ORIGINAL RESEARCH

Two Year Visual Acuity and Structural Outcomes in Patients with Diabetic Macular Oedema Treated with Intravitreal Aflibercept – A Retrospective Cohort Study

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Purpose: To assess visual and anatomical outcomes of intravitreal aflibercept for clinically significant diabetic macular oedema (DME).

Methods: For this retrospective single-center cohort study at a tertiary referral center, we performed a data warehouse query to identify 117 treatment-naive patients (139 eyes) undergoing intravitreal treatment with aflibercept for DME between January 2014 and May 2018. Changes in best-corrected visual acuity (BCVA) values (as measured with ETDRS letters), central retinal thickness (CRT) and total macular volume (TVOL) are reported over a two-year period at various time-points.

Results: The total number of injections per study eye was 5.5 ± 1.4 after one and 8.7 ± 2.2 injections after two years. Baseline visual acuity (VA) was 60.1 ± 14.5 letters. A gain of 4.8 and 9.2 letters from baseline was observed after one and two years, respectively (both $p \leq 0.01$). In comparison to the mean CRT at baseline (419 ± 174 µm), a CRT decrease was observed after one and two years of treatment (298 ± 115 µm and 319 ± 119 µm, respectively; both $p \leq 0.01$). Similarly, TVOL decreased from 10.12 ± 2.05 mm^3 to 8.96 ± 0.96 mm^3 and 9.01 ± 1.29 mm^3 (both $p \leq 0.01$).

Conclusion: This study demonstrates that treating DME with intravitreal aflibercept yields positive functional and structural outcomes over a two-year period. However, we observed fewer injection numbers, along with inferior VA and structural outcomes than has been reported in randomized clinical trials. Our results show similar results as in patients treated with ranibizumab due to DME in real-life settings.

Keywords: aflibercept, diabetic macular oedema, visual acuity, central retinal thickness

Introduction

In clinical settings, the frequency of anti–VEGF injections for diabetic macular oedema (DME) is less than in landmark studies.[1–3] In light of this, there is increasing controversy regarding the extent to which this negatively impacts functional and anatomical outcomes in real-life cohorts.[4]

The worldwide prevalence of diabetes mellitus (DM) is expected to rise from 415 million in 2015 to 642 million in 2040.[5] In conjunction with an increasing life expectancy of people with diabetes, diabetic retinopathy (DR) and its complications are an emergent cause of visual impairment.[6] With 21 million patients worldwide, DME is the most common reason for moderate vision loss in patients with DM and expected to increase in the future.[7]

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Visual prognosis was guarded in patients with DME prior to the introduction of anti–vascular endothelial growth factor (anti–VEGF).[8] In DME, the superiority of an anti–VEGF agent (bevacizumab) over focal laser was shown in the BOLT study with a gain in visual acuity (VA) of 8.0 Early Treatment Diabetic Retinopathy Study (ETDRS) letters versus 0.5 ETDRS letters in the laser group following one-year treatment.[9] The RESOLVE and RESTORE studies followed shortly, where efficacy and safety of ranibizumab treatment, as well as its superiority over laser treatment, was demonstrated.[10,11] These results were confirmed by several other prospective clinical trials, such as the RISE and RIDE study.[12] In 2014, aflibercept was shown to be superior to focal laser in DME in terms of functional and anatomical endpoints in the VISTA and VIVID trials.[13] The effect of aflibercept in treating DME is not only based on VEGF inhibition alone but also on an anti–inflammatory mechanism of action, namely the inhibition of the recently described Placental growth factor (PlGF) and extracellular signal-regulated protein kinase (ERK) pathway.[14] Notably, all the above-mentioned studies were prospective randomized clinical trials (RCT) and featured the same treatment regimen, i.e. intravitreal anti–VEGF injections were given in fixed intervals.

In comparison to these landmark RCTs, retrospective cohort studies performed in the UK, Denmark, France and Germany have reported considerably fewer injections per eye and worse visual outcomes.[15–18] It is therefore pertinent to consider whether this disparity in visual outcomes between RCTs and real-life data is accounted for by fewer anti–VEGF treatments, as reflected in real-life settings. This retrospective cohort study investigates the visual and anatomical outcome of treatment-naive DME patients treated with intravitreal aflibercept over two years in a national tertiary referral center.

