year follow-up; patients' characteristics are shown in Table 3. Of the 58 participants in the 1-year follow-up, 2 declined to participate in the follow-up, 9 patients died, and 10 were lost to follow-up. The group of participants with 4-year data and those without 4-year data were compared; the results showed no significant differences between the groups.

Results of the NEI VFQ-25 demonstrated a significant improvement in near-vision activities after 4 years of treatment, as compared with baseline (Table 4). The PROM SF-36 did not reveal statistically significant changes in any domains after 4 years of treatment, compared with baseline (data not shown).

From baseline to 1 year, the 37 patients included in the study showed a significantly increased VA, from a 66.5 to 70.9 ETDRS letter score. This improvement in VA was maintained at 2 and 3 years after treatment was started; however, after 4 years, a decline in mean VA from a 70.9 to 67.8 ETDRS letter score was seen. The reduction in CRT, approximately 100 μ m at 12 months, was sustained throughout the observation period. The first year, patients received a mean 5.1 anti-VEGF injections. In the second, third, and fourth years, approximately two anti-VEGF injections were administered yearly.

In total, 18 eyes (48.6%) were treated for DME, in addition to anti-VEGF therapy during the study period. Six eyes were switched from ranibizumab to aflibercept, which are both anti-VEGF agents. In 13 eyes, macular laser treatment was administered, and 7 eyes were treated with a total of 13 dexamethasone implants. Five eyes received adjunctive therapy, with both macular laser and dexamethasone implants. One eye developed corneal opacification secondary to herpetic keratitis, and cataract surgery was performed in two eyes.

The result showed that 12 of 37 fellow eyes received treatment for DME with anti-VEGF-treatment, laser treatment, or dexamethasone implant. Furthermore, five eyes received panretinal photocoagulation for PDR, and six eyes were treated with cataract surgery or YAG laser capsulotomy for posterior capsule opacification. For patients treated in both eyes with VEGF treatment, the relationship between the better- and worse-seeing eye was maintained in all patients except in one.

Discussion

The studies in this thesis describe patient-reported and medical outcomes in patients who started anti-VEGF injections for DME in a real-world setting between May 2012 and February 2014, at two county hospitals in Sweden.

Key findings

This longitudinal follow-up study followed a cohort with DME affecting their vision, who were about to start anti-VEGF treatment. During the study period, VRQoL, general health related to QoL, VA, and macular swelling were measured. Participants scored low in the PRO subscales and especially for general health, measured with the vision-specific PROM the NEI VFQ-25. The results of interviews yielded the following theme; to be at a crossroads and a crucial phase in life, with an uncertain outcome. Participants expressed concerns about the treatment procedure, which includes injections into the eye. They also experienced existential thoughts regarding hope for improved VA or fear of deterioration. The results at 1-year follow-up showed improved VRQoL, improved VA, and reduced macular swelling. At 4-year follow-up, the improvements in near vision and reduced central macular swelling remained.

General discussion

Approximately 50% of the included participants had two or more late complications. More than 81% received another treatment in addition to diabetes treatment at inclusion, for example, blood pressure, lipid treatment or anticoagulants. Nine of 59 included participants at baseline (nearly 15%) had died at the 4-year follow-up; this may indicate that these persons were relatively sick.

Overall, participants had low general health, as measured using the NEI VFQ-25, as compared with randomized studies (Bressler et al., 2014; Mitchell et al., 2013). One reason for the low general health scores may be explained by the results of interviews, which showed an overall theme of “to be at a

crossroads and a crucial phase in life, with an uncertain outcome.” This theme indicated that the participants experienced a burden at this point.

Another factor that could affect low general health is that our included participants were in a real-world setting, which means that they were less homogeneous with regard to a wider range in several baseline variables, for example age, HbA1c, weight, and blood pressure, in comparison with RCTs in which participants are more heterogeneous (Ziemssen et al., 2017). Having two or more late complications has long been associated with decreased well-being (Rubin & Peyrot, 1999; Smith-Palmer et al., 2016).

