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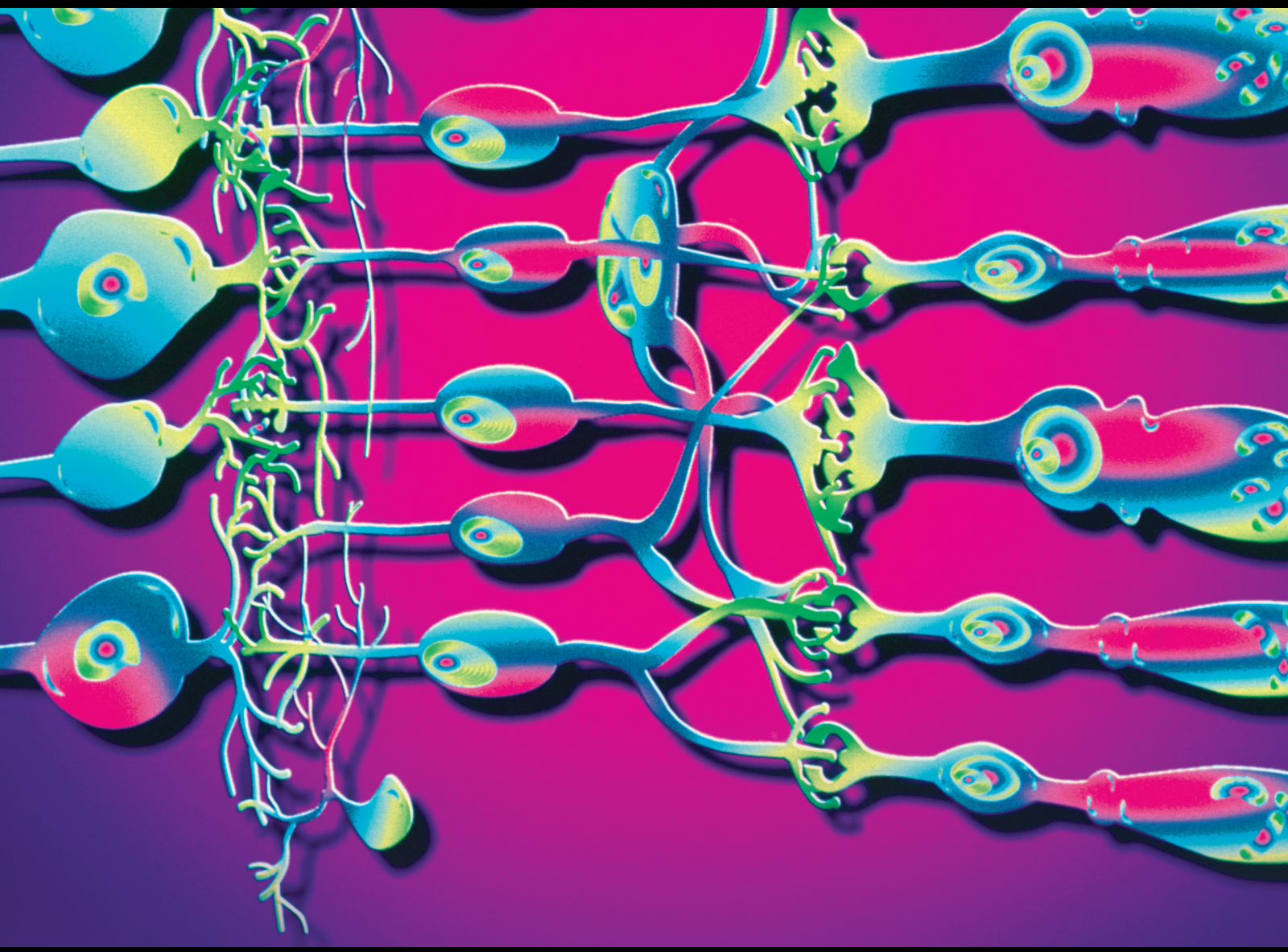

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Research Article

Long-Term Visual Outcomes for a Treat-and-Extend Antivascular Endothelial Growth Factor Regimen in Eyes with Neovascular Age-Related Macular Degeneration: Up to Seven-Year Follow-Up

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Purpose. To report long-term visual and anatomical outcomes in eyes with neovascular age-related macular degeneration (nAMD) treated with a treat-and-extend regimen (TER) of intravitreal antivascular endothelial growth factor (anti-VEGF) injections in real-world settings. *Methods*. Retrospective cohort study of consecutive patients with nAMD treated with a TER of anti-VEGF intravitreal injections by a single retina specialist (GC). Patients with nAMD who had at least one year of follow-up were identified using an electronic database. Best-corrected visual acuity (BCVA), comprehensive ophthalmologic examination, and macular OCT were performed at each visit. Patients received a loading dose of three monthly intravitreal injections and then were treated according to a TER of bevacizumab, ranibizumab, and/or aflibercept. The number of injections, BCVA, and central retinal thickness (CRT) were evaluated during the follow-up period. *Results*. 180 eyes from 180 patients were included in the study. Mean age was 75 ± 9 (range: 51–96). Mean BCVA was 0.77 ± 0.64 LogMAR at baseline, 0.69 ± 0.58 LogMAR ($p = 0.0057$) after loading phase, 0.64 ± 0.55 LogMAR ($p = 0.0001$) after 6 months of TER, and 0.76 ± 0.71 LogMAR after 6 years of treatment ($n = 32$ at year 6). CRT decreased significantly after the loading phase ($p = 0.0002$). The mean number of intravitreal injections per year was 7.6 during the first three years of treatment and then decreased to 5.9 during year 4 to 7. *Conclusions*. This retrospective study of 180 nAMD patients treated with a TER of intravitreal anti-VEGF demonstrates an initial improvement of BCVA after loading phase, followed by long-term visual stabilization for at least six years. These results were obtained with a high number of injections, averaging close to six injections per year during long-term follow-up. In light of the natural evolution of nAMD, these data support the long-term efficacy of this treatment under real-world conditions of heterogeneity of patients and type of anti-VEGF used.

1. Introduction

Age-related macular degeneration (AMD) is a major cause of visual impairment and blindness in the elderly population [1]. It is responsible for 46% of cases of severe visual loss in patients over the age of forty [2]. Neovascular AMD (nAMD) occurs in only 10% of patients with AMD but is responsible for most cases of blindness [3]. The management of nAMD has seen a tremendous breakthrough with the introduction of intravitreal (IVT) anti-VEGF injections: pegaptanib sodium in 2004, off-label bevacizumab in 2005, ranibizumab in 2006, and aflibercept in 2011 [4].

In 2006, the ANCHOR and MARINA trials demonstrated the safety and efficacy of ranibizumab in nAMD compared to sham and verteporfin photodynamic therapy [5, 6]. Subsequently, bevacizumab was shown to be noninferior to ranibizumab in terms of efficacy in the IVAN and CATT trials [7, 8]. Aflibercept injected monthly or every two months, after a loading dose of 3 monthly injections, was also shown to be noninferior to the monthly regimen of

ranibizumab in the VIEW 1 and 2 trials [9, 10]. Anti-VEGFs have since become the first-line of treatment in most cases of nAMD.

However, these pivotal trials were based on monthly injections, which in real-life long-term settings are of significant burden for patients, caregivers, healthcare practitioners, and healthcare systems [11]. Alternative treatment regimens therefore emerged. The PrONTO prospective study in 2009 introduced the Pro-Re-Nata (PRN) regimen consisting of a loading dose of 3 consecutive monthly injections, followed by monthly visits with OCT-guided retreatment based on disease activity. After 2 years of PRN regimen, they achieved similar visual outcomes in comparison to monthly injections, but with fewer intravitreal injections [12]. However, subsequent studies observed that the PRN regimen may not offer the same results demonstrated in the PrONTO study [13, 14].

Real-life data issued from the landmark trials for nAMD treatment was examined in the SEVEN-UP study [15]. Long-term outcomes from the ANCHOR and MARINA trials could not be extrapolated from the 2-year results and frequent injection was found to be needed in order to preserve visual acuity in the long run [15]. The need for an alternative treatment regimen offering adequate outcomes while requiring less frequent visits was evident; the idea of an individualized strategy known as "treat-and-extend regimen (TER)" was introduced in 2007 by Richard Spaide [16]. TER consists of a loading phase of 3 monthly injections, followed by a maintenance phase where patients are given an injection at each visit and treatment interval is gradually extended or shortened, based on the absence or presence of disease activity [17]. Several trials have since demonstrated the efficacy of TER, but visual acuity outcomes remained inferior to the data obtained in the original landmark randomized clinical trials [18–20].

With the intent of promoting data-driven practices, we conducted this study to assess the real-world long-term outcomes of intravitreal anti-VEGF treatment based on the TER in patients with nAMD.

2. Methods

This study was designed as a retrospective cohort study of consecutive patients followed and treated for nAMD by a single retina specialist (GC) at a single private retina practice in Montreal, QC, Canada, between 2009 and 2017. Patients included in the study were those with a diagnosis of nAMD who were receiving anti-VEGF injections on the basis of the TER and who had at least 12 months of follow-up after their first injection at our clinic; we excluded patients that did not have a proper loading phase (defined as less than 3 monthly injections within a timeframe of up to 18 weeks) or that were not compliant to TER during the first year of follow-up and treatment (noncompliance was defined as a missed visit, with a delay superior to one month in the subsequent visit after the missed visit). Patients were not excluded on the basis of noncompliance after the first year of follow-up and treatment. All patients were older than 50 years with either a newly diagnosed treatment-naïve nAMD or a previously treated nAMD. Patients with visual acuity worse than 20/320 (Snellen) were also included in the study, in contrast to the MARINA trial [6]. In patients with bilateral disease at first visit, we randomly selected which eye to include in the study. Exclusion criteria included choroidal neovascularization (CNV) secondary to other maculopathies, diabetic retinopathy, vein occlusions, and inflammatory maculopathies. Patients previously treated elsewhere using photodynamic therapy, intravitreal steroids, or thermal laser were not excluded. Patients with other common ocular comorbidities such as cataract or glaucoma were also not excluded. Data was sampled at baseline visit, month 3 (after loading phase), month 6, year 1, and then every "6 months" after that. Of note, some patients had few visits per year and therefore would have a visit not exactly at midyear or beginning of a year; in those cases, we attributed that data to the closest date it would correspond to, that is, either midyear or beginning of a year. In a minority of cases, patients had so few visits that data sampling at a specific timepoint did not occur although the patient's data was still sampled at the precedent and following timepoint (but with no visit/data in between). Also, in order to be eligible for the number of injections per year and anti-VEGF agent used per year analysis, only complete years of follow-up were considered; in situations where patients had a follow-up of, for instance, six years and a few months, only the complete six years were presented in those analysis, and the remaining months of the incomplete year seven were discarded (no extrapolations were made).

We identified 186 patients eligible for participation in the study. Six patients were excluded because of incomplete charts due to concomitant follow-up elsewhere. Ultimately, 180 eyes from 180 patients were included in the study. Data extracted from the charts included baseline characteristics such as demographics (age and sex) as well as past ocular history (lens status, history of glaucoma or pars plana vitrectomy). Information from the initial ophthalmic visit and subsequent follow-ups was also recorded, including involved eye, BCVA (Snellen), the intravitreal anti-VEGF agent injected (bevacizumab, ranibizumab, or aflibercept), central retinal thickness (CRT) as seen on OCT, and ophthalmic adverse events. The local research department confirmed that no ethical approval was required given the retrospective nature of this study, as there was no deviation from the usual standard of care. This study was conducted in concordance with the World Medical Association Declaration of Helsinki.

