ANTI-VEGF THERAPY IN DIABETIC MACULAR EDEMA: THREE-YEAR CLINICAL OUTCOME FROM THE SWEDISH MACULA REGISTER

A REAL-WORLD DATA STUDY

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TABLE OF CONTENTS

ABBREVIATIONS

BCVA = Best Corrected Visual Acuity

CRT = Central Retinal Thickness

DME = Diabetic Macular Edema

DRCR net = Diabetic Retinopathy Clinical Research Network

ETDRS = Early Treatment Diabetic Retinopathy Study

IOP = Intraocular Pressure

OCT = Optical Coherence Tomography

PRN = Pro Re Nata

RCT = Randomized Controlled Trial

SD = Standard Deviation

SMR = Swedish Macula Register

T&E = Treat and Extend

VA = Visual Acuity

VEGF = Vascular Endothelial Growth Factor

wAMD = Wet Age-Related Macular Degeneration

1. POPULÄRVETENSKAPLIG SAMMANFATTNING
(SUMMARY IN SWEDISH FOR GENERAL AUDICENCES)

Diabetes makulaödem (DME) är en av vanligaste orsakerna till synnedsättning på vuxna och förekomsten har ökat tillsammans med ökade förekomst av typ 2 diabetes mellitus. Diabetesretinopati är vanligaste förändringen i ögat som en komplikation av diabetes där blodkärlen i näthinnan förtjockas och retinala kapillärer blir otäta vilket resulterar i syrebrist samt läckage av extracellulär vätska i näthinnan. Detta resulterar i nybildning av kärl för att kompensera syrebristen. Vid diabetes makulaödem ser man vätska även i makula som är området för det skarpa seendet.

Svenska makularegistret (SMR) startades år 2008 för uppföljning av patienter med våt åldersbetingad våt makuladegeneration (wAMD) i syfte för att insamla real-world data (RWD) för bättre information om effektivitet i klinisk praxis. Under senaste decenniet har laserbehandlingen blivit ersatt av anti-VEGF behandlingen tillsammans med steroider som den nya standardbehandlingen för wAMD och DME. Anti-VEGF behandlingen i form av injektioner har visat sig vara väldigt effektiv mot DME men behandlingsscheman samt val av läkemedel ser olika ut på olika kliniker.

Denna studie inkluderade 39 ögon av 28 patienter som blev nyinsatta på anti-VEGF behandling och behandlades mellan 1 Januari 2016 och December 31 2019 i Akademiska sjukhuset, Uppsala. Behandlingen resulterade i att synen förbättrades och svullnaden i området för skarpa seendet minskade. Detta motsvarar väl resultat från andra RWD-studier. Synen förbättrades dock inte i samma utsträckning som i kontrollerade randomiserade studier utförda under de senaste 10 åren. Det kan bero på att i randomiserade studier är kontroller och behandlingar standardiserade men i verkligheten förekommer variation i uppföljning beroende på både patient och klinikens resurser.

Med tanke på bättre resultat i kontrollerade studier så är det viktigt att forska vidare effektivaste behandlingsschemat och kontrollera långtidsuppföljningar i form av RWD-studier för att uppnå liknande resultat även i kliniken.

2. ABSTRACT

Objective

The purpose of the study was to evaluate the efficacy of anti-VEGF treatment in patients with diabetic macular edema (DME) in real-world setting by comparing change in best-corrected visual acuity (BCVA) and central retinal thickness (CRT) compared to number of given injections and baseline BCVA.

Methods

Retrospective longitudinal observation study using data from Swedish Macula Register (SMR) of anti-VEGF treatment-naive patients treated at the Uppsala University Hospital in Sweden between January 1 2016 and December 31 2019. Thirty-nine eyes of 28 patients were included in the study.

Results

The study participants had a baseline BCVA of 64.6 ± 12.4 letters and CRT 373.9 ± 109.1 μm. VA gain at 12 months was 3.5 ± 10 letters, at 24 months 4.5 ± 8.6 letters and at 36 months 4.6 ± 10.1 from baseline. Macular edema reduced from baseline to CRT at 12 months 304.5 ± 92.7 μm, at 24 months 300.1 ± 87.4 μm and at 36 months 294.5 ± 102.4 μm. Patients received during the 3 year follow-up period a total of 5.3, 2.6 and 3.3 anti-VEGF injections during the first, second and third year respectively.

Conclusions

These results in improvement of visual acuity and reduction in central macular thickness were comparable to outcome reported from previous real-world studies. Adherence to monitoring and treatment schedule together with more individualized injection frequency is important in the future to achieve better visual outcomes.

3. BACKGROUND

3.1 Introduction

Diabetic macular edema is one of the leading causes of visual impairment with a growing prevalence together with an increasing number of patients with Diabetes mellitus type II (1). Macular edema develops in approximately 30% of patients who have diabetes within 20 years (2). Recent advances in pharmacological therapies during the last 10 years have shifted the treatment from laser photocoagulation to anti-vascular endothelial growth factor (anti-VEGF) therapy with improved results. Intravitreal injections of anti-VEGF have been found to provide significant benefits in the treatment of macular edema and therefore has become the standard of choice (3).

Macular edema is characterized by the presence of extracellular fluid inside the retinal layers of the macula mostly due to retinal capillary hyperpermeability and the overactivation of several growth factors such as VEGF that continues to increase the retinal capillary permeability.