One year after treatment initiation, participants had significantly improved scores for the subscales general health, general vision, near activities, mental health, and composite score with the NEI VFQ-25, as in other cohorts (Mitchell et al., 2015). This finding indicates that objectively measured improvement in the ETDRS letter score is reflected in improved NEI VFQ-25 scores.

Four years after treatment start, the NEI VFQ-25 subscale near vision showed significant improvement as compared with baseline, which is in line with another study that also showed increased near vision in the NEI VFQ-25 (Garweg et al., 2019). Having good near vision positively affects daily life so it can be assumed that this is useful for our patients in their everyday life. In the interviews, participants expressed a desire to be able to read or do needlework, for example, and that doing such activities would increase their QoL.

Notably, self-rated near vision scores had increased at the 4-year follow-up, but objectively measured VA using ETDRS letters had not. A person’s own experience regarding VA is most important for individuals. A possible explanation for the above finding could be that participants included in the studies in this thesis received greater attention than other similar patients via contact during the questionnaires and interviews.

In this thesis, the PROM NEI VFQ-25 showed significant changes but the SF-36 did not show any significant changes at any time during the study. This is expected, as the SF-36 is a generic questionnaire; the NEI VFQ-25 is vision-specific and participants respond to questions related to their experience of their vision, which would lead to observable changes. This points out the importance of choosing the correct PROM in a study.

When comparing the results from the studies in this thesis with those of similar international studies (Bressler et al., 2014) that used the NEI VFQ-25, it is important to note the differences in eye care between Sweden and other

countries. In Sweden, eye care is the same for everyone whereas there may be socioeconomic inequalities in the access to eye care in other countries. This can lead to decreased NEI VFQ scores related to the psychological dimensions (Trento et al., 2017). Even if conditions differ among countries, it is still important to use PROMs in studies regarding eye care.

PROMs are useful tools that are increasingly applied to obtain data on patients' perceptions of their health and experiences of receiving care (Kingsley & Patel, 2017). A newly published thesis showed the importance of patients being able to talk about their daily life experiences with DM. In line with this, a new PRO questionnaire has been designed to have this function and to be used in clinical care settings; this has been included in the Swedish National Diabetes Register (NDR) (Svedbo Engström et al., 2018; Svedbo Engström et al., 2016). Another way of allowing patients to express their own experiences is to listen to their stories about living with DM by performing interviews. In this thesis, the results of interviews provided a deeper understanding of how the included patients experienced their situation. This knowledge is important for health care personnel in diabetes care and at eye clinics, to be able to support patients. The present participants expressed a feeling of anxiety before receiving their first injection and had thoughts like wondering whether it would hurt or if they would see the needle. The present results are in line with previous findings showing that most people receiving this treatment experience a high level of anxiety before their first injection (Spooner, 2019). In the interviews, several participants expressed becoming so worried when they first heard about the new injection treatment that they hesitated before deciding to receive it.

The fact that the present participants were interviewed gave them an opportunity to communicate their experiences before receiving their first injection. Many participants expressed relief at being given the opportunity to ask questions and discuss the treatment. This indicates that most people starting anti-VEGF treatment need an opportunity to discuss the treatment, either with a diabetes nurse or at the eye clinic.

Many participants in this thesis also expressed fear of decreased VA or blindness. It has been shown in some studies that regardless of the cause for decreased VA, the person often experiences fear and frustration (Weber & Wong, 2010), and the degree of vision decrease leads to a greater burden (Willis et al., 2017). To help relieve patients of the burden of retinopathy and anti-VEGF treatment, eye clinics and diabetes care professionals may need closer cooperation and clarification of where the responsibility lies for different aspects of information and support for patients. Questions needing clarification may include the following: How is the contact between eye clinics and diabetes care? Who follows up when a patient has been told that

anti-VEGF treatment is indicated? Can diabetes care professionals understand the information from the eye clinic and support patients in those aspects of care?