In order to better study the obtained data, we divided the cohort in two subgroups according to the treatment status at initial presentation: the "treatment-naïve" subgroup consisted of eyes with no previous nAMD treatment prior to first injection at our clinic, and the "previously treated" subgroup contained eyes that had received previous nAMD treatment (including prior anti-VEGF injections) prior to first injection at our clinic.

2.1. Treatment Regimen. Patients underwent an initial loading phase of 3 consecutive monthly injections. Subsequently, injections were given on a monthly basis until disease stability. The treatment intervals were then extended

by 2 weeks per interval, up to a maximum of 12 weeks. If there were signs of recurrent disease at a given follow-up, (1) if the dosing interval was 6–8 weeks, the interval was decreased by 2 weeks and (2) if the dosing interval was 10–12 weeks, the interval was decreased by 4 weeks. This algorithm would be followed until resolution of recurrent disease. On the second attempt at extending, if disease instability occurred at the same interval as the previous recurrence, no further attempt was made to extend, and the last stable interval was maintained assuming disease stability. Disease instability was defined as new or persistent haemorrhage, intra- or subretinal fluid on OCT or leakage on fluorescein angiography (FA); FA was performed when available and not on a routine basis. Our definition of disease stability is absence of disease instability. In cases of severe recurrences, particularly if associated with new haemorrhages, the treatment interval would immediately be reduced back to monthly injections.

2.2. Choice of Anti-VEGF Agent and Injection Technique. Patients were treated with 0.5 mL IVT injections of either bevacizumab 1.25 mg (Avastin®), ranibizumab 0.5 mg (Lucentis®), or aflibercept 2.0 mg (Eylea®). These drugs were obtained commercially. Careful aseptic technique was used to fill the syringes directly from the vial. Topical anesthesia with proparacaine hydrochloride (0.5%) and asepsis with 5% povidone-iodine solution were applied prior to injections. Injections were performed 3.5 to 4.0 mm posterior to the limbus in the inferotemporal quadrant. The choice of anti-VEGF agent was guided by Dr. GC, based on his discretion and on the provincial funding for anti-VEGF agents. The decision to switch from one anti-VEGF agent to another was mostly based on the persistence of CNV activity (intra- or subretinal fluid) despite six consecutive monthly injections.

2.3. Optical Coherence Tomography (OCT). OCT imaging was performed on all patients. Between 2009 and 2017, the OCT machines used were the CIRRUS 5000 machine (Carl Zeiss Meditec, Jena, Germany) and the Nidek RS-3000 (Nidek, Gamagori, Aichi, Japan). Eyes with available central retinal thickness (CRT) (measured using the map provided with the OCT software) were included in the analysis of CRT through the follow-up period. Adjustments were made to correct for different types of machines by converting CRT from Nidek RS-3000 (RS) to Cirrus (CR) equivalent using the following formula: $CR = 8.00 + 1.01 \times RS$.[21]. In 2016, a data loss occurred in the Nidek machine leading to significant loss of CRT data from 2009 to 2016. Patients with no baseline CRT were therefore excluded from the CRT analysis since their baseline OCTs were not available.

2.4. Statistical Analysis. The primary outcome measures were BCVA over time and the number of injections per year, following the first injection, from years one to seven. Secondary outcomes included the anti-VEGF agent used and CRT. BCVA was measured on an imperial scale (Snellen) and converted into LogMAR for statistical analysis [22]. LogMAR visual acuities were also converted to equivalent ETDRS letter scores to illustrate the distribution of change in BCVA from baseline [23]. Of note, in Figures 1 and 2, we also presented BCVA data in ETDRS equivalent ± Snellen equivalent to ease interpretation for readers [24]. Baseline demographics were summarized by presenting the number and percentage for categorical variables and the average ± standard deviation (SD) for continuous variables. The association between variables was tested using unpaired and paired *t*-test for continuous variables with a parametric distribution. For continuous variables with a non-parametric distribution, the Mann–Whitney *U* and Wilcoxon signed-rank tests were used. Because the duration of follow-up was heterogeneous within the cohort due to different inclusion timepoints for each patient, the analysis was performed at regular intervals: 3 months, 6 months, 1 year, and every six months after. Differences with a p value less than 0.05 were considered statistically significant. p values were not adjusted for multiple comparisons. Statistical analysis was conducted using Microsoft Excel (Microsoft Corp., Redmond, WA).

3. Results

3.1. Baseline Demographic Characteristics. One hundred eighty participants (180 eyes) were included in this study. The mean follow-up per patient was 4.0 ± 1.5 years (range: 1 to 7 years) during the study period. Table 1 illustrates baseline characteristics of patients prior to first injection at the clinic.

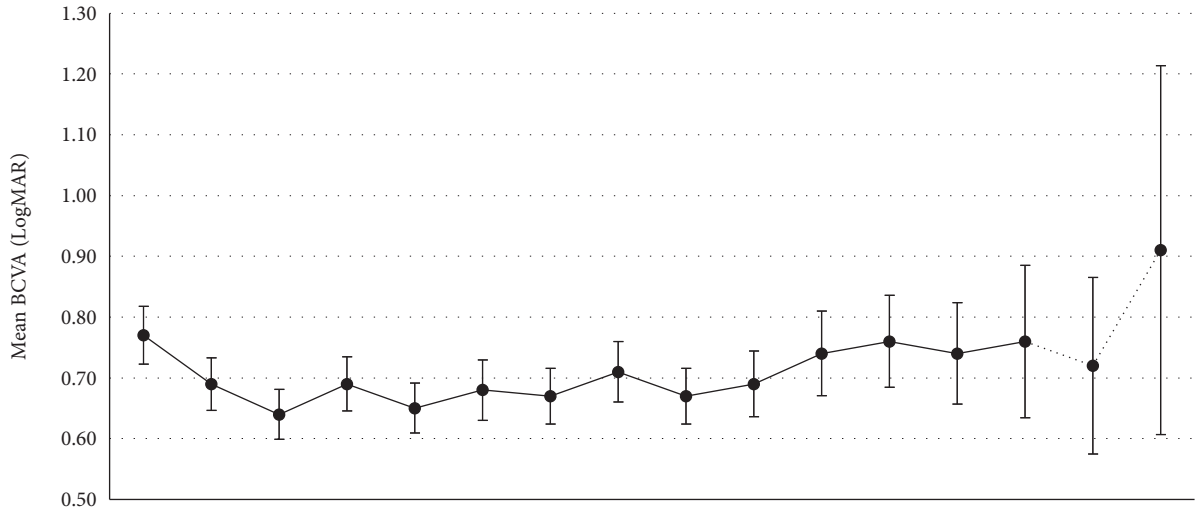
There were 105/180 (58.3%) female patients. The mean age was 75 ± 9 with ages ranging from 51 to 96. Regarding past ocular history, 92/180 eyes (51.1%) were pseudophakic, 15/180 (8.3%) had glaucoma and 1/180 (0.6%) had previous pars plana vitrectomy surgery.

Although 121/180 (67.2%) eyes were treatment-naïve at baseline, 59/180 (32.8%) had a history of past nAMD treatment(s): 58/180 (32.2%) IVT anti-VEGF injection(s), 1/180 (0.6%) IVT corticosteroid injection(s), and 3/180 (1.7%) argon laser for extrafoveal CNV. None had previous photodynamic therapy.

Eye involvement at baseline was as follows: 146/180 (81.1%) patients had nAMD in a single primary eye at initial presentation and 34/180 (18.9%) patients had bilateral disease at initial presentation.

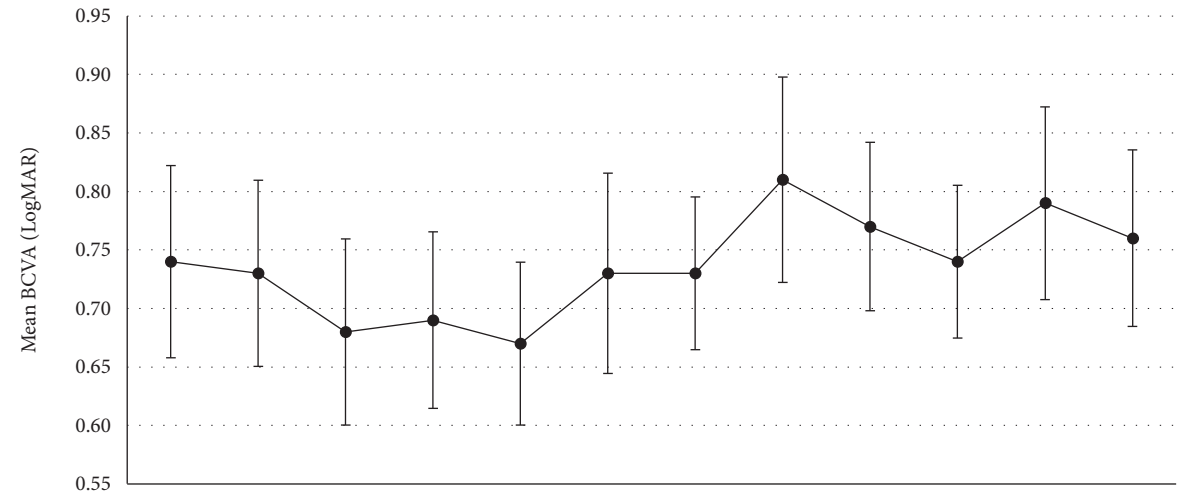
3.2. Baseline Ophthalmological Parameters. Mean BCVA and mean CRT at baseline were compared between two subgroups based on treatment status. In treatment-naïve eyes, the mean BCVA was 0.83 ± 0.64 LogMAR compared to 0.64 ± 0.60 LogMAR in the previously treated eyes: there was no statistically significant difference in BCVA at baseline ($p = 0.0689$). Similarly, no statistically significant difference was found between those subgroups in terms of CRT ($p = 0.7141$), as demonstrated in Table 2.