Different anti-VEGF treatments have been compared most comprehensively by the DRCR.net Protocol T study where visual outcomes were evaluated in patients with macular edema treated with bevacizumab, ranibizumab and aflibercept. No statistically significant difference was found for visual acuities of 20/40 or better (4). However for 20/50 or worse, aflibercept was found to have better results compared with ranibizumab and bevacizumab after 1 year follow-up with VA gains of 18.9, 14,2 and 11.8 respectively. The differences in efficacy were however reduced after 2 year follow-up when comparing aflibercept with ranibizumab with VA gains of 18.1 and 16.1 respectively.

Largest gains in BCVA have been documented in trials that have used the most frequent administration of anti-VEGF. Real-world-studies suggest that ranibizumab and bevacizumab injections are administered less frequently in clinical setting than in clinical trials (5-7) and therefore the efficacy of anti-VEGF treatment may be less significant than earlier thought compared to other choices of treatment. Although studies have conclusively demonstrated the benefits of anti-VEGF treatment, many patients have shown to respond only partially to the treatment and are therefore being under-treated by treating with anti-VEGF injections alone (8).

Clinicians choose to follow DME-patients typically using one of two approaches: pro re nata (PRN) where patients are followed every month regardless of their disease activity and treated in case of activity during the follow-up or treat-and-extend (T&E) where the follow-up interval is slowly increased aiming in the longest possible visit-free interval for the patient together with best possible treatment. The T&E approach was first introduced in 2009 for neovascular age-related macular degeneration (nAMD) with an aim to reduce the treatment burden by reducing the number of visits. Studies have shown better results for T&E in nAMD (9) with fewer number of injections and better visual outcomes. Similar results were even seen in the RETAIN-study where the aim was to demonstrate non-inferiority of T&E to PRN with ranibizumab using best-corrected visual acuity. The T&E regimen resulted in reduction of 46% of clinical visits with similar BCVA change after 24 months (T&E + 6.1 vs PRN +6.2 letters, both $p < 0.0001$) (10).

3.2 Pathophysiology

Under normal physiological conditions, the healthy blood-retinal barrier (BRB) consists of the inner and outer layers that regulate fluid transport through the barrier and dehydrate the retina. Retinal Müller glial cells and astrocyes stabilize the tight junctions between endothelial cells together with pericytes and microglial cells that produce factors to maintain the inner BRB (11,12). The outer barrier is composed of retinal pigment epithelium cells. Hyperglycemia results in increased glycosylation end products and free radicals. Damage of the BRB occurs together with diabetic neuroretinopathy and can lead to increased vascular permeability and result in retinal edema that affects the passage of light through the neuroretinal layers (11). This can lead to acute visual symptoms or more commonly chronic irreversible changes of the retinal layers.

The breakdown of tight junctions, loss of pericytes and endothelial cells and that the extracellular matrix becomes stiffer leads eventually to leakage of fluid to the extracellular space (13). Retinal hypoxia together with hyperglycemia lead to the activation of several inflammatory markers such as the inflammatory intercellular adhesion molecule-1 (ICAM-1) that are expressed in the endothelial surface. Increased retinal hypoxia results in up to 10-times increased VEGF expression which further increases the breakdown of BRB even more.

Although anti-VEGF therapy has become the standard choice of treatment, there are many other inflammatory cascades activated that could offer us new targets of treatment in the future. Inflammatory degeneration through changes in inflammatory mediators such as IL-1β, IL-6, IL-8, IFN-γ and TNF-α are induced by Muller glial cells and studies suggest that these inflammatory-derived changes are not only a response to the damage but more likely a cause of the damage that can be found even before the manifestation of clinical symptoms (4).

3.3 Current treatments

Anti-VEGF

Ranibizumab (Lucentis®) was the first FDA-approved treatment (2012) against DME. Randomized controlled studies such as RISE and RIDE have shown that the number of patients with a 15 letter gain in visual acuity was nearly doubled in patients treated with ranibizumab compared to placebo (14).

Aflibercept (Eylea®) gained recognition after the VIVID and VISTA studies (United States and Europe respectively) where aflibercept given every 4 or 8 weeks resulted in significant gains of visual acuity compared with patients treated with laser photocoagulation alone (15 letter gain in 41.2-42.9% with aflibercept and 13.6-18.9% with photocoagulation alone). Aflibercept has therefore been approved by the FDA (2014) for the treatment of DME and is together with ranibizumab the most commonly used anti-VEGF treatments (15).

Bevacizumab (Avastin®) is a monoclonal antibody originally developed as chemotherapy but is widely used off-label due to its significantly lower cost for the treatment of diabetic macular edema although not being approved by the FDA. Randomized control trials such as the BOLT-study (16) has shown a mean gain of 8.6 letters at 2 years compared with a mean loss of -0.5 letters with laser treatment (17).

Corticosteroids

Corticosteroids are usually applied for patients with little to no response to anti-VEGF injections. Ozurdex®, an intravitreal implant with slowly degradable dexamethasone was approved by the

FDA in 2014 for the treatment of DME. Corticosteroids have shown to be especially effective in pseudophakic patients with poor response to anti-VEGF therapies whereas phakic patients experienced an initial improvement followed by decline and cataract formation (18). Ozurdex-implants have shown to result in better real-life results compared to anti-VEGF as it is not administered as often as anti-VEGF injections and might therefore result in better compliance.