Methods
Study Setting and Design
This is a retrospective cohort study performed at the University Eye Hospital at the Ludwig-Maximilians University, Munich, Germany. This study was designed to report on real-life VA and structural outcomes including retinal volumetrics for DME patients treated with aflibercept at a tertiary referral center. Ethical approval for this study was obtained from the Institutional Review Board of the University Eye Hospital Munich in Germany. The study adheres to the Declaration of Helsinki. All data

warehouse queries were approved by the local data protection officer. Written informed consent for the retrospective use of anonymized data was provided by all patients included in this study.

Data Source and Patient Characteristics
Clinical information was extracted from a data warehouse that has been active since 2012.[19] It contains clinical findings from the patients' electronic health record (EHR) and investigative results of more than 330,000 patients.[20] This includes retinal thickness and volume values in the nine circular macular grids defined by the ETDRS study group obtained from optical coherence tomography (OCT) imaging (SPECTRALIS, Heidelberg Engineering, Heidelberg, Germany). Segmentation errors were manually verified in the Heidelberg Eye Explorer (SPECTRALIS viewing software).

Data warehouse queries with the following criteria were performed. Firstly, all eyes with the ICD-10 coded diagnosis of DM type one or two, and diabetic eye disease (ICD-10: E10.3 and E11.3) were identified (8084 eyes; 4072 patients).[21] Only eyes that were anti–VEGF treatment naïve and received intravitreal injections with aflibercept from January 2014 to May 2018 were selected (139 eyes; 117 patients). Patients receiving intravitreal injections with other drugs (bevacizumab, ranibizumab, or steroids) were excluded from the study. Moreover, patients with other ophthalmic comorbidities like age-related macular degeneration [H35.3] and retinal vein occlusions [H34.8] were also excluded.

Treatment Regimen
Since approval by the European Medicines Agency (EMA) in 2014, aflibercept has been available as a first-line treatment for DME.[22] Patients were initiated on a loading phase of three monthly intravitreal aflibercept injections, followed by injections if needed as per clinicians' discretion.

Study Outcomes
The main study outcomes were change in mean best-corrected visual acuity (BCVA) and (central retinal thickness) CRT. The BCVA was defined as the VA value tested with correction of auto-refraction measurements (ARK-1s, Nidek, Gamagōri, Japan) using an ETDRS chart. If no ETDRS letter score was available, the decimal visual acuity was used for extrapolation to ETDRS letters. In these cases, the median ETDRS value of all eyes from this cohort within the same decimal visual acuity was chosen. CRT signifies the central

foveal thickness in ETDRS grid I (as defined by the ETDRS study group) calculated by the SPECTRALIS OCT at a given visit. Secondary outcome measures were: the total macular volume (TVOL), the mean number of injections delivered per study eye; the proportion of eyes within a change in VA less than 10 and 15 ETDRS letters and gain or loss of ≥10 and ≥15 ETDRS letters, respectively. TVOL was defined as the total retinal volume within the macular ETDRS grid and reported in mm^3. All outcomes were reported for baseline (measurements prior to the first injection), day 30, 60, 120, 150,180, 360, 540, and 720 following the first injection. Timepoints 360 and 720 were considered one-year and two-year outcomes. To unify checkpoints, values for the timepoints were generated by linear interpolation for each eye. That is, in the absence of a BCVA value at a given time-point (eg day 30), a value was extrapolated via linear interpolation from temporally proximal measurements (eg at day 21 and 35). If a patient missed the timepoint at all (eg measurements available at baseline and day 68), no data for the day 30 timepoint were interpolated and the patient was defined as lost-to-follow -up onwards in the analysis.

Statistical Methods

All statistical analysis was performed by using the programming language "R" (R Foundation for Statistical Computing, Vienna, Austria).[23] The number of eyes eliminated from analyses was reduced by using a last-observation-carried-forward (LCOF) method for the two years observation timepoint. Mean values between two different timepoints were compared by Wilcoxon Rank-Sum test. Levene's test was performed for all timepoints to assess the homogeneity of the variances. Calculated means in text and figures are expressed with ± error margin corresponding to the standard deviation, unless otherwise specified. A p-value < 0.05 was considered statistically significant. The Wilcoxon-Mann–Whitney test was used to compare outcomes between subgroups. Due to the diverging group size, p-values could not be reported.