3.3. Number of Injections per Year. Table 3 illustrates the number of injections per year in the total cohort and compares the previously treated and treatment-naïve subgroups. For the total cohort, the mean number of injections



Time (years)	0	M3	M6	Y1	Y2	Y3	Y4	Y5	Y6	Y7
n	180	180	180	180	172	155	92	55	32	9
BCVA										
LogMAR	0.77	0.69	0.64	0.69	0.68	0.71	0.69	0.76	0.76	0.91
ETDRS*	46.5	50.5	53.0	50.5	51.0	49.5	50.5	47.0	47.0	39.5
Snellen*	20/118	20/98	20/87	20/98	20/96	20/103	20/98	20/115	20/115	20/163

(a)



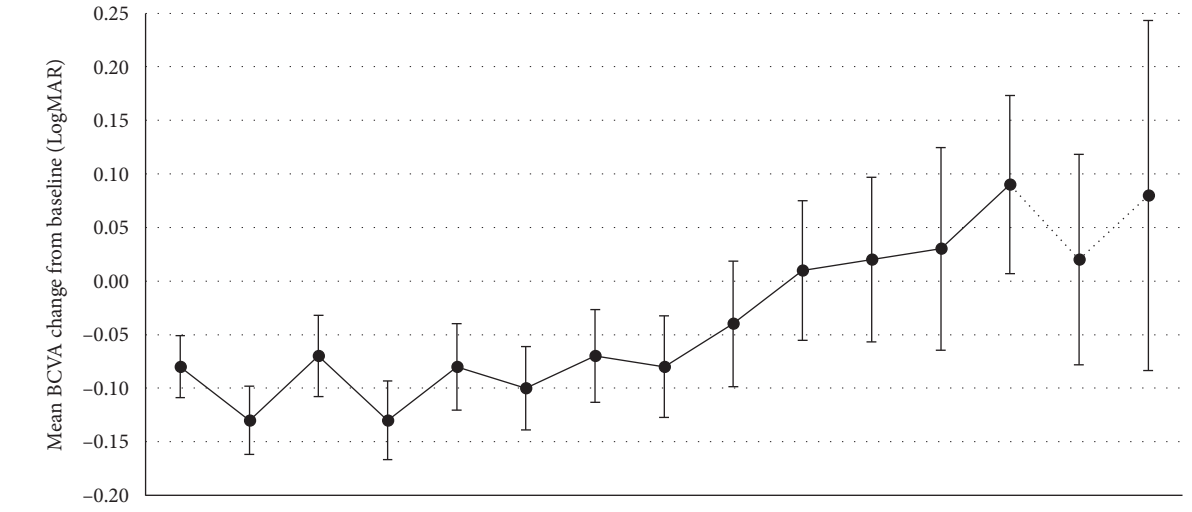
Time (years)	0	M3	M6	Y1	Y2	Y3	Y4	Y5
n	55	55	55	55	54	55	54	55
BCVA								
LogMAR	0.74	0.73	0.68	0.69	0.73	0.81	0.74	0.76
ETDRS*	48.0	48.5	51.0	50.5	48.5	44.5	48.0	47.0
Snellen*	20/110	20/107	20/96	20/98	20/107	20/129	20/110	20/115

(b)

Figure 1: (a) Long-term mean BCVA (all patients). (b) Mean BCVA in subgroup of patients with at least 5 years of follow-up. Note: variance is expressed in form of standard error of the mean; data depicted as dotted lines must be interpreted with caution as it represents a sample size of $n < 30$. *ETDRS and Snellen equivalents were calculated from LogMAR values.

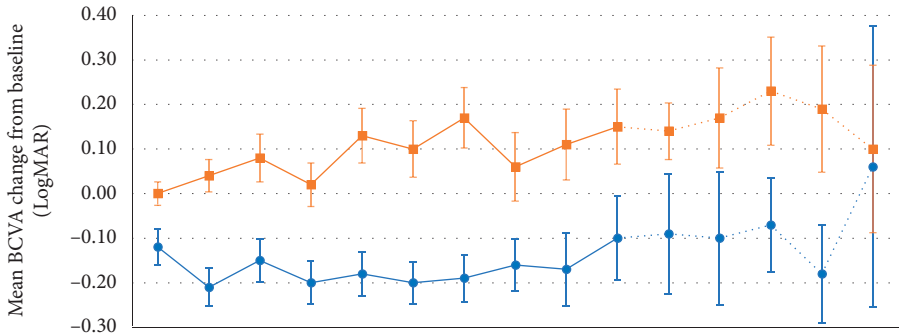
per year was 9.1 ± 2.2 for the first year, 7.1 ± 2.4 for the second year, 6.7 ± 2.9 for the third year, and an average of 5.9 from years 4 to 7.

We compared the treatment-naïve and the previously treated subgroups. Both subgroups required a high number of injections during their first year of treatment and there was no



Time (years)	M3	M6	Y1	Y2	Y3	Y4	Y5	Y6	Y7
n	180	180	180	172	155	92	55	32	9
BCVA									
LogMAR	−0.08	−0.13	−0.07	−0.08	−0.07	−0.04	0.02	0.09	0.08
ETDRS∗	4.0	6.5	3.5	4.0	3.5	2.0	−1.0	−4.5	−4.0

(a)



Time (years)	M3	M6	Y1	Y2	Y3	Y4	Y5	Y6	Y7
Treatment-naïve subgroup									
n	121	121	121	116	101	49	28	15	4
BCVA									
LogMAR	−0.12	−0.21	−0.15	−0.18	−0.19	−0.17	−0.09	−0.07	0.06
ETDRS*	6.0	10.5	7.5	9.0	9.5	8.5	4.5	3.5	−3.0
Previously treated subgroup									
n	59	59	59	56	54	43	27	17	5
BCVA									
LogMAR	0.00	0.04	0.08	0.13	0.17	0.11	0.14	0.23	0.10
ETDRS*	0.0	−2.0	−4.0	−6.5	−8.5	−5.5	−7.0	−11.5	−5.0

Treatment-naïve subgroup
Previously treated subgroup

(b)

Figure 2: (a) Long-term mean BCVA change from baseline. (b) Mean BCVA change from baseline according to previous treatment status. Note: variance is expressed in form of standard error of the mean; data depicted as dotted lines must be interpreted with caution as it represents a sample size of $n < 30$. *ETDRS and Snellen equivalents were calculated from LogMAR values.

statistically significant difference in the number of injections between the subgroups at that timepoint ($p = 0.5055$). During the two subsequent years, a statistically significant difference in the number of injections was noted: on average, the previously treated subgroup required 0.9 (at year 2) and 1.2 (at year 3) more injections than the treatment-naïve subgroup ($p = 0.0372$ and $p = 0.0116$, respectively). There were no statistically significant differences between these subgroups from years 4 to 7.

Table 1: Baseline demographics of patients and eyes.

Total number of patients/eyes	180
Age	
Mean (years) ± SD	75 ± 9
Range (years)	51–96
Sex, n (%)	
Male	75 (41.7%)
Female	105 (58.3%)
Laterality of disease at first visit, n (%)	
Unilateral	146 (81.1%)
Bilateral	34 (18.9%)
Past ocular history, n (%)	
Pseudophakic	92 (51.1%)
Glaucoma	15 (8.3%)
Pars plana vitrectomy	1 (0.6%)
*Past nAMD treatment, n (%)**	
None	121 (67.2%)
Anti-VEGF	58 (32.2%)
Intravitreal corticosteroid	1 (0.6%)
Argon laser for extrafoveal CNV	3 (1.7%)
Photodynamic therapy	0 (0.0%)

*Categories not mutually exclusive, except for "Past nAMD treatment: None".

Table 2: Baseline ophthalmological characteristics.

	Total number of patients (BCVA: $n = 180$, CRT: $n = 56$)	Treatment status*		p value
		Treatment-naïve subgroup (BCVA: $n = 121$, CRT: $n = 48$)	Previously treated subgroup (BCVA: $n = 59$, CRT $n = 8$)	
Mean BCVA (LogMAR)	0.77 ± 0.64	0.83 ± 0.64	0.64 ± 0.60	0.0689
Mean CRT (μm)	402 ± 194	406 ± 188	378 ± 241	0.7141

*Definitions: treatment-naïve eyes = no previous nAMD treatment prior to first injection at our clinic; previously treated eyes = previous nAMD treatment prior to first injection at our clinic.

Table 3: Number of injections per year in the total cohort and among the treatment-naïve and previously treated subgroups.

Timepoint	All eyes		Treatment-naïve subgroup		Previously treated subgroup		p value
	n	Number of injections, mean ± SD	n	Number of injections, mean ± SD	n	Number of injections, mean ± SD	
Year 1	180	9.1 ± 2.2	121	9.2 ± 2.2	59	9.0 ± 2.3	0.5055
Year 2	178	7.1 ± 2.4	120	6.8 ± 2.5	58	7.7 ± 2.2	0.0372
Year 3	172	6.7 ± 2.9	116	6.3 ± 2.9	56	7.5 ± 2.7	0.0116
Year 4	102	6.2 ± 2.8	56	6.3 ± 2.7	46	6.2 ± 3.1	0.8632
Year 5	72	5.6 ± 3.1	38	5.6 ± 3.3	34	5.1 ± 3.0	0.9684
Year 6	42	5.7 ± 2.8	24	5.3 ± 3.0	18	6.2 ± 2.5	0.2736
Year 7	11	6.1 ± 4.2	6	5.7 ± 4.5	5	6.6 ± 4.3	0.7344

3.4. Visual Outcomes. Table 4 demonstrates the evolution of BCVA across selected timepoints. Mean BCVA improved significantly during the first year of treatment. Mean BCVA at month 3, month 6, and year 1 was compared to baseline BCVA. BCVA improved from 0.77 ± 0.64 LogMAR to 0.69 ± 0.58 LogMAR after the loading phase at month 3 ($p = 0.0057$), 0.64 ± 0.55 LogMAR at month 6 ($p = 0.0001$), and 0.69 ± 0.60 LogMAR at year 1 ($p = 0.0585$). Mean BCVA improvement from baseline was significant during year 2 ($p < 0.05$) and thereafter regressed close to baseline values from years 3 to 6 (there was no statistically significant difference between the mean BCVA at each timepoint compared to baseline from years 3 to 6). This is illustrated further in Figure 1(a). We conducted a subanalysis of a subgroup of patients that had at least 5 years of follow-up ($n = 55$), in order to present their BCVA evolution over 5 years which is illustrated in Table 5 and Figure 1(b): this subgroup of patients had an initial improvement of BCVA within the first year of treatment (although not statistically significant), and overall, baseline BCVA was maintained over the course of 5 years.

Mean BCVA change from baseline was −0.08 ± 0.39 LogMAR at month 3, −0.13 ± 0.43 LogMAR at month 6, and −0.07 ± 0.51 LogMAR at year 1. Mean BCVA

Table 4: Evolution of BCVA and CRT across selected timepoints.

Timepoint		Visual acuity				Anatomical outcomes		
Year	Month	n	BCVA, mean (LogMAR) ± SD	BCVA change from baseline, mean (LogMAR) ± SD	p value*	n	CRT, mean (μm) ± SD	CRT change from baseline, mean (μm) ± SD	p value*
	0	180	0.77 ± 0.64	—	—	56	402 ± 194	—	—
	3	180	0.69 ± 0.58	−0.08 ± 0.39	0.0057	49	313 ± 140	−86 ± 152	0.0002
	6	180	0.64 ± 0.55	−0.13 ± 0.43	0.0001	45	286 ± 102	−116 ± 164	0.0001
1	12	180	0.69 ± 0.60	−0.07 ± 0.51	0.0585	48	313 ± 143	−91 ± 175	0.0007
	18	173	0.65 ± 0.54	−0.13 ± 0.48	0.0007	49	302 ± 136	−89 ± 168	0.0005
2	24	172	0.68 ± 0.65	−0.08 ± 0.53	0.0485	51	306 ± 155	−107 ± 210	0.0006
	30	171	0.67 ± 0.60	−0.10 ± 0.51	0.0105	42	304 ± 175	−105 ± 204	0.0018
3	36	155	0.71 ± 0.62	−0.07 ± 0.54	0.1360	35	354 ± 237	−52 ± 203	0.1345
	42	135	0.67 ± 0.53	−0.08 ± 0.55	0.0831	33	324 ± 182	−64 ± 198	0.0743
4	48	92	0.69 ± 0.52	−0.04 ± 0.56	0.4534	4	283 ± 85	−106 ± 255	—**
	54	82	0.74 ± 0.63	0.01 ± 0.59	0.8189	—	—	—	—
5	60	55	0.76 ± 0.56	0.02 ± 0.57	0.7782	—	—	—	—
	66	50	0.74 ± 0.59	0.03 ± 0.67	0.7383	—	—	—	—
6	72	32	0.76 ± 0.71	0.09 ± 0.47	0.3081	—	—	—	—
	78	26	0.72 ± 0.74	0.02 ± 0.50	0.7795	—	—	—	—
7	84	9	0.91 ± 0.91	0.08 ± 0.49	—**	—	—	—	—

* p value for BCVA/CRT change at different timepoints in comparison to baseline BCVA/CRT. **Sample size too small to conduct statistical analysis.