There seems to be a gap between diabetes care and eye clinics regarding information and support to people affected by DR. It is important to take into account what happens when a person goes to the eye clinic and the eye examination show changes in the macula, by considering who gives the person information about what their finding means and how it is followed up in diabetes care. It is also important to understand the person's social context, to be able to support self-management (Rankin et al., 2014). The present results showed a lack of knowledge regarding DR and its relationship with diabetes among participants; caregivers may expect that patients will have greater knowledge. To overcome this gap, patient-centered education and engaging approaches may yield more positive outcomes than only providing information given during consultations (Trento et al., 2019).

Group-based education is an educational model that has shown positive outcomes (Socialstyrelsen, 2018). As anti-VEGF treatment for retinopathy has become relatively common, the content in group-based education may need updating. In Sweden, the availability of group-based diabetes education is poor (Husdal et al., 2017), although it is recommended that patients with DM be offered to participate in such education (Socialstyrelsen, 2018). The involvement from individuals affected by DM in their own care, and when setting treatment goals are low despite the level of diabetes specific education in the diabetes-nurses that work with this patient group has improved the last years (Husdal et al., 2017). One aspect that should be considered is when and how people with DM obtain updated information about the disease, different treatment regimens, and new recommendations. Some people live with DM for many years, and the research and recommendations change over time.

The results in this thesis showed that the total cohort had a significant improvement in VA at 1-year follow-up. When the cohort was divided into two groups based on improvement in VA, approximately 50% of included participants experienced a significant improvement in VA at 1-year of follow-up. However, it is important to take into account that patients with improved VA had a lower VA at baseline than those without improved VA. Lower VA at baseline provides a greater potential for improvement. Another 4-year follow-up study from Sweden showed a similar improvement in VA; the VA at baseline was 3 ETDRS letters lower than that in our study (Epstein, 2018).

It is notable that previous RCTs did not present results for two groups. In an RCT follow-up study, the improvement in VA was 10.3 (\pm 9.1) ETDRS letters for 62% of participants (Massin et al., 2010); in another study, 65.2% had an

improvement of ≥ 5 letters (Mitchell et al., 2011). It is important to report the VA at baseline to be able to evaluate improvement in comparison with other studies. At the 4-year follow-up in this thesis, VA had decreased but remained higher than that at baseline. In our study at baseline, the group with improved VA at 1-year follow-up had a lower ETDRS letter score at baseline than the group without improved VA.

It has been pointed out that the results of real-world studies of anti-VEGF injections for DME regarding improvement in VA are lower than those of RCTs (Blinder et al., 2017). This may depend on whether anti-VEGF treatment for DME in a real-world setting is initiated with a better VA than in the first clinical studies. In a real-world study from Denmark, participants had scores of nearly 64 ETDRS letters at baseline (Hodzic-Hadzibegovic et al., 2018), compared with 60 ETDRS letter in an early RCT (Massin et al., 2010).

A large proportion of the cohort in this thesis had previously been treated for DME, which may have affected the outcome in this real-world study. It has been found that no previous treatment is an important factor for a positive outcome (Campos et al., 2018; Plaza-Ramos et al., 2019). The improvement in VA after anti-VEGF treatment seems to depend on the initial grade of VA (Cai & Bressler, 2017). In the present thesis, the visual improvement outcomes were lower than those of clinical studies; however, because this was a real-world study, it included a broader population (Hodzic-Hadzibegovic et al., 2018), and the outcomes also depend on baseline VA. One real-world study showed that VA outcomes were considerably lower than those of RCTs, and the best improvement was achieved in the eyes with worse VA at baseline (Ciulla, 2018). Another real-world study showed that VA was improved 24 months after the start of treatment with anti-VEGF for DME (Koc et al., 2018) but the baseline ETDRS letter scores in that study group were 49, compared with 63 among our participants. It is important to pay attention to the VA both at baseline and at follow-up, to be able to assess the results of anti-VEGF treatment by taking into account the VA at baseline and compare the results after treatment.