Results
Patient Characteristics and Treatment Frequency

At baseline, 139 eyes of 117 patients were included in the analysis. The mean age was 62.2 ± 11.8 and 68% of the patients were female. 5.5 ± 1.4 and 8.7 ± 2.2 aflibercept injections were delivered per study eye in year one and year two, respectively (Table 1).

Visual Acuity Outcomes

We observed an improvement of visual acuity over the observation period of two years (Figure 1; Supplemental Table 1). A statistically significant gain in mean VA was observed at each of the time-points from day 60 onwards. Mean VA at baseline was 60.1 ± 14.5 letters compared to 64.9 ±15.9 and 69.3 ±12.1 ETDRS letters after one and two years, respectively (both p≤ 0.01). At year one, the proportion of eyes gaining more than 10 and 15 letters (26.4% and 16.5%, respectively) was greater than those who lost more than 10 and 15 letters (2.2% and 6.6%). This trend was also observed after two years with 35.5% and 29.0% gaining more than 10 or 15 letters, whereas 3.2% and 0% lost the same number of letters, respectively (Figure 2; Supplemental Table 2).

Structural Outcomes

In comparison to baseline, a statistically significant decrease of CRT was observed for all time-points (Figure 1; Supplemental Table 1). Improvement was greatest at the first observational time-point (342 ± 115 μm at 30 days from 419 ± 174 μm at baseline; p=0.133) and decreased progressively up to a steady-state (approximately 300 μm) after 90 days (p=0.01) until the end of the observation period. Likewise, statistically significant improvement compared to baseline was observed for TVOL (Figure 3; Supplemental Table 1). Total macular volumes decreased from 10.12 ± 2.05 mm^3 at baseline up to a plateau of approximately 9 mm^3 after 180 days (p≤ 0.01).

Table 1 Patient Characteristics

	Baseline	90 Days	One Year	Two Years
Patients (n)	117	107	82	31
Eyes (n)	139	122	91	31
Gender female (n; %)	38 (32.5%)	34 (31.8%)	27 (32.9%)	11 (35.5%)
Mean age (years)	62.2 ± 11.8 [33.0 to 93.0]	62.3 ± 11.3 [33.0 to 88.0]	61.7 ± 10.4 [40.0 to 88.0]	61.1 ± 9.6 [40.0 to 80.0]
Total injections (n)	0	2.9 ± 0.6	5.5 ± 1.4	8.7 ± 2.2