Table 5: Evolution of BCVA in subgroup of patients that completed at least 5 years of follow-up.

Timepoint		Visual acuity			
Year	Month	n	BCVA, mean (LogMAR) ± SD	BCVA change from baseline, mean (LogMAR) ± SD	p value*
	0	55	0.74 ± 0.61	—	—
	3	55	0.73 ± 0.59	−0.01 ± 0.41	0.9228
	6	55	0.68 ± 0.59	−0.06 ± 0.46	0.3548
1	12	55	0.69 ± 0.56	−0.05 ± 0.52	0.5114
	18	54	0.67 ± 0.51	−0.07 ± 0.49	0.3014
2	24	54	0.73 ± 0.63	−0.01 ± 0.48	0.8651
	30	54	0.73 ± 0.48	−0.02 ± 0.46	0.7739
3	36	55	0.81 ± 0.65	0.08 ± 0.49	0.2489
	42	54	0.77 ± 0.53	0.03 ± 0.53	0.6794
4	48	54	0.74 ± 0.48	0.00 ± 0.50	0.9708
	54	53	0.79 ± 0.60	0.06 ± 0.57	0.4329
5	60	55	0.76 ± 0.56	0.02 ± 0.57	0.7782

Note. $n = 55$ patients completed at least 5 years of follow-up; 28/55 (50.9%) treatment-naïve, 27/55 (49.1%) previously treated. * p value for BCVA change at different timepoints in comparison to baseline BCVA.

change from baseline went from −0.04 ± 0.56 LogMAR at year 4 ($n = 92$) to 0.02 ± 0.57 LogMAR at year 5 ($n = 55$). Although this change was not statistically significant, it demarcated the point in our observational study where mean BCVA change from baseline shifted from an improvement to a deterioration. At year 6, mean BCVA change from baseline was 0.09 ± 0.47 LogMAR ($n = 32$), which is not statistically significant ($p = 0.3081$). Beyond month 78, sample size decreases from 26 to 9 patients, which hinders further analysis. This is also illustrated in Figure 2(a). We conducted a subanalysis comparing BCVA change from baseline of treatment-naïve and previously treated subgroups. This subanalysis demonstrated that mean BCVA change from baseline was overall significantly better in the treatment-naïve subgroup in comparison to the previously treated subgroup, results of which are illustrated in Table 6 and Figure 2(b).

Figure 3 illustrates the distribution of change in equivalent ETDRS score from baseline across selected timepoints. At year 1 ($n = 180$), 42/180 patients (23.3%) gained ≥15 ETDRS letters, 125/180 (69.4%) gained or maintained vision (≥0 ETDRS letters), and 154/180 (85.6%) were considered to have stabilized disease (less than 15 ETDRS letter loss), and only 26/180 (14.4%) lost ≥15 ETDRS letters. At year 6 ($n = 32$), 6/32 (18.8%) gained ≥15 ETDRS letters, 19/32 (59.4%) gained or maintained vision, 22/32 (68.8%) were considered to have stabilized disease, and 10/32 (31.3%) lost ≥15 ETDRS letters. The results from the remaining years are summarized in Figure 3.

Table 6: Comparison of BCVA change from baseline between the treatment-naïve subgroup and previously treated subgroup.

Timepoint		Treatment-naïve subgroup		Previously treated subgroup		
Year	Month	n	BCVA change from baseline, mean (LogMAR) ± SD	n	BCVA change from baseline, mean (LogMAR) ± SD	p value
	3	121	−0.12 ± 0.45	59	0.00 ± 0.20	0.0466
	6	121	−0.21 ± 0.46	59	0.04 ± 0.28	0.0001
1	12	121	−0.15 ± 0.53	59	0.08 ± 0.41	0.0041
	18	116	−0.20 ± 0.52	57	0.02 ± 0.37	0.0037
2	24	116	−0.18 ± 0.54	56	0.13 ± 0.46	0.0002
	30	116	−0.20 ± 0.51	55	0.10 ± 0.47	0.0002
3	36	101	−0.19 ± 0.53	54	0.17 ± 0.50	0.0001
	42	87	−0.16 ± 0.54	48	0.06 ± 0.53	0.0217
4	48	49	−0.17 ± 0.57	43	0.11 ± 0.52	0.0155
	54	44	−0.10 ± 0.63	38	0.15 ± 0.52	0.0595
5	60	28	−0.09 ± 0.71	27	0.14 ± 0.33	0.0444
	66	26	−0.10 ± 0.76	24	0.17 ± 0.55	0.1556
6	72	15	−0.07 ± 0.41	17	0.23 ± 0.50	0.0414
	78	12	−0.18 ± 0.38	14	0.19 ± 0.53	0.0512
7	84	4	0.06 ± 0.63	5	0.10 ± 0.42	—*

*Sample size too small to conduct statistical analysis.

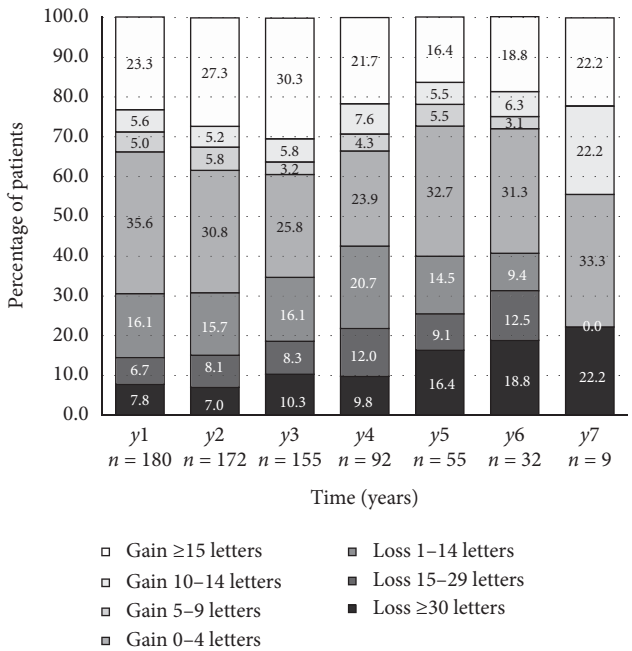


Figure 3: Distribution of changes in BCVA from baseline (equivalent ETDRS letter score). Note: ETDRS equivalent was calculated from LogMAR values.

3.5. Anatomical Outcomes. Table 4 also illustrates the evolution of mean CRT across selected timepoints. Mean CRT improved significantly in the first year of treatment. Mean CRT at month 3, month 6, and year 1 was compared to baseline CRT. Mean CRT improved from 402 ± 194 μm to 313 ± 140 μm after the loading phase at month 3 ($p = 0.0002$), 286 ± 102 μm at month 6 ($p = 0.0001$), and 313 ± 143 μm at year 1 ($p = 0.0007$). Mean CRT change from baseline was −86 ± 152 μm at month 3, −116 ± 164 μm at month 6, and −91 ± 175 μm at year 1. Mean CRT improvement from baseline was considered statistically significant until year 2. This improvement did not maintain statistical significance at year 3.

3.6. Type of Anti-VEGF Used. Figure 4 highlights the types of anti-VEGF drugs used in the study. A total of 5352 IVT injections were given throughout the course of the study: 3893/5352 (72.7%) ranibizumab, 1202/5352 (22.5%) aflibercept, and 257/5352 (4.8%) bevacizumab. Most eyes received more than one type of anti-VEGF agent throughout the study period; only 47/180 (26.1%) of eyes received strictly one type of anti-VEGF.

We conducted a subanalysis of eyes that were switched from an anti-VEGF agent to another due to the persistence of CNV activity (intra- or subretinal fluid) despite six consecutive monthly injections. There was a total of 55 switches, 48/55 (87.3%) of which mostly occurred in the first three years of treatment. Most of the switches (46/55 (83.6%)) consisted of a transition from ranibizumab to aflibercept.

3.7. Loss to Follow-Up and Adverse and Surgical Events. Eighteen patients (10%) were lost to follow-up during the seven years of follow-up, distributed evenly throughout the seven years mostly secondary to very poor visual prognosis, relocation, death, or unknown reasons. Of note, other than these eighteen patients, the decline in sample size over the course of the study is due to the fact that total follow-up per patient was not even, as it ranged from 1 year to 7 years of follow-up. Adverse and surgical events that could have impacted BCVA are recorded in Table 7. During the course of the study, three cases of endophthalmitis occurred out of a total of 5352 injections (0.056%). 41/180 (22.8%) patients underwent cataract surgery and 12/180 (6.7%) had YAG-laser capsulotomy. Seven patients required pars plana vitrectomy (PPV) for the following reasons: 3/180 (1.7%) for injection related endophthalmitis, 2/180 (1.1%) for injection related retinal detachment, and 2/180 (1.1%) for vitreous haemorrhage. Of note, one patient underwent a second PPV for silicone oil removal following initial PPV for RD; these two surgeries took place within the same BCVA/CRT

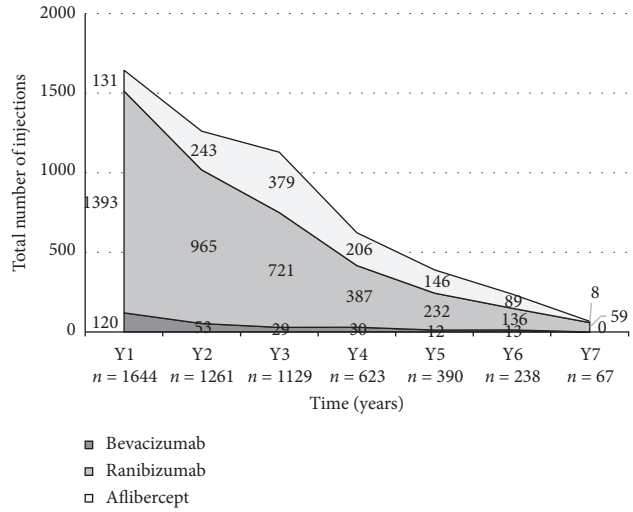


Figure 4: Type of anti-VEGF agent used per year.

Table 7: Noteworthy events and possible confounders throughout study duration.

Timepoint	n	Cataract surgery	YAG-laser capsulotomy	Pars plana vitrectomy	Endophthalmitis	Retinal detachment
Year 1	180	6	4	1	1	0
Year 2	178	12	4	2	0	2
Year 3	172	9	1	2	1	0
Year 4	102	8	2	2	1	0
Year 5	72	6	0	0	0	0
Year 6	42	0	1	0	0	0
Year 7	11	0	0	0	0	0
Total	180	41	12	7	3	2

sampling interval. We conducted a subanalysis comparing BCVA prior to versus after cataract surgery: mean BCVA change after cataract surgery was -0.15 ± 0.29 LogMAR ($p = 0.0005$); 19/41 (46.3%) patients demonstrated an improvement of BCVA after cataract surgery.