The central retinal thickness (CRT) measured with OCT showed a significant reduction from baseline to the 1-year follow-up, and this reduction was sustained until the 4-year follow-up. At present, there is no clear correlation between the grade of OCT and VA and no clear answer on how these two correlate (Peng & Tsai, 2018). One study showed that the change in OCT could only explain a small part of the change in VA and cannot be seen as a trustworthy measure (Bressler et al., 2019). The grade of macular swelling does not affect VA; however, if macular swelling persists for a long time, there can be a chronic damage. Thus, it is important to reduce swelling. This may

indicate that a high OCT is not a reliable measure to indicate treatment (Wells et al., 2015).

During the first year of treatment, participants received a mean 5 anti-VEGF injections; in the following years up to the 4-year follow-up, approximately two anti-VEGF injections were administered yearly. This pattern is in line with a large, single-center study in which the six injections were given the first year, which declined in subsequent years (Hodzic-Hadzibegovic et al., 2018). The number of anti-VEGF injections are lower in real-world settings, according to some studies (Kodjikian et al., 2018; Virgili et al., 2018) whereas a study from Denmark showed no reduction in injection frequency (Vorum et al., 2016). A PRN regimen seems to be preferred in clinical settings (Sugimoto et al., 2019).

At the 4-year follow-up, many participants in our study had received many forms of treatment, including previous cataract surgery, panretinal photocoagulation, and macular laser treatment. This means that they had problems with VA and may have experienced worry when the treatment did not lead to improved VA. And HbA1c for the total cohort had decreased in comparison with baseline. There was no correlation between HbA1c at baseline and at 4-year follow-up and VA, which is in line with another real-world study (Shalchi et al., 2018). However, other studies report that high HbA1c at baseline may be associated with less improvement (Bansal et al., 2015; Bressler et al., 2019). Our results showed that the subgroup without improved VA had higher HbA1c at baseline than at the 4-year follow-up. It is therefore important to consider the HbA1c level before treatment start. It has been shown that retinopathy can occur in 10–20 years, despite controlled HbA1c (Lind et al., 2019); therefore, it is important to always consider the HbA1c level.

Decreased DR has been seen in patients who initiate intensive diabetes treatment, with rapid or large blood-glucose reduction (Bain et al., 2019). Patients diagnosed with DME often want to decrease their blood glucose as fast as possible, to avoid more serious eye complications (Feldman-Billard et al., 2018). When a person is diagnosed with DME, it is important to inform them about good control of their blood sugar levels. At group level, there is no correlation between HbA1c and DME but some connection may exist at individual level.

Methodological considerations

Requests for participation in this study were made of participants during a regular visit to an eye clinic, where they received information about anti-VEGF treatment. It was ensured that there was no risk of patients misunderstanding the information. The PROMs SF-36 and NEI VFQ-25 were distributed to participants, who completed them at home and returned them at their next appointment. Participants had the opportunity to ask questions at the clinic, and the response rate was good at baseline. At 1-year follow-up, questionnaires were posted to participants, which they could complete at their convenience. However, it could be easy for participants to forget to complete and/or return the questionnaire. A reminder together with a duplicate questionnaire was sent to patients after a couple of weeks, if needed. At the 4-year follow-up, questionnaires were completed in telephone interviews. By then, participants were familiar with the questions.

It is important to consider how to distribute PROMs as there are advantages and disadvantages to mailing questionnaires or completing them by phone. The response rate is naturally higher when respondents are called on the telephone (Wolffsohn et al., 2000), although in this situation, the respondent may experience time pressure. The PRO questionnaire SF-36 did not show any changes in the results or significant results in relation to DME even though the SF-36 has been used in the research fields of diabetes and retinopathy (Jansson et al., 2018). This points out the importance of choosing a relevant PROM in studies.

This study was performed in a real-world setting, which is important as results from real-world studies are used to support clinical decision-making, to generate evidence for systematic literature reviews, and to complement results of RCTs in clinical research that is aligned with clinical use. Real-world studies often have greater variability and a broader spectrum of participants than RCTs (Ziemssen et al., 2017). Inclusion criteria and baseline values can affect the results; therefore, it is important to perform follow-up studies in different settings.