Corticosteroids have shown to result in cataract progression in long term use in phakic patients. Boyer et al (19) reporting an incidence of cataract formation of 67.9% compared with placebo 20.4%. Other dexamethasone studies have reported an incidence of cataract formation between 0% and 50% (20). Other side effects include the elevation of IOP (> 25mmHg 32% compared with 4.3% placebo) and endophtalmitis. These adverse events related to intravitreal corticosteroids seem to be dose dependent (21,22).

Laser photocoagulation

Laser photocoagulation treatment had been the standard choice of treatment since the 1980s. Focal and grid laser treatment of retinal thickening and leaking microaneurysms have been replaced by anti-VEGF and corticosteroid treatments as they have shown to be more effective in clinical trials (1).

3.4 Visual acuity scoring

The ETDRS chart is a visual acuity scoring system that was first used in the Early Treatment Diabetic Retinopathy study (ETDRS) in 1976 developed by Ferris et al based on the Bailey-Lovie chart. ETDRS testing involves participants to read letters from a chart with a logarithmic reduction of size of the letters with the same number of letters in each row. The scoring system is based on the number of correctly read letters with a maximum score of 85 letters which is the same as 20/20 vision or Snellen 1.0.

4. METHODS

4.1 Study design and participants

The purpose of the conducted retrospective longitudinal observational study was to analyze collected data of anti-VEGF treated DME patients with central macular involvement treated at the Uppsala University Hospital ophthalmology clinic between 2016-01-01 and 2019-12-31. A separate study will be carried out for patients treated at other ophthalmology clinics in Sweden during the same period.

Approvement from the institutional ethics review board was obtained. The study adhered to the tenets of the Declaration of Helsinki. Patient consent was obtained before entering data into the register. The author declares that he has no conflict of interest.

Swedish Macula Register is a web-based register including data on nAMD patients since 2007 and in 44 eye clinics in Sweden and since 2019 modules have been added to register treatment for diabetic retinopathy and retinal vein occlusion. The register coverage is 87% (2019) of all treatments for nAMD in Sweden (23). Patient data is entered to the Swedish Macula Register manually when starting intravitreal treatment for diabetic macular edema or neovascular AMD.

4.2 Inclusion criteria and exclusion criteria

Treatment-naive patients with no prior intravitreal injections who started treatment for diabetic macular edema during 2016 were included. Patients who had started anti-VEGF treatment before 2016 and continued their treatment during the study period were not included. The baseline visit was the first visit at which patients were prescribed their first anti-VEGF injection. Patients with previous treatment with laser photocoagulation were included in the study.

Patients were excluded if they were treated simultaneously for proliferative diabetic retinopathy. Patients were also excluded from the study in the absence of enough follow-up visits to analyze the effect of the treatment.

4.3 Data collection

Collected data included: sex, age, symptoms, visual acuity (VA) with ETDRS or Snellen, type and number of injections, treatment interval, treatment scheme PRN/T&E, side effects to treatment, IOP, focal and scatter laser photocoagulation sessions, pars plana vitrectomy, corticosteroid treatment, systemic co-morbidities including hypertension and dyslipidemia and cataract surgery as well as lens status. When Snellen chart was used to measure visual acuity, it was converted to ETDRS according to Gregori et al (24).

Data was recorded manually from the patient healthcare system Cosmic to the Swedish Macular Register together with the visits. Missing visits were added manually after the visits during a retrospective recheck of all the visits during 9/2020. Data from the register was automatically transformed into an excel sheet for further analysis.

OCT photos were evaluated manually by ophthalmologists in addition to values calculated automatically by the machine. OCT machines by Zeiss were used until 3/2016 and as of 4/2016 the machines were widely replaced by Topcon OCT. Decisions regarding treatment including frequency of visits and choice of treatment were based on visual acuity as well as macular edema (CRT) compared to earlier visits and therefore reflect real-world clinical practice.

4.4 Outcome measures

The primary outcome measure was the mean change in VA at 12 months, 24 months and 36 months compared to baseline. Secondary outcomes were change in macular edema in CRT and change in VA and CRT in comparison to number of given injections.

4.5 Statistical analysis

Data was described using median, mean and 1st and 3rd quartile. Standard deviation (SD) was used for continuous variables and percentages and frequency for variables with categories. Statistical analyses were performed using SAS (SAS institute) and Microsoft Excel. Statistical significance was considered at p-values < 0.05.

5. RESULTS

5.1 Baseline characteristics and study participants

A total of 39 eyes were included from 28 unique patients. Out of the 28 unique patients 9 (32%) were female patients and 19 (68%) were male patients. The mean age of the patients was 63.8 ± 11.6 years. Prior laser treatment of DME was performed in 15 eyes (38%). Only anti-VEGF naive participants were included in the study. The mean VA at baseline was 64.6 ± 12.4 letters (median 69.0; range 35-85). The mean Snellen at baseline was 0.436 ± 0.2217. The baseline CRT was 373.9 ± 109.1 µm (median 367; range 160-665). 26 participants (93%) had a diagnosis of Diabetes mellitus type II while 2 participants (7%) had a diagnosis of Diabetes mellitus type I. The duration of follow-up was 0-1 years in 1 eye (3%), 1-2 years in 7 eyes (19%) and over 2-3 years in 29 eyes (78%). 2 participants (7%) were excluded before starting the treatment due to being treated simultaneously for proliferative diabetic retinopathy.