4. Discussion

The advent of anti-VEGF revolutionized the treatment of nAMD. Despite ongoing efforts to find an ideal treatment regimen that balances visual outcomes and patient burden, the gold standard has not yet been established. Several studies like the TREX-AMD (2017), TREND (2018), and CANTREAT (2019) trials demonstrated noninferiority of ranibizumab with TER versus monthly regimen in treatment-naïve eyes, in patients treated up to 1 year [25–27]. Similarly, systematic reviews by Gemenetzi and Patel, Rufai et al. and Okada et al. suggested that TER is superior to PRN and comparable to monthly injections in the short term and highlighted the need for more real-word long-term data [20, 28, 29]. Of note, although we present statistically significant change in BCVA as p value <0.05 (cf. Table 4), we personally prefer looking at data from Figure 3 and conclude that patients either had disease stabilization or not: based on Figure 3, patients who had less than 15 ETDRS letters (3 lines) loss in comparison to baseline were essentially considered to have "disease stabilization," and those that did not were considered to be progressing [15, 30].

Our study was a retrospective cohort study presenting real-world longitudinal data on patients with nAMD treated with anti-VEGF injections based on the TER. We included 180 eyes from 180 patients and reported visual acuity and anatomic outcomes as well as data regarding the number of injections per year. Our population was well-balanced at baseline and baseline BCVA and CRT was comparable among treatment-naïve and previously treated patients.

In our study, the mean number of injections per year for the whole cohort was higher in the first year of treatment (9.1 ± 2.2). The mean number of injections steadily declined over the next years and on average, the patients received close to six injections per year between years 4 and 7. We compared treatment-naïve and previously treated eyes and demonstrated that although a high number of injections is required in both subgroups in the first year of treatment, treatment-naïve eyes required on average less injections long-term. The difference was statistically significant at years 2 and 3. The most commonly used agent in our study was ranibizumab (72.7%), consistent with current trends on first-line choice of drug in Canada, as demonstrated by the CAN-PAT survey [31].

In 2017, Berg et al. published long-term follow-up data on TER for nAMD. Their patients required an average of 6.4 injections per year over the course of 7 years for treatment-

naïve eyes [32]. Their result is consistent with our findings for treatment-naïve eyes as our subanalysis demonstrates an average of 6.5 injections per year in the same time frame. Mekjavic et al. and Khanani et al. also reported similar results over the course of 5 years, with an average of 6.1 and 6.3 injections per year, respectively, in their treatment-naïve eyes [33, 34]. Interestingly, in their cohort of 210 eyes, Mrejen et al. reported a higher number of injections (mean of 8.3 injections per year over the course of 6 years) in eyes with similar baseline characteristics. A possible reason why Mrejen et al. reported a higher number of injections is the inclusion of bilateral eyes at baseline where the worse eye dictates the visit interval for the other eye that could require less visits; they report a 13.5% rate of bilateral disease at the study inclusion timepoint [35].

In regard to visual acuity outcomes, data from BCVA change from baseline demonstrated a mean improvement of −0.08 LogMAR following the loading phase at month 3 and −0.13 LogMAR at month 6, results that were statistically significant. The statistically significant improvement from baseline BCVA was mostly maintained until the end of year 2 (except at timepoint year 1: $p = 0.0585$). From years 3 to 4, mean BCVA change from baseline demonstrated a sustained mean improvement (<0.00 LogMAR), although not considered statistically significant. From years 5 to 7, mean BCVA change from baseline demonstrated a slight worsening (>0.00 LogMAR) in comparison to baseline values, which was not considered statistically significant. In our subanalysis comparing treatment-naïve eyes versus previously treated eyes, we demonstrated that treatment-naïve eyes had significantly better BCVA outcomes.

Other studies have demonstrated an overall similar trend in visual acuity outcomes regarding mean BCVA change from baseline. Berg et al. reported an improvement of −0.11 LogMAR reaching −0.17 LogMAR at year 2. Despite a decrease in the amplitude of improvement following year 2, the statistically significant improvement was maintained until year 4. Subsequently, between years 6 and 7, visual acuity started deteriorating below baseline, although not considered statistically significant. They hypothesized that this long-term decline in vision could be explained by macular atrophy [32]. In Mrejen et al.'s cohort study, the visual acuity changes followed a similar tendency. There was an improvement in year 1 (−0.09 LogMAR) and year 2 (−0.11 LogMAR) followed by BCVA stabilization in the subsequent years. Similar to our results, Mekjavic and Zaletel Benda reported a BCVA improvement that peaked at year 1 followed by stabilization until year 5. Like us, they noted that their mean BCVA change from baseline shifted above 0.00 LogMAR between year 4 and year 5, although not statistically significant [33].

Khanani et al. included 93 eyes with good baseline BCVA (20/20–20/60) and showed that 65/93 (69.9%) of eyes had a BCVA equal or better than baseline at year 1, and 15/26 (57.7%) at year 5 [30]. We obtained very similar results in our study: 125/180 (69.4%) of eyes had a BCVA equal or better than baseline at year 1 and 33/55 (60.0%) at year 5. This is further illustrated in Figure 3. In addition, Figure 3 highlights the clinical significance of our results beyond statistical significance: the majority of our patients were considered to have sustained or improved BCVA at all timepoints from year one to seven, and in the long run, only less than a third of patients did not have "disease stabilization" (less than 15 ETDRS (3 lines) loss in comparison to baseline), which supports the long-term efficacy of anti-VEGFs under TER in real-world settings.

In regard to anatomical outcomes, we demonstrated a reduction in CRT. There was a statistically significant decrease of −91 μm at year 1. The improvement was maintained during the following year. This seems in line with the findings obtained by Berg et al. [32].

Additionally, 41/180 (22.8%) of patients in our study underwent cataract surgery (Table 7), which might impact BCVA outcomes, but we didn't exclude these patients since cataract progression and surgery is part of real-world conditions in the nAMD patient population. In our subanalysis comparing BCVA prior to versus after cataract surgery, only 19/41 (46.3%) patients demonstrated an improvement of BCVA after cataract surgery, but mean BCVA change after cataract surgery was -0.15 ± 0.29 LogMAR ($p = 0.0005$), which corresponds to a mean improvement of 7.5 equivalent ETDRS letters after cataract surgery. Of note, Mrejen et al. found no statistically significant association between BCVA and cataract surgery in nAMD patients under long-term real-world conditions; 30/210 (14.3%) of eyes had cataract surgery over the course of their 6 year study [35]. Nonetheless, data is ambiguous on this topic, and a more recent study from Kessel et al. focused on this subject specifically and concluded that cataract surgery improved BCVA by an average of 7.1 ETDRS letters 6 months after surgery in nAMD patients with a mean BCVA of 52 ETDRS letters prior to surgery; their data reflects our findings [36].

Furthermore, 7/180 (3.9%) eyes underwent pars plana vitrectomy for complications related to nAMD or its treatment, but these patients were not excluded from our study, as we strived to represent real-world outcomes of this disease. Despite these limitations, our study provides robust statistically and clinically significant conclusions that add to the body of knowledge on real-world data for TER in the treatment of nAMD. We report 3/5352 (0.056%) cases of endophthalmitis, which is within norms, but slightly higher than the latest literature on this subject, as the pooled endophthalmitis rate from 20 large retrospective studies on IVT anti-VEGF injections was reported to be 144/510,396 (0.028%) [37].

Our study has some limitations intrinsic to its retrospective nature and real-world setting. There is lack of information on baseline data on nAMD duration in previously treated eyes and potential demographic confounders (e.g., education status, socio-economic status, marital status, access to relatives/help for visits, etc.). Also, data sampling not occurring exactly at the defined timepoints is a limitation. Excluding patients that were noncompliant to TER in the first year of follow-up and treatment must be taken into account as it has an impact on external validity. Conversion of BCVA from Snellen to LogMAR and ETDRS is another limitation. The choice of the initial drug was not independent of baseline characteristics and may have been a confounder for the number of injections and visual outcomes;

the choice of the initial drug was at the discretion of the retina specialist and depended on the provincial funding for anti-VEGF agents. Mixing different anti-VEGF agents could also be a confounder, but it corresponds to the real-life practice of many clinicians. Progression of cataract and cataract surgery is also a confounder to be taken into account in such studies. In cases where patients had bilateral disease, the eye requiring a shorter interval of injection according to TER dictated the interval for the other eye that could have possibly required less frequent visits for injections under TER, which nonetheless is inherent to real-world settings. Intrinsic to the retrospective nature of the study, the number of patients decreased significantly after year 6 and data beyond that timepoint must be interpreted with caution. Of note, all of our patients have free coverage for anti-VEGFs in Canada; insurance coverage is therefore not a limitation in this study.

To conclude, this retrospective study of 180 eyes with nAMD treated with intravitreal anti-VEGF injections using the TER demonstrates an initial improvement of visual outcomes during the first few years of treatment, followed by visual stabilization for up to 7 years for the majority of our patients. This study also highlights the need for a high number of visits/injections per year (roughly 6 injections per year) throughout long-term follow-ups under the real-life conditions of the TER in nAMD. Overall, we demonstrated long-term efficacy of this treatment in real-world conditions: heterogeneity of patients, occasional struggles with visit compliance, various types of anti-VEGFs used, and so on. Our results are comparable to similar long-term real-world studies on the TER in nAMD.

Data Availability

The database used to support the findings of this study may be provided upon request, by contacting the corresponding author.

Ethical Approval

The local research department confirmed that no ethical approval was required given the retrospective nature of the study, as there was no deviation from the usual standard of care. The study was conducted in concordance with the World Medical Association Declaration of Helsinki.

Consent

Direct written patient consent was not obtained for data collection and analysis since no identifying information has been included.

Disclosure

This paper was presented at the 18th Congress of the European Society of Retina Specialists (EURETINA) on the 21st of September 2018 in Vienna, Austria, and at the 2019 Annual Meeting of the Association for Research in Vision and Ophthalmology (ARVO) on the 28th of April 2019 in Vancouver, BC, Canada.

Conflicts of Interest

The authors declare that there are no conflicts of interest in regard to this study. Marc Saab and Ghassan Cordahi are consultants for Alcon, Allergan, Bayer, and Novartis. The remaining authors have no financial disclosures.

Authors' Contributions

Simon Javidi and Ali Dirani contributed equally to this work.

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Research Article

Results of Ranibizumab Treatment of the Myopic Choroidal Neovascular Membrane according to the Axial Length of the Eye

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Aim. A retrospective evaluation of the results of treatment of myopic choroidal neovascularization (mCNV) with intravitreal injections of ranibizumab in a *pro re nata* (PRN) regimen in three groups of patients distributed according to axial length. *Methods*. The paper presents a retrospective multicenter study carried out with the cooperation of several Departments of Ophthalmology in the Czech Republic. The study included 60 eyes of 60 patients suffering from mCNV, divided according to axial length into three groups. The first group consisted of 20 patients with an axial length of the eyes shorter than 28 mm (Group 1), the second group included 27 patients with axial lengths ranging from 28 mm to 29.81 mm (Group 2), and 13 patients had axial lengths longer than 30 mm (Group 3). All patients were first administered 3 initial intravitreal ranibizumab injections at monthly intervals (loading phase), and other injections were administered according to a PRN treatment regimen. Patients were evaluated before treatment and then at intervals of 3, 6, 9, and 12 months. The effect of ranibizumab treatment on the functional and morphological parameters of the affected eye was evaluated. *Results*. The average baseline BCVA ± SD in Group 1 was 52.6 ± 12.5 letters of ETDRS optotypes, and at the end of the one-year follow-up, it was 63.3 ± 11.8 letters. The average baseline of CRT ± SD in this group was 377.4 ± 80.0 μm, and in the 12th month, it was 311.1 ± 63.7 μm. The average baseline BCVA ± SD in Group 2 was 50.2 ± 9.0 ETDRS letters, and at the end of the follow-up, it was 60 ± 12.4 letters. The average baseline of CRT ± SD in Group 2 was 391.2 ± 85.2 μm, and in the 12th month, it was 323.9 ± 91.2 μm. In Group 3, the average baseline of BCVA was 48.5 ± 14.5 ETDRS letters, and at the end of the one-year follow-up, it was 55.7 ± 16.1 letters. The average baseline CRT ± SD for Group 3 was 342.1 ± 94.9 μm, and after 12 months, it was 287.8 ± 88.4 μm. An improvement of BCVA by ≥15 letters of ETDRS optotypes was achieved by 3 patients of 20 (15%) in Group 1, by 5 patients of 27 (18.5%) in Group 2, and by 3 patients of 13 (23.1%) in Group 3. All these changes were statistically significant in comparison with the input values ($p < 0.05$). *Conclusion*. Ranibizumab treatment in patients with mCNV in our study resulted in statistically significant improvement in BCVA and a decrease in CRT in all groups of patients. Our results from a routine clinical practice correspond with the results of large clinical studies; we confirm a particularly good effect of treatment in patients with axial lengths of the eye smaller than 28 mm.