Participants included in the study received additional attention when completing the questionnaires. In particular, participants who were interviewed expressed relief at being able to talk about the treatment before the first injection.

The different aspects of trustworthiness are important when carrying out interviews (Polit & Beck, 2016). To achieve the best possible level of trustworthiness, the participants' characteristics and the analysis process were

described in detail. Citations from the participants were provided and discussions were held among the research group during the analysis process. Using both interviews and questionnaires can help to increase the study's credibility (Polit & Beck, 2016). To strengthen the credibility of the interviews, the interviewer concluded the interview by asking the respondent to confirm their understanding of the interview content. The transferability of the interview findings relied on including a wide range of participants of different ages and genders. The result should therefore reflect a 'normal' group of people about to receive anti-VEGF injections for DME in a real-world setting. The dependability was increased by using an interview guide, and having the same person carry out all the interviews. To improve confirmability, the interviewer tried to be actively aware of the need not to influence or steer the respondents in any direction and let them answer the questions in their own words.

Strengths

One strength of the included studies was that they were performed in a real-world setting. The importance of real-world studies has been pointed out (SBU, 2016) when new treatments are approved. It is also important to develop real-world evidence (RWE) to complement evidence from RCTs. RWE studies can yield results from a broader cohort that better reflects the everyday reality at clinics (Blonde 2019).

An important aspect in this thesis was that PROM data were collected in addition to medical data, which gives a broader understanding of participants' experiences. The interviews further supplemented these results, providing a deeper understanding regarding participants' situations.

Another strength was that one of the most frequently applied vision-specific PROM was used. The NEI VFQ-25 has been used in studies measuring VRQoL, as the questionnaire is designed to measure vision-related health status in people with diseases of the eyes (Mangione, 2000).

Limitations

One limitation of this study is the relatively small number of participants. However, because anti-VEGF treatment had recently been approved for DME, it was important to start the project as soon as possible, once the treatment was available at eye clinics.

It was difficult to recruit participants for this study, and the inclusion period was extended. After nearly 2 years, inclusion was concluded so as to begin compiling the results.

It would have been desirable if the cohort had been larger, to achieve better generalizability of the results. The small number of participants may be seen as a weakness; however, because this is real-world follow-up study from Sweden, the present findings offer a perception of how these patients experience their health, the injection treatment, and the effects of treatment. It would have been preferable if the data collection was conducted at a larger number of eye clinics, to recruit more participants in a shorter time.

In this project, there was no reference group, which can be seen as a limitation. However, when the study began, anti-VEGF treatment for DME had only recently been approved. As anti-VEGF treatment is considered the best choice for treatment of DME, it would be unethical to have a reference group. The decision was made to include all patients who met the inclusion criteria.

Conclusions

This real-world study showed that the cohort had relatively low general health at baseline. In interviews, participants expressed feeling that they were at a crossroads and in a crucial life phase, with an uncertain outcome. They experienced worry about anti-VEGF injections into the eye and fear of vision loss. The results also showed that participants had a low level of knowledge regarding the correlation between DM and DR. After 1 year, VA had improved and retinal thickness was reduced in approximately 50% of participants. Results from the PRO questionnaire showed that patients with improved VA also reported improved general health. Four years after treatment began, visual improvement had decreased but macular swelling remained at a lower level throughout the study. Participants' general health had improved further, and they had significantly improved near vision.

It would be useful for patients if cooperation between ophthalmological and diabetes care could be enhanced, to achieve a holistic view of the patient and their situation. Such cooperation could be in the form of a team comprising different health care professionals focusing on different aspects of care for patients with DM and other functions, similar to an interprofessional diabetes foot ulcer team (Ogrin et al., 2015).