Table 1 Participant characteristics at baseline

Participant characteristics	
Patients, n	28
Male/female, n	19/9
Age, years	63.8 (11.6)
Diabetes mellitus type 1, n	2
Diabetes mellitus type 2, n	26
Eyes, n	39
ETDRS, letters	64.6 (12.4)
CRT, µm	373.9 (109.1)
Phakic, n	28
Pseudophakic, n	11
Glaucoma, n	1
Previous laser, n	9

Values in table are presented as the mean with standard deviation (SD) in parenthesis
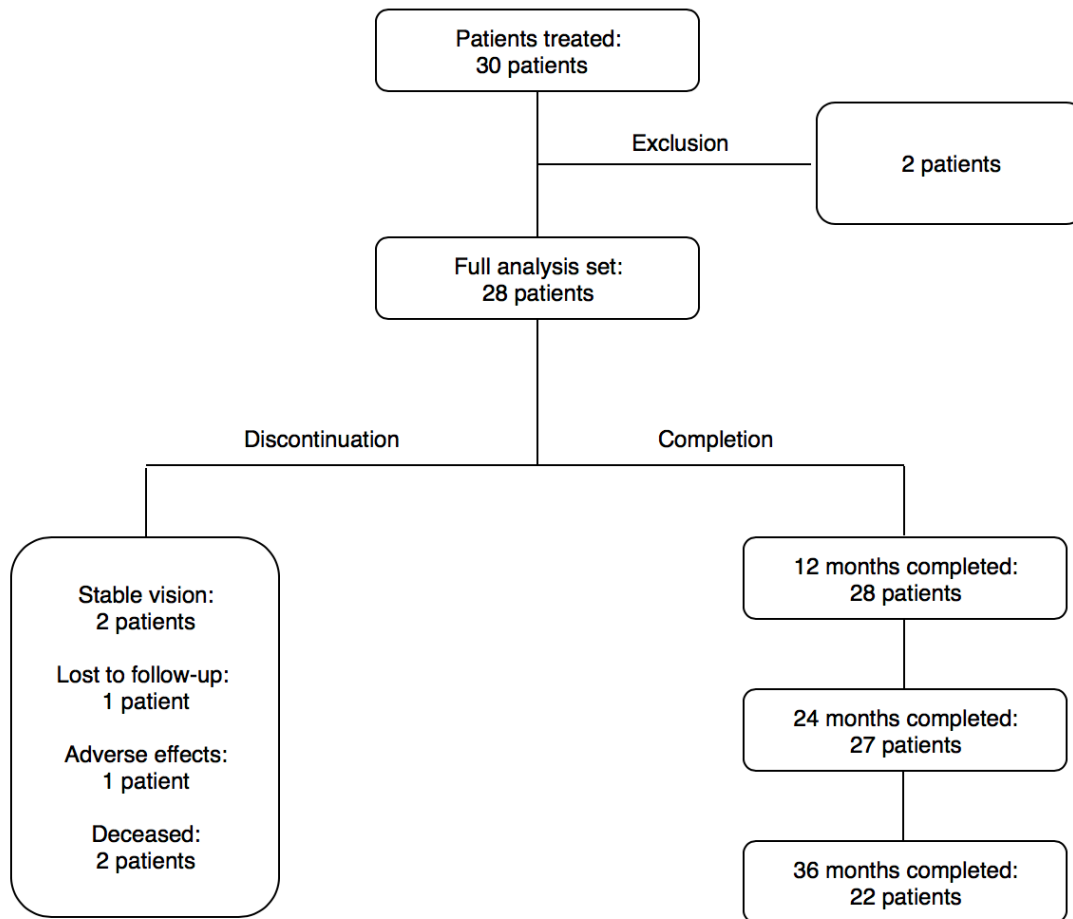
Figure 1 Flowchart of patients with anti-VEGF treatment-naive diabetic macular edema (DME) and treated with intravitreal injections during the follow-up period 2016-2019.

5.2 Visual acuity and CRT

Visual acuity at baseline, 6 months, 12 months, 24 months and 36 months are presented in Figure 2. The mean baseline for all the participants was 64.6 ± 12.4 letters, at 6 months 66.6 ± 16.1 letters, at 12 months ± 68.1 letters, at 24 months $68.8 \pm 15.1$ letters and at 36 months 69.1 ± 13.5 letters. Visual acuity was mostly improved during the first 12 months of treatment as shown in Figure 2. The proportion of eyes with VA ≥ 70 letters increased from 46% at baseline to 64% at 36 months. The proportion of eyes with a VA gain of > 15 letters after the treatment period was 23%.

Figure 2 Change in best-corrected visual acuity (BCVA) Early Treatment Diabetic Reinopathy Scale (ETDRS) letter score during the follow-up period of 36 months.