Note: n = number.
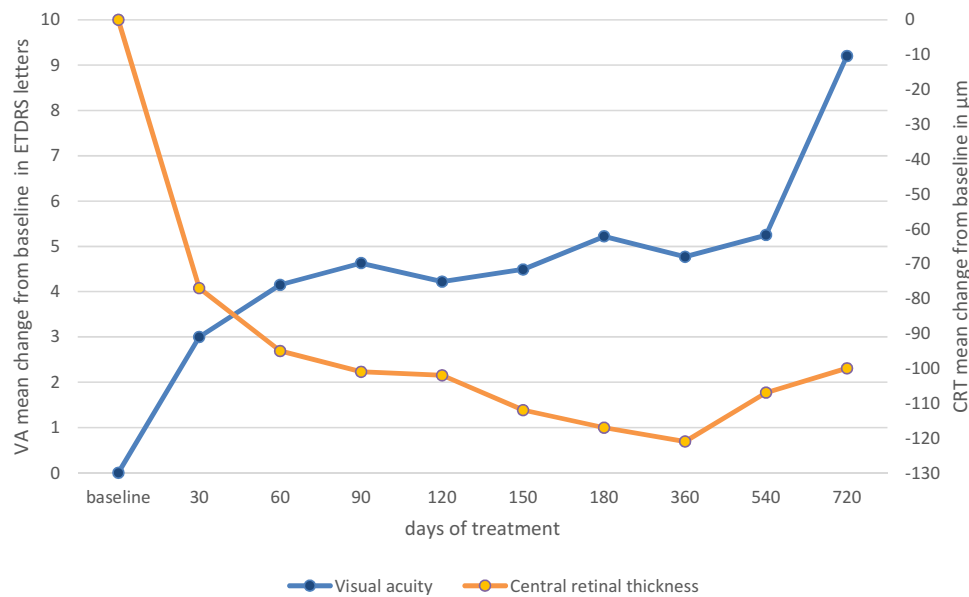
Figure 1 Mean change in visual acuity (VA; y-axis left) and central retinal thickness (CRT; y-axis right) from baseline over observation period.
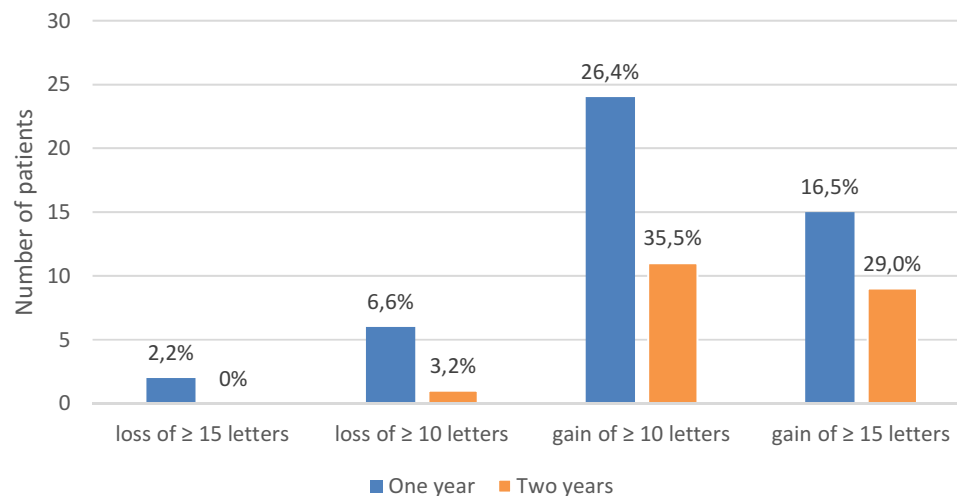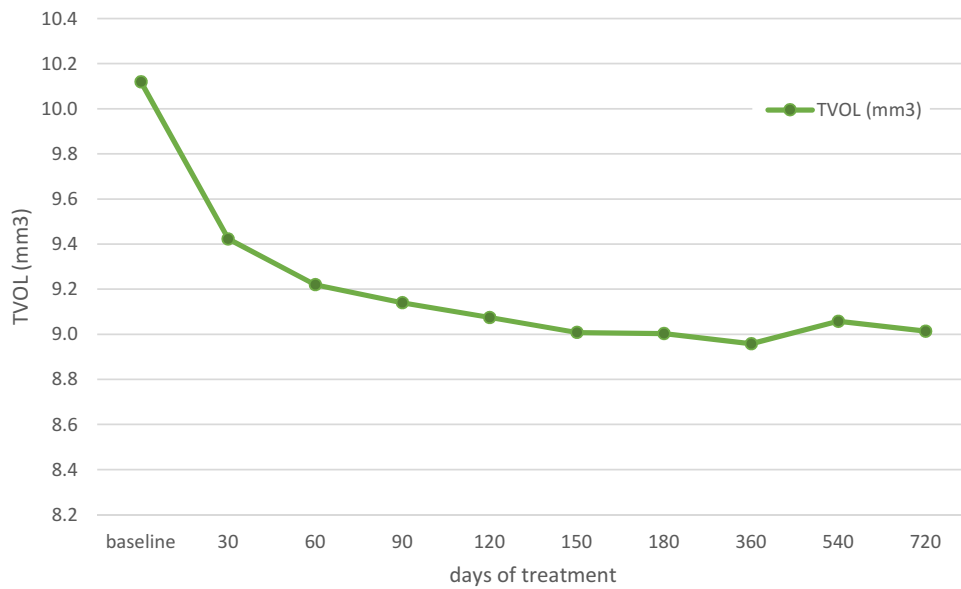