Further studies

Based on the results of this study, some important aspects can be pointed out that require further investigation. In interviews before their first anti-VEGF injection, participants expressed worry about the injection and their vision. It is important to further examine the kind of information and support such patients' needs, to relieve their worries. Another interesting aspect for further study is which factors affect the treatment outcomes regarding both medical and PRO results.

Continuing to follow these patients in a real-world setting over time is also important, to determine whether the positive effects of treatment remain stable over time, as well as using PROMs to see how patients experience their general health.

Finally, it is important to further study the cooperation between eye clinics and diabetes care, such as who is responsible for providing the information and support required by patients.

Swedish summary

Bakgrund Diabetes Mellitus kan leda till komplikationer och när ögats kärl drabbas kallas det retinopati. Retinopati kan leda till svullnad i gula fläcken (makulaödem) samt allvarlig synnedsättning. Synnedsättning är ofta förenat med rädsla och oro att bli blind. Traditionellt har dessa komplikationer behandlats med laser, men 2011 blev en ny behandlingsform, anti-VEGF injektioner i ögat, godkänt av läkemedelsverket. Denna behandling började då implementeras på ögonklinikerna.

Syfte Det övergripande syftet med avhandlingen var att beskriva hur personer erfar injektionsbehandlingen med anti-VEGF vilket benämns patientrapporterade utfallsmått och huruvida medicinska resultat avseende synförmågan förbättras. Patienterna följdes upp i en real-world långtidsstudie.

Metod Deltagare inkluderades på två ögonkliniker på två mellanstora sjukhus i Sverige mellan 2012 och 2014. Patientrelaterade utfallsmått mättes med ett ögonspecifikt frågeformulär för livskvalitet; National Eye Institute Visual Function Questionnaire 25 questions (NEI-VFQ-25) och ett generellt formulär för hälsorelaterad livskvalitet; The Short Form-36 Health Survey (SF-36). Data som samlades in var patientrapporterade utfallsmått, medicinska data som synskärpa och grad av svullnad i gula fläcken samt sociala bakgrundsfaktorer. Data samlades in vid tre tillfällen; före behandlingsstart, efter ett år och efter fyra år som analyserades statistiskt. Dessutom genomfördes kvalitativa intervjuer före behandlingsstart och analyserades med hjälp av kvalitativ innehållsanalys.

Resultat Totalt blev 59 personer inkluderade i studien. Medelåldern var 69 år och det var en jämn fördelning mellan könen. Före behandlingsstart visade det ögonspecifika frågeformuläret NEI-VFQ-25 att deltagarna upplevde en låg generell hälsa. Ett övergripande tema identifierades från de kvalitativa intervjuerna innan behandlingen påbörjades ”att vara vid ett vägskalet och en avgörande fas i livet med en osäker utgång”. Deltagarna beskrev tankar och bekymmer om till exempel praktiska funderingar kring hur behandlingen skulle gå till och hur det skulle kännas att få injektioner i ögat. Därtill uttrycktes existentiella tankar kring hopp att få en förbättrad synskärpa eller rädsla för att synen skulle försämrans. Resultatet vid ettårsuppföljningen visade att 30 deltagare hade förbättrat synskärpan och rapporterade en förbättring

inom flera områden mätt med formuläret NEI-VFQ-25. De övriga 27 deltagarna hade inte förbättrat synskärpan eller något område med formuläret NEI-VFQ-25. Vid fyraårsuppföljningen samlades data från 37 personer och resultatet visade att deltagarna signifikant förbättrat den upplevda synskärpan på nära håll. Frågeformuläret SF-36 visade inte några signifikanta förändringar vid något tillfälle.

Slutsats: Personer som drabbats av diabetesrelaterad synförändring och ska påbörja anti-VEGF injektionsbehandling upplever en låg generell hälsa och uttrycker oro inför injektionsbehandlingen och är oroliga för synförsämring. Ett år efter att anti-VEGF behandlingen startade har flera områden i frågeformuläret NEI-VFQ-25 signifikant förbättrats, makulaödemet minskat och synskärpan förbättrats. De positiva effekterna kvarstod vid fyraårs uppföljningen.

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