ETDRS by visit
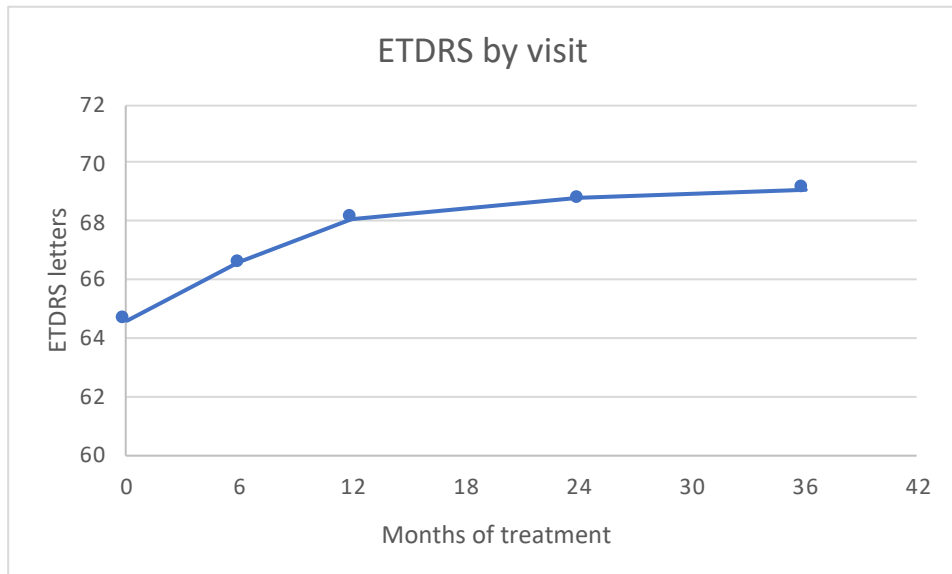
CRT at baseline, 6 months, 12 months, 24 months and 36 months are presented in Figure 3. The mean CRT for all the participants was at baseline 373.9 ± 109.1 μm, at 6 months 320.1 ± 86.2, at 12 months 314.5 ± 92.7 μm, at 24 months 307.9 ± 97.4 μm and at 36 months 306.2 ± 103.4 μm.

Figure 3 Mean change in central retinal thickness (CRT) over the course of 36 months of treatment with aflibercept or ranibimuzab. CRT was measured using optical coherence tomography (OCT).

Central retinal thickness by visit
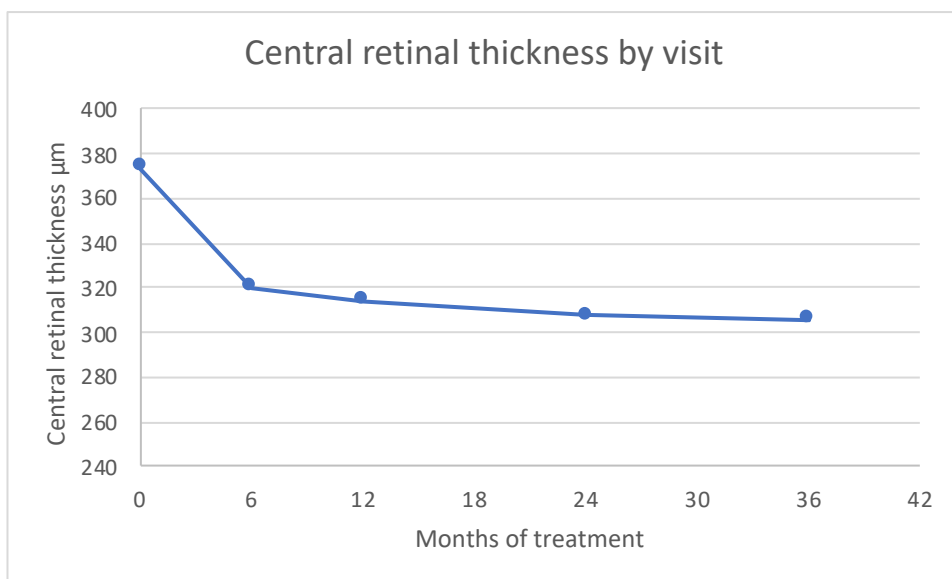
CRT at baseline and after 3, 6, 9 and 12 injections of aflibercept and/or ranibizumab are presented in Figure 3.1. The mean CRT was for all the participants at baseline 373.9 ± 109.1 μm, after 3 injections 314.5 ± 98.7 μm, after 6 injections 317.2 ± 71.0 μm, after 9 injections 327.2 ± 101.9 μm and after 12 injections 301.1 ± 100.8 μm.

Figure 3.1 Mean change in central retinal thickness (CRT) after 3, 6, 9 and 12 injections of aflibercept and/or ranibizumab. CRT was measured using optical coherence tomography (OCT).
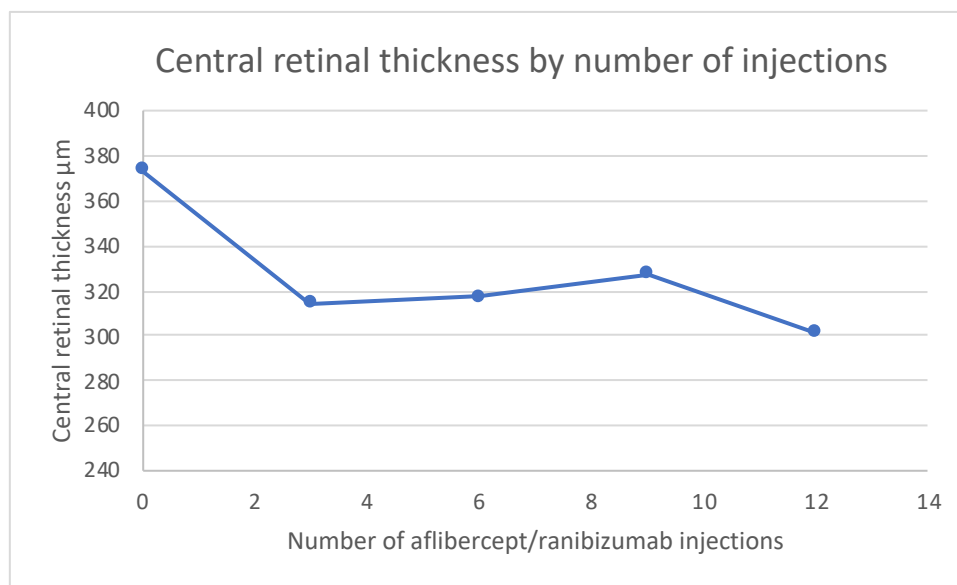
5.3 Treatment practice and number of visits and injections