Figure 2 Change in visual acuity from baseline after one and two years of observation. Number of patients is provided on the y-axis. Bar figures indicate the number of patients (%) with a certain gain/loss of letters compared to all observed patients at this timepoint.
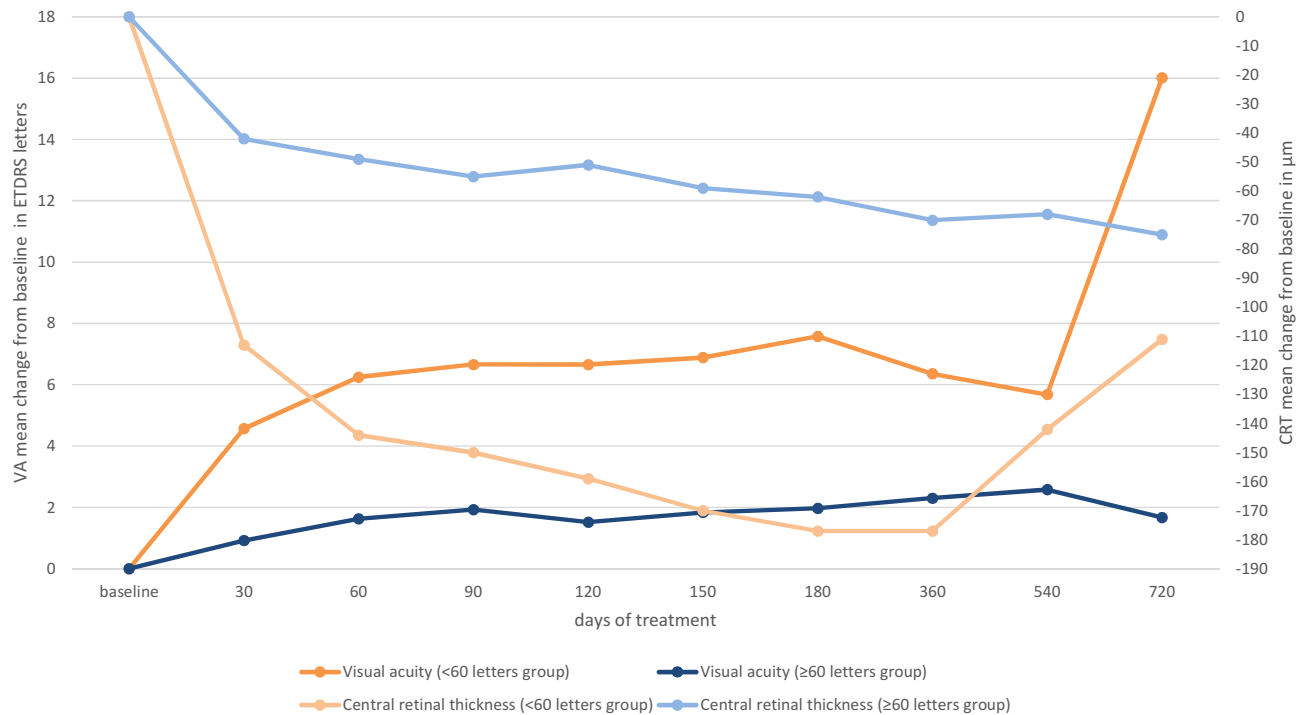
Outcomes Stratified by Baseline Visual Acuity

VA at baseline has previously been described as an independent predictor of visual and structural outcomes following treatment with anti-angiogenic therapy in DME.[24] The median BCVA was 60 letters in this cohort. This cut off was used to stratify our results accordingly. Our data shows that gain in VA was higher in eyes with baseline VA < 60 letters compared to those ≥60 letters (Figure 4, Supplemental Table 3). Mean baseline VA of the cohort with a baseline VA < 60 letters were 47.1 ± 8.4 letters,

which improved to 53.4 ± 14.3 and 63.1 ± 15.4 letters at years one and two, respectively (both, p≤ 0.01). This contrasts with eyes with a baseline VA ≥ 60 where the mean VA at baseline was 71.6 ± 7.3 compared to 73.4 ± 10.3 and 73.4 ± 7.6 after one (p=0.01) and two years (p=0.06), respectively. When compared to baseline, mean changes in VA were statistically significant for all timepoints in the <60 letters cohort. However, statistically significant differences in the ≥60 letters groups were only evident at 90, 180, and 540-day timepoints (Supplemental Table 3).

Figure 3 Total volume (TVOL) of the macular ETDRS grid during observation period.

Figure 4 Change in visual acuity (y-axis left) and central retinal thickness (y-axis right) from baseline over observation period stratified by baseline visual acuity.