1. Introduction

Myopia is the most frequent cause of decreased visual acuity in the total population, particularly in East Asia, where it affects approximately 40% of adults aged over 40 years [1]. Pathological myopia is the most serious form of myopia, and its definition includes a refractive error of minimally −6.0 dioptres or axial length of the bulbus of 26 mm and more, accompanied by degenerative changes in the sclera, choroid, and retina [2–4].

Choroidal neovascularization based on pathological myopia (myopic CNV) is one of the most serious complications of pathological myopia in patients of the productive age, with a prevalence of 0.04% to 0.05% in the total population [5, 6]. It develops as a result of the mechanism of wound healing following ruptures of Bruch's membrane and represents the most dangerous sight-threatening event in pathological myopia.

The prevalence of myopic CNV is estimated to be 0.05% among patients older than 49 years in the Blue Mountains Eye Study [7] and 0.04% in patients over 40 in the Peking ophthalmic study [8]. The prevalence also differs according to population and demographic characteristics. According to data from the United States, 5.2% patients with axial lengths higher than 26.5 mm showed the signs of myopic CNV [9], whereas in Japan manifestations of mCNV were recorded in 11.3% eyes with refraction higher than −8 D or axial lengths more than 26.5 mm [10]. It has been reported that myopic CNV occurs more frequently in women, and the prevalence in the female population ranging between 52% and 87.7% [11].

Ranibizumab is a recombinant humanized monoclonal antibody of size 48 kDa lacking the Fc fragment [12]. The safety and effectiveness of intravitreal treatment with ranibizumab in the case of myopic CNV has been demonstrated in several clinical studies [13–19]. Ranibizumab is the first anti-VEGF preparation approved in many countries throughout the world for the treatment of visual affection due to myopic CNV, and it is recommended as the first-choice drug [20].

This study evaluates the treatment of intravitreally administered ranibizumab in a *pro re nata* (PRN) regimen in patients with myopic CNV, distributed according to axial lengths into three subgroups: less than 28 mm, 28-29.9 mm, and more than 30 mm.

2. Methods

2.1. Selection of Patients. This was a multicenter retrospective observational study from a routine clinical practice in the University Hospital in Hradec Kralove, Masaryk University Hospital in Brno, University Hospital in Ostrava, and University Hospital in Kralovske Vinohrady, Prague, which took place in the period from July 2017 to August 2019. The criteria for inclusion were as follows:

Pathologic myopia with an axial length of 26 mm or more, presence of active subfoveal or juxtafoveal CNV, which was demonstrated by means of fluorescent angiography (FA), and a one-year follow-up period (Figure 1). The criteria for exclusion were as follows: CNV resulting from causes other than myopia (e.g., age-related macular degeneration (AMD), central serous chorioretinopathy, diabetic retinopathy, retinal vein occlusion, vasculitis, and uveitis), previous treatment of CNV (including photodynamic therapy (PDT) and intravitreal injections of anti-VEFG drugs), and other possible causes of decreased BCVA (e.g., advanced cataract and other disease of the retina and/or the anterior segment). All included patients were treatment naïve, and no one patient was bilaterally affected. The baseline BCVA ranged between 75 and 25 letters of the ETDRS optotypes (Snellen 20/32–20/320) on the affected eye.

2.2. Data Collection. In the course of the one-year follow-up, BCVA was measured in all patients, and slit-lamp examination, biomicroscopy in artificial mydriasis after instillation of 0.5% tropicamide, and optical coherence tomography (OCT) by means of an OCT Cirrus 4000 (ZEISS, Oberkochen, Germany) were performed. These examinations were carried out at each ward round: prior to the commencement of treatment and in the 3rd, 6th, 9th, and 12th month. The axial length of the eye was measured only at the first visit by means of a Zeiss IOL Master 500 Biometry A Scan apparatus or a NIDEK US-4000 Ultrasound apparatus. FA was performed at the first visit (Visucam 500, ZEISS, Oberkochen, Germany) and in cases of doubts in the assessment of disease activity. BCVA was determined by means of standardized ETDRS optotypes in all centers. CRT was defined as the distance between the internal limiting membrane and RPE in the fovea. All patients signed the form of informed consent prior to administration of the intravitreal injections. The protocol of the study observed the principles of the Helsinki Declaration. We did not evaluate fundus differences among eyes in the whole group of patients (diffuse atrophy, tessellate fundus, patchy atrophy, lacquer cracks, etc) despite the fact that it is an interesting consideration. Surgical intervention was performed in an operating room. Preparation of the drug and its administration took place under aseptic conditions. Ranibizumab (0.5 mg in 0.05 ml) was administered under local anesthesia using a 30-gauge needle trans-sclerally 3.5 mm (in pseudophakic eyes) to 4.0 mm (in phakic eyes) from the limbus.

2.3. Criteria for Readministration. Ranibizumab treatment was applied in the PRN dosing regimen, i.e., the first three injections were followed by controls with possible addition of another injection if the signs of CNV activity continued according to the condition on OCT (intra- and subretinal fluid and RPE ablation) and also if new macular hemorrhage was observed. FA was performed in cases of doubts in the assessment of disease activity, when the signs of CNV activity have been demonstrated on the basis of increasing hyperfluorescence (leakage).

We have chosen the loading dose consisting of three-month intravitreal injections to get the greatest effect both anatomically and functionally because we knew that the follow-up controls would follow every three months, which

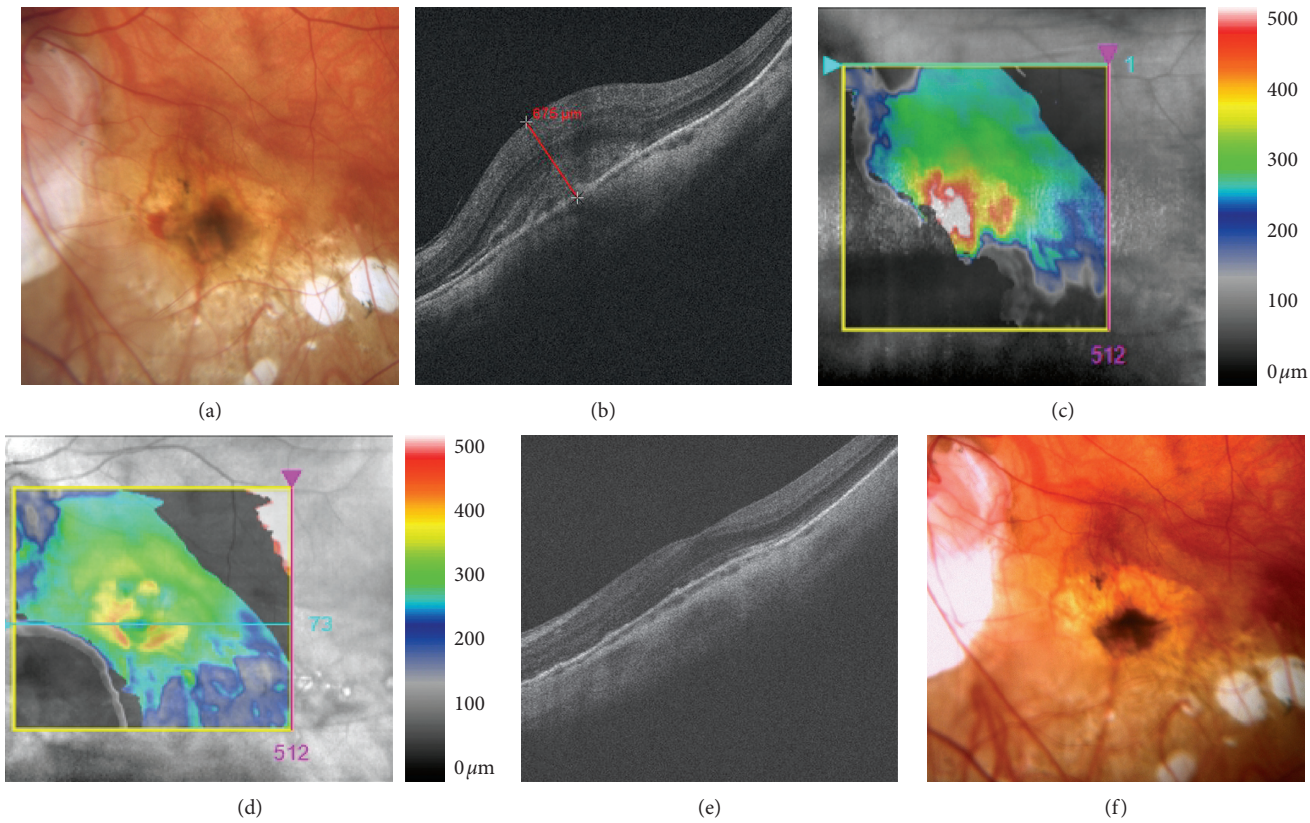

Figure 1: Choroidal neovascularization in a patient with pathological myopia. (a) Fundus photography before Lucentis treatment. Acute neovascular membrane and subretinal hemorrhage in the nasal part. (b-c) HD-OCT before treatment. Hyperreflective tissue grows through retinal pigment epithelium. Central retinal thickness is 675 μm. (d-e) HD-OCT after treatment. A decrease of edema and improvement of foveolar depression. (f) Fundus photography after treatment. Reduction of neovascular membrane, and hemorrhages are not presented.

was the most achievable interval in real clinical practice. The system of quarterly follow-up visits is based on the possibilities in real clinical practice and patient's ability to undergo these controls. Evaluated were the changes in BCVA on ETDRS optotypes, CRT development according to OCT, and the safety profile of the preparation. Although this was a retrospective multicenter study, the retreatment criteria were the same everywhere and resulted from the treatment conditions in real clinical practice at all centers.

2.4. Statistical Analysis. Statistical analysis was performed by means of the software IBM SPSS Statistics 23. Quantitative data are expressed by the mean and extent. BCVA and CRT values were analysed using the Wilcoxon test. Changes in BCVA and CRT were evaluated by means of the paired t-test. Pearson's correlation coefficient was employed to evaluate the correlation between the axial length and the resultant BCVA and CRT. Statistical significance was defined as $p < 0.05$.