During the follow-up period anti-VEGF injections were administered as presented in Figure 4. During the first year participants received 5.3 ± 2.9 injections of aflibercept or ranibizumab, 1.2 ± 1.8 injections of aflibercept and 4.1 ± 3.0 injections of ranibizumab. During the second year 2.6 ± 2.6 injections of aflibercept or ranibizumab, 1.6 ± 2.5 injections of aflibercept and 1.0 ± 1.7 injections of ranibizumab. During the third year 3.3 ± 3.1 injections of aflibercept or ranibizumab, 3.3 ± 3.2 injections of aflibercept and 0.1 ± 0.3 injections of ranibizumab.

The type of anti-VEGF treatment was switched in 19 (68 %) participants. In 17 (61%) participants the treatment was switched from ranibizumab to aflibercept. In 2 participants (7%) the treatment was switched from aflibercept to ranibizumab. Treatment was switched in 15 participants (54%) due

to change in clinic routine for first choice of treatment due to economic reasons from ranibizumab to aflibercept and in 4 participants (14%) due to unsatisfactory response to treatment. Standard routine was 3-5 monthly initial injections and after a follow-up visit individual injection interval depending on the disease activity. Ranibizumab and aflibercept have been found to have similarly consistent efficacy in previous publications including the DRCR.net Protocol T study. Better VA gains have been documented with aflibercept compared ranibizumab in eyes with 68 letters or fewer with VA gains of 12.8 and 12.3 respectively. However change in the effect of treatment due to the switch in treatment was not separately analyzed in this study considering small size of the difference in efficacy.

A slow release dexamethasone implant Ozurdex was used only in 4 participants once and in one of the participants twice. Considering the small amount of use in our clinical setting, analysis regarding the effect was not performed. Kodjikian et al have reported VA gain of +9.6 letters for a mean of 1.6 injections during a follow-up period of 10.3 months compared to VA gain of 4.7 letters for a mean of 5.8 injections during a follow-up period of 15.6 months in patients treated with anti-VEGF.

Figure 4 The number of received anti-VEGF injections during the different follow-up years of treatment in anti-VEGF naive patients with diabetic macular edema.
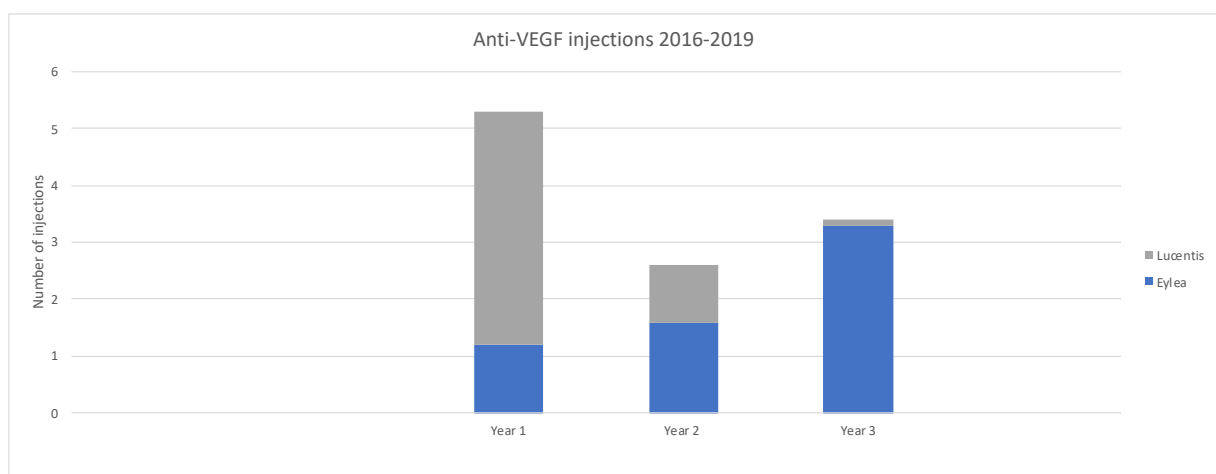
5.4 Adverse effects

Ocular side effects and systemic adverse events over the three-year study period included one case (3%) of uveitis, one case (3%) of vitreous hemorrhage, one case (3%) of amotio and one case (3%) of visual disturbance (spot/floaters). No cases of cataract-formation, endophtalmitis or treatment-demanding ICP increases due to the treatment were recorded during the follow-up period.

Serious side effects or hospitalizations due to treatment were not noted. However, one of the participants had after 5 treatments of ranibizumab injections a myocardial infarction. The participant did not receive any further treatment after the event.