A similar trend was observed for structural outcomes: Eyes with baseline VA ≥ 60 letters showed lower absolute CRT values than those <60 letters at year one (314 μm and 285 μm, respectively) and two (318 μm and 280 μm, respectively), but the cohort with baseline VA < 60 letters featured the greatest improvement of CRT ([Figure 4](#), [Supplemental Table 3](#)). Improvement in CRT was statistically significant for both subgroups for all time-points ($p \leq 0.01$).

Discussion
Main Findings
In DME patients treated with aflibercept only, we observed statistically significant improvements in VA and CRT after

one and two years. Mean injections delivered per study eye over one and two years were 5.5 and 8.7, respectively. The lower amount of injections administered during the second year of treatment might be related to the disease-modifying character of anti–VEGF in DME.[25] VA increased by 4.8 and 9.2 letters in years one and two when compared to baseline (60.1 ± 14.5 letters; p≤ 0.01). This functional improvement went along with a decrease in CRT from 419 μm to 298 μm after one year and to 319 μm after two years. From 139 eyes at baseline, treatment duration was less than the observation period in 48 (34.5%) and 108 (77.7%) eyes after year one and year two for reasons discussed later.

Clinical Outcomes in RCTs are Superior to Real-Life Data

In RCTs with fixed injection regimes of ranibizumab, the visual and structural outcomes were superior to our study results.[12,13,26,27] This was likely achieved through higher treatment frequency with up to 12 and 22 injections after years one and two, respectively. Indeed, similar results are reported in RCTs assessing the efficacy of aflibercept therapy only, with again up to 12 delivered injections per study eye over one year.[13,26] Throughout all RCTs cited above, the gain in VA was greater than what was observed in our real-life cohort study (4.8 letters after one year). A concomitant and similar trend in CRT is present, with the RCTs reporting a decrease of 169 μm to 195 μm at year one in contrast to 121 μm in this real-life cohort. In addition to higher injection numbers, stricter patient selection, exclusion of non-adherent patients, and early detection of complications may account for the difference in outcomes observed between cohorts in clinical trials and everyday clinic.[28]

Comparing Our Results to Published Real-Life Data

Several real-life studies have been published for ranibizumab in DME treatment.[2,15,17,18,29-32] A commonality of these studies is that the number of injections, functional outcomes, and structural outcomes are comparatively worse than in the pivotal RCTs. Even though our study reports values that are consistent with the real-life data previously published for DME patients undergoing anti–VEGF treatment, direct comparison is impossible. The heterogeneity between the retrospective cohorts as well as treatment outcomes can be overseen in Table 2.

A French study group reported a gain of 10.7 letters at 12 months from only 5.4 injections, which seems outstanding at the first glance. In fact, this above-average gain is resulting from the cohorts' low baseline VA of only 48 letters, which has been described as an independent predictive factor in anti–VEGF treatment for DME.[24] Our results fit into the decrease in CRT after one year, which ranges between 20% and 30% from baseline, independently of baseline thickness.[2,15,17,29,32] Almost 90% of DME patients have a sponge-like structure on OCT which causes diffuse retinal swelling.[33] Therefore, both CRT and TVOL should be considered when observing treatment outcomes in eyes with DME. Total macular volume in healthy eyes is reported to be around 8.5 mm^3.[34] We observed a TVOL of approximately 9 mm^3 in DME patients undergoing intravitreal treatment after two years, which might suggest residual cystoid fluid within the macular area even after long-term treatment.

So far, real-life data on aflibercept treatment in eyes with DME is rare. A recently published study including 102 eyes from the United Kingdom describes a similar structural improvement in patients treated with aflibercept only as observed in this study.[32] Interestingly, the one-year visual acuity gain was higher than in our cohort (+9.9 vs. +4.8 ETDRS letters). An explanation for this fact might be as published before, the struggle with low compliance and high non-adherence rates of our patients.[28] This results in a lower amount of injections delivered per study eye (6.9 vs. 5.5), concomitantly resulting in a lower gain of VA in this cohort.