3. Results

The study included altogether 60 eyes in 60 naive patients who were examined in four Departments of Ophthalmology in the Czech Republic. The baseline demographic data of patients are presented in Table 1. All patients were treated with ranibizumab. The patients were divided into 3 groups according to the axial length. Group 1 consisted of 20 eyes (33.3%), Group 2 consisted of 27 eyes (45%), and Group 3 included 13 eyes (21.7%). The average axial length of the eyes in Group 1 was 27.08 ± 0.6 mm (range 26–27.9 mm), in Group 2 28.83 ± 0.55 mm (range 28–29.81 mm), and in Group 3, 31.61 ± 1.74 mm (range 30–35.1 mm). In Group 1, the average age of patients was 62 years (range 36–84 years), of whom 15 were women (75%), the average age of Group 2 was 63.1 years (range 35–83), of whom 25 were women (92.6%), and in Group 3, the average age was 55.5 years (range 28–80) and included 8 women (61.5%). The average number of intravitreal injections of ranibizumab was 4.0 ± 1.5 in the whole cohort: 3.88 ± 1.3 in Group 1, 3.59 ± 1.6 in Group 2, and 2.9 ± 1.3 in Group 3 ($p = 0.14$). No subsequent complications related to intravitreal ranibizumab administration were observed, e.g., serious intraocular inflammation, hemophthalmus, or development of secondary glaucoma.

3.1. Analysis of Visual Acuity. The baseline BCVA ± SD in the total cohort of patients was 51.0 ± 11.5 letters of ETDRS optotypes: in Group 1, it was 52.6 ± 12.5 letters, 50.2 ± 9.0 letters in Group 2, and 48.5 ± 14.5 letters in Group 3 ($p = 0.182$). The development of BCVA is represented in

Table 1: Baseline demographic, anatomical, and vision characteristics of all groups of eyes separated by axial length.

	All patients 26.0–35.1 mm ($n = 60$) (100%)	Group 1 <28 mm ($n = 20$) (33.3%)	Group 2 28.0–29.81 mm ($n = 27$) (45%)	Group 3 >30 mm ($n = 13$) (21.7%)	p
Mean age (years)	61 ± 14.3	62 ± 15	63.1 ± 12.5	55.5 ± 16.3	0.240
Female, no.	15 (75%)	15 (75%)	25 (92.6%)	8 (61.5%)	0.431
CRT (μm)	376 ± 86.2	377.4 ± 80	391.2 ± 85.2	342.1 ± 94.9	0.325
BCVA (ETDRS)	51.0 ± 11.5	52.6 ± 12.5	50.2 ± 9	48.5 ± 14.5	0.182

Figure 2. The final BCVA in all patients at the end of the follow-up was 60.0 ± 13.2 letters of ETDRS optotypes: 63.3 ± 11.8 letters in Group 1, 60 ± 12.4 in Group 2, and 55.7 ± 16.1 in Group 3 ($p = 0.14$).

The changes relative to the baseline value were statistically significant in the course of the whole follow-up ($p < 0.05$) (Figure 3). Improvements in BCVA by ≥15 letters of ETDRS optotypes were achieved by 3 patients of 20 (15%) in Group 1, by 5 patients of 27 (18.5%) in Group 2, and by 3 patients of 13 (23.1%) in Group 3.

A decrease in BCVA by ≥ 15 letters of ETDRS optotypes was found in four patients during the first 6 months of the follow-up as the result of the following changes: one case of RPE atrophy in the macula, one case of development of a macular hole, and one case where the patient underwent a laser refractive surgery with gradual development of haze. An RPE rupture developed in one patient immediately after the first injection of ranibizumab. These patients were excluded from further evaluation.

A comparison of the results of changes in BCVA after one-year follow-up has not revealed a statistically significant difference between groups. The difference between the first and second group was 3.3 letters of ETDRS optotypes ($p = 0.22$), between the second and third, 4.3 letters of ETDRS optotypes ($p = 0.19$), and between the first and third, 7.6 letters of ETDRS optotypes ($p = 0.11$).

3.2. Anatomical Results. The baseline value of CRT ± SD in the total cohort of patients was 376 ± 86.2 μm: in Group 1, 377.4 ± 80 μm, in Group 2, 391.2 ± 85.2 μm, and in Group 3, 342.1 ± 94.9 μm ($p = 0.3$). The development of CRT values is represented in Figure 4. At the end of the follow-up in the 12th month, CRT ± SD in the total cohort was 312 ± 82.9 μm: in Group 1, 311.1 ± 63.7 μm, in Group 2, 323.9 ± 91.2 μm, and in Group 3, 287.8 ± 88.4 μm ($p = 0.176$) (Figure 5). At the end of the follow-up, residual macular edema (intraretinal and/or subretinal) was found in 16.7% of all patients, of whom 4 patients were from Group 1 (6.7%), 5 from Group 2 (8.3%), and 1 from Group 3 (1.7%).

3.3. Correlation between Axial Length and Final BCVA and CRT. After a one-year follow-up period, the correlation between the axial length and the final average value of BCVA and CRT was evaluated using Pearson's correlation coefficient. For the total cohort, this value for correlation of axial length and BCVA was −0.19 and for axial length and CRT was 0.16. This means that the higher axial length of the eye related to the smaller final gain of BCVA and the smaller decrease in CRT.

4. Discussion

A number of clinical studies have described the benefit of anti-VEGF treatment in patients with mCNV [13–22]. These papers have demonstrated that in the course of a one-year follow-up after treatment with ranibizumab, 65–92.7% eyes with mCNV resulted in an improvement in BCVA of at least 5 letters of ETDRS optotypes, which is better than in the case of treatment using PDT. The present retrospective study has evaluated the functional and anatomical results of ranibizumab treatment, in the PRN regimen, of naive eyes with mCNV distributed into 3 subgroups according to axial lengths. The cohort consisted of a relatively large group ($n = 60$) of patients, and BCVA improvement in the total cohort at the end of a one-year follow-up was +9.0 letters of ETDRS optotypes; on average, 4.0 ± 1.5 injections were administered.

The randomized, multicenter, double-blind study Radiance evaluated two individualized application regimens of ranibizumab treatment in 277 patients with mCNV (in the first group, patients received two introductory injections followed by treatment in the PRN regimen; in the second group only one introductory injection was administered) [19].

On the basis of the results of the study, it is evident that no statistically significant differences have been demonstrated in the efficiency of treatment between the first and second groups at the end of a one-year follow-up. The average improvement in BCVA was +13.8 letters of ETDRS optotypes in Group 1 (the average number of ranibizumab injections being 4.0), and in Group 2, the average improvement was +14.4 letters (the average number of ranibizumab injections being 2.0). At the final checkup in the 12th month, 64.2% of all patients showed no signs of CNV activity.

The present study has recorded a gain in the total cohort on average by 9.0 letters of ETDRS optotypes after 12 months from the beginning of treatment, with a median of 3.0 injections in the course of a one-year follow-up. Our results could be influenced by a smaller number of patients and worse baseline values of BCVA (51.0 letters of ETDRS optotypes in the total cohort versus 55.8 letters in the Radiance study).

The Radiance study is for the time being the only study evaluating the results of ranibizumab treatment according to

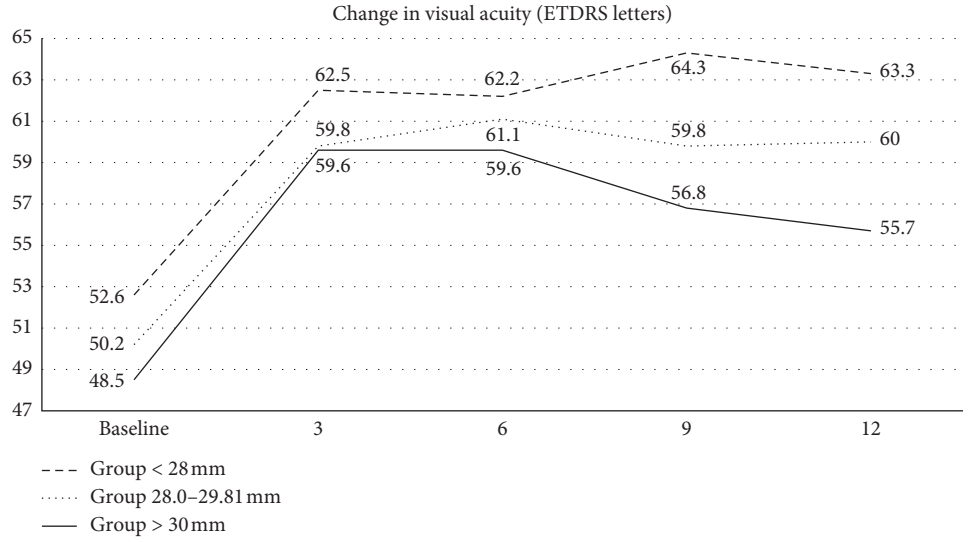

Figure 2: Functional outcomes over time for eyes with mCNV with different axial lengths. All groups showed BCVA improvement from baseline to the final 12-month follow-up; however, the group with axial length <28 mm showed the greatest letter gain.

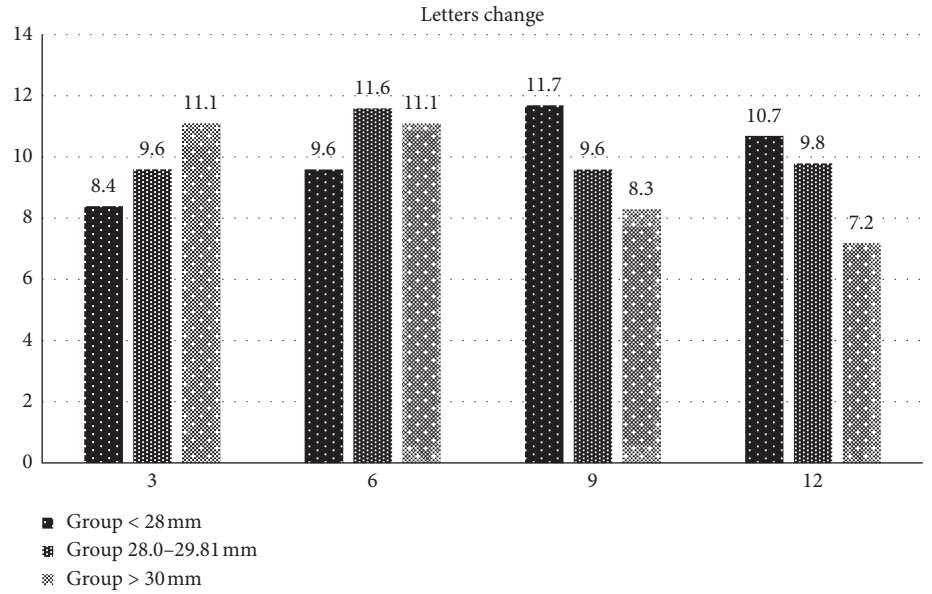

Figure 3: The mean change in ETDRS letters from baseline for three groups with different axial lengths during the first year of ranibizumab treatment.

the axial length of the eye in myopic patients during a one-year follow-up [23]. In the first group with axial lengths <28 mm (41 patients), an average gain of +16.8 ETDRS letters was recorded, with the average number of injections 3.95. In the second group with axial lengths of 28–30 mm (34 patients), the average gain was +13.6 ETDRS letters (2.8 injections). The third group consisted of individuals with axial length more than 30 mm (30 patients), in which the average gain was +13.4 ETDRS letters with an average number of 3.8 injections in a year.