5.5 Participant withdrawal

Before completing 36 months of follow-up a total of 6 participants were withdrawn from the study. 2 participants failed to complete the study due to deaths unrelated to treatment. One within two years from starting the treatment due to cardiac complications of diabetes after not continuing the treatment as a preventive measure after a cardiac infarction and one after 24 months related to the participants diseases. One participant discontinued after 24 months due to nature of the treatment in the form of intravitreal injections. Two participants were withdrawn from further treatment due to stabile vision.

6. DISCUSSION

This study has demonstrated significant improvements in VA and reduction of macular edema by the use of anti-VEGF injections in the treatment of DME over a period of 36 months similarly to other real-world studies published. Approximately 25% of the participants improved their VA with 10 letters or more after 36 months of treatment with a mean improvement of 4.5 and 4.8 letters after 12 and 24 months respectively.

The observed improvements in our retrospective study of real-world data were however significantly lower than the results from the largest randomized clinical trials VISTA and VIVID (25) where participants received aflibercept injections every 4 to 8 weeks with a VA gain of 10.7 and 12.5 letters respectively at 24 months. Other RCTs including DRCR.net Protocol I, RIDE, RESOLVE and RESTORE have resulted in similar VA increases of 6.1 to 13.3 letters at 12 months (26-28).

Kodjikian et al (29) summarized in a wide literature-review (2018) results from 32 real-life observational studies the pharmacological management of (DME) and the efficacy of anti-VEGF and dexamethasone implants concerning 6842 eyes treated with anti-VEGF injections. A mean gain of +4.7 letters for a mean of 5.8 injections with a mean follow-up of 15.6 months was observed with a final VA of 62 letters. VA gains of subgroups of participants with VA<50, 50<VA<60 and VA>60 letters were 10.5, 9.3 and 8.8 letters respectively.

Urbancic et al (30) observed 123 participants in real-world practice to evaluate 2-year visual outcome in patients with DME treated with anti-VEGF injections between January 2016 and March 2019. VA at baseline was 60.9 ± 15.2 letters (median 63, range 7-85) and CRT 440.7 ± 132.5 μm. Participants received 4.5 ± 2.1 (median 5, range 1-9) and 2.6 ± 2.3 (median 2, range 0-8) injections during the first and second year respectively with a VA gain of 2.1 ± 16.8 letters (mean change of $+5.7 \pm 17.9$ letters).s

Curry et al (31) observed prospectively 36 participants over a 2 year period in real-world practice to evaluate the effectiveness of a T&E regimen of aflibercept in a clinical setting in anti-VEGF naive participants (or participants with minimal exposure to anti-VEGF with ≤ 6 treatments in the

previous 12 months) in Australia. 26 participants were eligible to participate in the study. VA at baseline was 69.7 letters (range 59-78) and CRT 416.6 μm (range 309-725 μm). The mean BCVA increased by 3.8 letters and CRT decreased by 127.2 μm at 24 months.

Ziemssen et al (32) observed in a wide real-world setting (OCEAN-study) the efficacy of ranibizumab injections for the treatment of DME with 1226 participants over a period of 24 months in Germany. The study participants received a mean of 4.42 injections during the first 12 months and 5.52 during the second year. Mean VA at baseline was 60.6 letters and during the follow-up a mean VA gain of 4.42 letters at 12 months and 5.52 letters at 24 months was documented. The results are comparable to multiple other smaller studies made and Ziemssen et al concluded that under-treatment with lower number of injections was the largest challenge in real-life setting compared clinical trials. Despite the lower frequency of given injections, VA gains of ≥ 15 letters were achieved at 24 months in 23,5% of eyes.

Bhandari et al (33) observed in the 1-year outcomes from the Fight Retinal Blindness! Registry the efficacy of ranibizumab and aflibercept in clinical practice. A total of 383 eyes of 291 patients were followed from multiple countries. The study participants received a mean of 8 injections when treated with aflibercept and 6 injections when treated with ranibizumab during the 12-month period. Mean VA at baseline was 67.8 for ranibizumab and 64.7 for aflibercept and mean CRT was 407 and 433 μm for respective groups. VA gain at 12 months was higher for aflibercept with a mean gain of 6.1 compared to a gain of 3.3 letters for ranibizumab. Eyes in the aflibercept group showed a significantly greater reduction in CRT compared to those treated with ranibizumab with a mean decrease of 126 μm compared to 89 μm. Aflibercept-treated eyes with worse vision and thicker macula at baseline showed larger VA gains as well as more significant CRT reductions after 12 months of treatment.

The VA improvements in clinical setting appear to be significantly lower in comparison to RCTs based on outcomes since starting anti-VEGF injection treatment in DME. Participants in real life setting receive a significantly lower number of injections compared to participants in clinical trials where the treatment schedule often consists of six monthly injections followed by monthly follow-up visits and injection as required. Participants in our follow-up however received a total of 5.3, 2.6 and 3.3 anti-VEGF injections during year 1, 2 and 3 respectively which is significantly lower than the monthly injections in clinical trials such as RISE and RIDE (22) or the 13.5 and 22.6 injections

during the 24 month period in VIVID and VISTA trials respectively. However, our results are similar compared to other real-world studies including the results from Kodjikian et al where participants received a mean of 5.8 injections with a mean gain of 4.7 letters during a mean follow-up of 15.6 months. Similar results regarding the number of anti-VEGF injections were also documented by Urbancic et al (30) with 4.5 and 2.6 received injections during year 1 and 2. However the authors concluded that the number of injections in their case should be increased in the future in order to achieve better visual outcomes considering the low VA gains.