Reasons for Treatment Period Being Less Than Observation Period

Generally, a retrospective cohort study is more error-prone than a prospective observational study due to the high lost-to-follow-up rate.[35] We report 34.5% (48 eyes) and 77.7% (108 eyes) not being observed further onward beyond year one and two, respectively. The main reason for this in our dataset is that the treatment duration of study eyes is less than the observation period. There are several reasons for treatment duration being less than observation period: (i) study eyes received an upload of three aflibercept injections before being referred to their private ophthalmologist for further treatment; (ii) intravitreal therapy has been finished successfully; (iii) real loss-to-follow up. In total 20 out of 139 eyes were discharged after an initial upload of 3 aflibercept injections to further care of a not hospital-based ophthalmologist. In 43

Table 2 Selected Retrospective Real-Life Results of Eyes Treated with Anti–VEGF for DME After 12 Months. For VA, CRT and Number of Injections Mean Values are Reported

	Eyes @ Baseline (n)	VA @ Baseline (ETDRS Letters)	Δ VA (ETDRS Letters)	CRT @ Baseline (μm)	Δ CRT (μm;%)	Anti–VEGF Agent	Injections (n)
Maggio et al[2]	170	63.0	5.0	518	−104 (20,1)	R	5.7
Patrao et al[15]	200	54.4	6.6	490	−134 (27,3)	R	7.2
Hrarat et al[17]	106	48.3	10.7	519	−164 (31.6)	R	5.4
Wecker et al[18]	479	61.0	6.2	n/a	n/a	R	6.0
Best et al[29]	72	56.5	6.9	470	−108 (23.0)	R	5.3
Holekamp et al[30]	121	56.9	4.7	n/a	n/a	R	3.1
Ziemssen et al[31]	1226	60.6	4.4	n/a	n/a	R	4.4
Lukic et al[32]	99	59.7	9.9	431	−125 (29.0)	A	6.9
This study	139	60.1	4.8	419	−121 (28.9)	A	5.5

Note: R=ranibizumab; A=aflibercept.

and 87 eyes respectivley, the therapy has been finished successfully before the observation point after one and two years was reached. Calculating the difference between eyes not being further observed and category (i) and (ii) leaves us with an estimated real loss-to-follow- up rate compared to a baseline of 3.5% (5 eyes) after year one and 13.7% (19 eyes) after year two. Poor compliance and treatment adherence are known explanations for lost-to-follow-up in patients treated for DME.[28] We used appropriate statistical methods and a last-observation-carried-forward approach for the last observation point to minimize the bias resulting from eyes with observation time being less than study time. We are fulfilling the recommended follow-up threshold being above 60% for our one-year results.[35]

Implications for Practice and Research

This study implies that functional and structural outcomes achieved with aflibercept as a first-line agent for DME are comparable to the results achieved with ranibizumab in a real-life setting. Prospective multicenter studies comparing aflibercept and ranibizumab in a real-life setting are necessary to verify treatment outcomes, even though in the light of the high inconsistency of real-life cohorts (Table 2). Moreover, the comparability between available anti–VEGF agents should be addressed specifically to obtain results with a higher level of evidence.

Interestingly, each eye should have received eight injections within the first year if the treatment regimen (as according to the label) was followed strictly. This is 2.5 injections more than observed in this study with a mean number of 5.5 injections. Reasons for this

mismatch include all, cancelled or not attended appointments from the patient side as well as holidays or administrative reasons such as capacity constraints. The identification of these reasons is an important aim for further studies. Improvement in treatment frequency can only be achieved if the limiting factors are well known. Two-year functional and structural outcomes provided by this study give an estimate about the therapeutic regime in DME patients when choosing aflibercept as a first-line anti–VEGF agent. Informing the patient about the probable number of delivered injections during year one and two of treatment may be beneficial for compliance and adherence.

Conclusion

Almost all RCTs report better functional and structural outcomes than real-life observations. The limited capacity of everyday practice and patient behavior (ie, missed and cancelled appointment) result in fewer injections and therefore worse outcomes in real-life cohorts. More than a third of eyes gained more than 10 ETDRS letters, compared to 3% of eyes losing the same number of letters for two years observation period. Here, we report outcomes consistent with previously reported real-life data in ranibizumab patients, thus providing further evidence that intravitreal aflibercept is an effective treatment for DME patients to achieve positive functional and structural outcomes over a minimum of two years.

Data Sharing Statement

The data described in this article are openly available in the Open Science Framework at DOI:10.17605/OSF.IO/TPA6U.

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