Participants with lowest baseline VA showed the highest VA gain which is comparable to findings in other studies. Similarly, participants with highest baseline VA showed the lowest VA gain which is regarded as the ceiling effect. These participants however often maintain their high baseline VA well and were therefore prevented from further vision loss. This could also explain the low to moderate VA gain of 4.5 ± (median 3; range -2-8) at 12 months considering the high median baseline VA of 69 letters in our study with a range of 35-85 letters compared to 60 and 65 letters for the VIVID/VISTA and DRCR.net Protocol T trials. (15,8)

OCT imaging is used as the standard for DME diagnosis as early stages of DME may otherwise be missed. However, differences in OCT criteria values occur depending on the used imaging device which results in variation between different studies. For instance the OBTAIN (34) study used an OCT criteria-value of > 250 μm for OCT imaging devices as DRCR network defined the thickness-threshold as > 290 μm in women and > 305 μm in men resulting in significant variation when comparing the baseline OCT values of participants accepted for these studies. Chronic macular edema causes irreversible changes in the retina with time leading to permanent loss of visual function compared to initial development where the loss of visual function is often reversible. Well-defined uniform criteria together with immediate start of treatment if necessary is therefore important to achieve best possible outcome and comparability between studies.

In our study the mean CRT at baseline was for all the participants 373.9 ± 109.1 μm, at 6 months 320.1 ± 86.2, at 12 months 314.5 ± 92.7 μm, at 24 months 307.9 ± 97.4 μm and at 36 months 306.2 ± 103.4 μm. The most significant reductions in mean CRT were observed during the first 12 months and changes much more significant than in visual acuity. These results are comparable with outcome from other real-world studies such as results from Urbancic et al (30) where a CRT

reduction of -101 ± 136.8 μm was measured after 2 years of treatment in eyes with a baseline VA of < 70 letters and -72.4 ± 119.9 with a baseline VA of > 70 letters.

Despite significant results achieved with anti-VEGF treatment, a significant proportion of patients are unresponsive to the treatment and do not achieve clinically significant results in vision as seen in real-world studies. Although corticosteroids offer an additional treatment by treating many of the inflammatory mediators involved, targeting other components of macular edema may lie in the future. According to previous studies only 33-45% (35) appear to respond well to anti-VEGF treatment. The reason remains complex however as it seems like many signaling pathways are not affected by VEGF. This results in many participants with poor to intermediate response to anti-VEGF treatment. Intravitreal corticosteroids have shown to have best efficacy (18) in patients with pseudophakic eyes or patients with planned cataract surgery in the future. Patients with diabetic macular edema undergoing cataract surgery without anti-VEGF treatment resulted in poorer visual outcome compared to patients treated with anti-VEGF (36). Intravitreal corticosteroids have also shown to be more effective in patients who are not able to follow the intensive injection scheme with anti-VEGF injections.

Adherence to monitoring and treatment is one of the major challenges in anti-VEGF treatment. In a German real-world study with 134 participants treated with anti-VEGF a non-adherence rate of 44% was seen (37). Reasons for missed visits were mostly patient-related and included the high visit burden and other comorbidities together with patient age and mobility limitations and lack of motivation in patients.

Concerning adverse effects with anti-VEGF treatment cataract formation has been reported between 0% and 15.4% (29). Statistically significant elevations of IOP in anti-VEGF studies have not been reported according to Kodjikian et al (29). Only one case of endophtalmitis was reported among 31 articles and 2897 injections (29). Reported adverse effects in this study were few. No cases of cataract formation, elevations of IOP or endophtalmitis were documented. No serious ocular adverse events were reported apart from a participant with a myocardial infarction. Although being treated with ranibizumab, considering the participant's excessive history of complications of diabetes including cardiovascular complications with previous myocardial infarctions the event was likely related to the participants underlying condition. Considering the small number of participants, significant conclusions regarding adverse effects cannot be extrapolated.

Limitations of our study include the retrospective nature and a relatively small number of participants. Other limitations include variation in the number of received anti-VEGF injections. Retrospective studies have also some other limitations including the risk of missing data, patients lost to follow-up, high discontinuation rate, under-reporting and therefore possibly lower level of evidence. One of the main limitations with observational real-world studies is that a large number of studies are needed to draw conclusions from them as clinical practices may differ significantly in different clinics.

Strengths of our study include the nature of RWD-studies as well as high rate of participation (93%) which reduces the risk for selection bias. All eye examinations were carried out in the same clinic following the same study protocol.

Considering the high number of available RWD-studies with similar outcome after introducing anti-VEGF in the treatment of DME together with similar baseline and results it is possible to conclude that more intensive monitoring and treatment should be implemented especially in those with low baseline VA under 50 in the future to achieve similar results to those achieved in the largest randomized clinical trials.

In conclusion our study shows significant improvements in VA and reduction in central macular thickness using anti-VEGF injections in the treatment of DME over a period of 36 months. Despite lower number of received anti-VEGF injections in comparison with RCT studies the improvement in VA were maintained for the study time of three years, and the results in our study are similar to other real-world studies published.

7. ACKNOWLEDGEMENTS

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