In agreement with the Radiance study, we have found that the largest gain in BCVA was in the first group of patients (axial length <28 mm) and the smallest gain was in the third group (axial length >30 mm). This finding may be related to the prevalence of degenerative changes in the macula, which are more represented in the eyes with a larger axial length, and which do not make possible such improvement as was observed in the group with a smaller axial length.

Another possible explanation is the assumption that the larger eyes need a higher dose of intravitreal drug administration.

The present study has demonstrated in the first group of patients a gain of 10.7 ETDRS letters after 12 months from the commencement of treatment with an average number of 3.88 injections; in the second group, the gain was 9.8 ETDRS

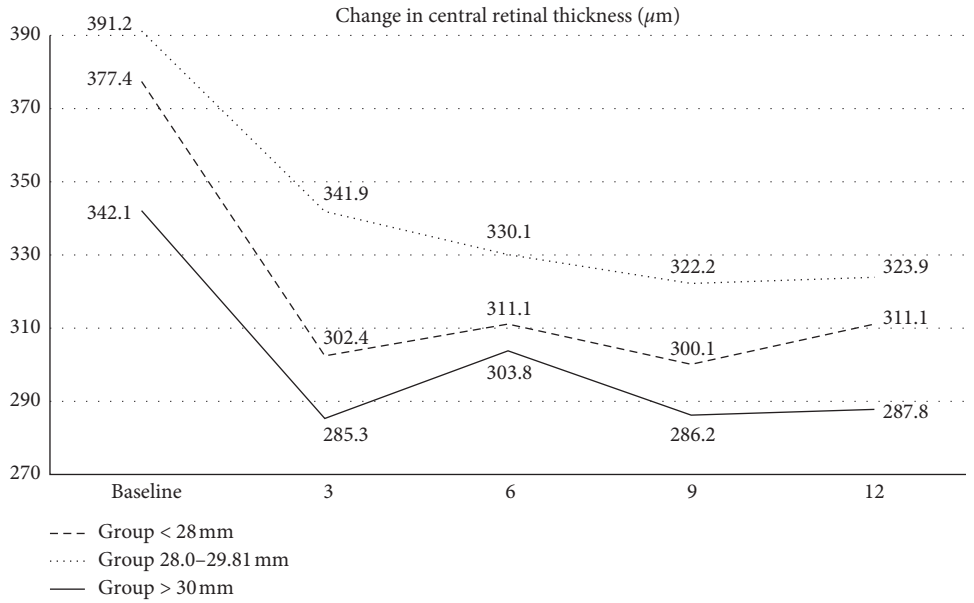

Figure 4: Anatomical outcomes over time for eyes with mCNV with different axial lengths. All groups showed a significant decrease in CRT from baseline to the final 12-month follow-up.

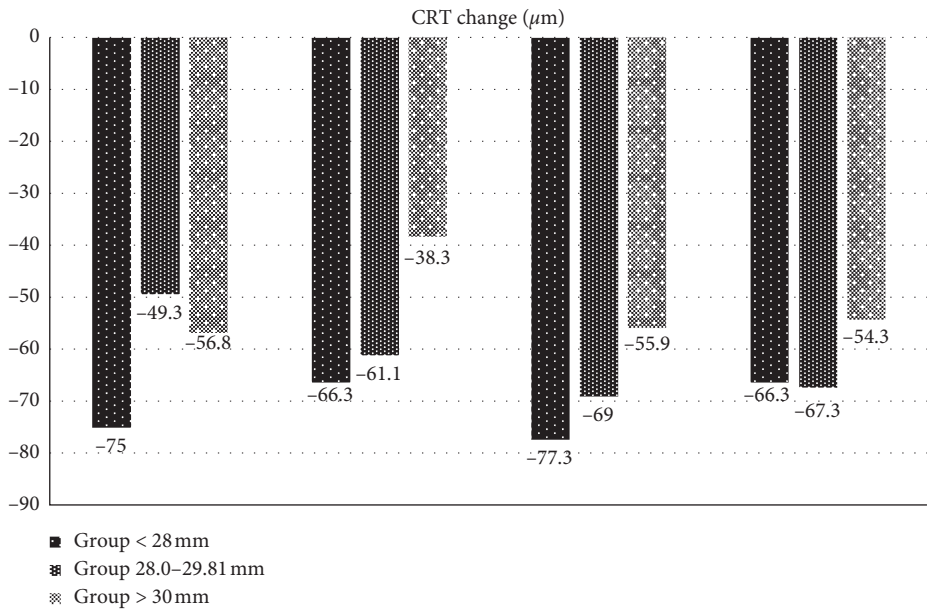

Figure 5: The mean change in CRT in micrometres from baseline for three groups with different axial lengths during the first year of ranibizumab treatment.

letters (average number of injections 3.59), and in the third group, the gain was 7.2 ETDRS letters (average number of injections 2.9). Comparison of the results of BCVA changes after a one-year follow-up and did not reveal a statistically significant difference between the groups, but indirect dependence was demonstrated between axial length and the resultant value of visual acuity.

The results of the study also correlate with the results of the paper by Wu and Kung [18], who published results of a one-year follow-up of patients with mCNV treated with ranibizumab in the PRN regimen. The average axial length of the eye was 28.24 ± 1.09 mm (in the range 26.07–29.63), and the average number of ranibizumab injections was 3.44 ± 0.92 (in the range 3–6). During the 12 months, in 19 eyes, only 3 introductory ranibizumab doses were administered (76%). The other 6 eyes (24%) needed between one and three more ranibizumab injections in the course of the follow-up. After a 12-month follow-up, an average improvement in BCVA of +14.4 letters of ETDRS optotypes ($p < 0.001$) with a decrease in CRT of −47.6 mm ($p = 0.012$) was observed. The baseline values of axial length, average number of ranibizumab injections, and functional and

anatomical results in our study are comparable with the study by Wu et al., and they have demonstrated a clinically significant improvement of BCVA and a decrease in CRT during a one-year follow-up.

Clinical trials are by their very nature carried out on a restricted study population. Despite this, the results of such trials are widely assumed to reflect outcomes that may be hoped to be achieved in future clinical practice.

The strengths of our study include evaluating the effect of ranibizumab treatment in groups of patients divided by axial lengths. Another strong point of our study is the multicenter design. Patients were enrolled in four university municipal hospitals throughout the Czech Republic. The limitations of our study are the retrospective and observational nature and the relatively small sample size compared with bigger clinical trials.

5. Conclusion

The study presents one-year real-life outcomes in treatment-naive patients with myopic CNV divided into three groups according to axial length of the eye and treated with ranibizumab in a PRN regimen. According to our experience, ranibizumab treatment with a *pro re nata* regimen results in a statistically significant visual acuity gain and improvement in retinal anatomic outcomes over a one-year follow-up in all groups of patients. The group with axial lengths >30 mm demonstrated a poorer functional and anatomical response to the treatment.

When comparing the results of BCVA and CRT changes after one year of follow-up, there was no statistically significant difference between groups. We have demonstrated that there exists an indirect dependence between the axial length of the eye and the resultant BCVA and also an indirect dependence with a decrease in CRT in the course of one-year treatment.

Data Availability

The data used to support the findings of this study are freely available and are included within the article.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Research Article

Four-Year Outcome of Aflibercept Treatment-Naïve Patients for Neovascular Age-Related Macular Degeneration: Evidence from a Clinical Setting

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Introduction. The objective of the study is to report 4-year treatment outcome with intravitreal Aflibercept injections for neovascular age-related macular degeneration (nAMD) as first life therapy in real-life. *Patients and Methods*. This is a prospective, monocenter, observational case series analysis. Data from treatment-naïve patients with nAMD with at least 4 years of follow-up were included in the analysis. Data including age, gender, and visual acuity measured on Early Treatment of Diabetic Retinopathy Study charts (ETDRS) and injection numbers were recorded. Spectral domain optical coherence tomography (SD-OCT) data at baseline, month 3, month 6, month 12, year 2, 3, and 4 were also recorded. Patients were treated with a modified treat and extend (T&E) regimen. *Results*. Of the 48 eyes with nAMD treated, only 31 eyes were available at the 4-year follow-up. The mean age was 81 ± 8 years. The VA gain was 7.3 ± 12.7 letters at 1 year 6.5 ± 12.5 letters at 2 years, VA gain 5.2 ± 17 letters at 3 years, and 6.2 ± 18.6 letters at 4 years. The reduction of central retinal thickness was 118 ± 187 μm at 4 years. Complete resolution of fluid was obtained in 18/31 eyes. The total number of injections was 5.7 ± 2.0 during the first year, 2.9 ± 2.9 during the second year, 3.5 ± 3.3 during the third year, and 4.0 ± 3.4 during the fourth year. The total number of injections was 16 ± 10.6, ranging from 3 to 52 injections. Ten eyes developed macular atrophy over the 4-year period. *Conclusion*. The results suggest that good long-term morphological and functional outcome can be achieved using Aflibercept in clinical setting.

1. Introduction

Age-related macular degeneration is the major cause of blindness in the elderly [1]. Neovascular AMD (nAMD) is characterized by choroidal neovascularization (CNV), which is diagnosed by stereoscopic biomicroscopic examination of the macula, optical coherence tomography (OCT), retinal angiographies, or OCT angiography [2, 3]. Antivascular endothelial growth factor (VEGF) is the gold standard of neovascular AMD and is recommended in the international guidelines as a first-line therapy [4].

Aflibercept has been approved by the UD Food and Drug Administration in November 2011, in Europe in November 2012 [5], and was available and reimbursed in neovascular AMD in France since November 2013. Both ranibizumab and aflibercept are approved for nAMD therapy. With anti-VEGF therapy, visual gain is generally obtained at the first year, which was maintained at the second year [6, 7]. At 4 years and 5 years, visual acuity dropped to baseline level in patients of the extension study, HORIZON and CATT [8, 9], or in the real-life study [10]. After 5 years, visual acuity gradually declined thereafter in a subsequent SEVEN-UP study [11].

While the abovementioned studies used ranibizumab or bevacizumab, few data were available in long term with Aflibercept. Unlike ranibizumab and bevacizumab, aflibercept binds to VEGF-A, VEGF-B, and another protein, placental growth factor (PIGF), which is believed to play a

role in progression of neovascular AMD. It has a higher affinity for VEGF and has longer half-life. Two-monthly injection of aflibercept has been shown to be safe and effective as monthly injection of ranibizumab in the treatment of nAMD in phase III of VIEW-1 and VIEW-2 studies at one year [12] and at 2 years [13]. In addition, switching to aflibercept in ranibizumab-refractory cases lead to anatomical improvement [14, 15]. Thus, we supposed that aflibercept may yield better long-term visual outcomes.

The objective of the study is to evaluate the visual and anatomical outcome at 4 years with modified T&E regimen in naïve patients treated with aflibercept and investigate the factors associated with the final vision.

2. Patients and Methods

2.1. Study Design. This is a prospective observational, consecutive case series conducted in the Ophthalmology Department of Lille Catholic Hospitals. This study was performed in accordance with the Helsinki Declaration. Institutional review board was approved by the local ethic committee, and informed consent was obtained from all patients.

2.2. Patients. Patients with neovascular AMD who presented to Saint Vincent hospital of Lille Catholic Hospitals from November 2013 to May 2015 and starting with Aflibercept therapy were enrolled. We have already reported the two-year results [6]. This is a consecutive study based on previous research.

Inclusion criteria included naïve patients with neovascular AMD treated with aflibercept. Exclusion criteria were (1) age ≤60 years, (2) other vitreoretinal disease, (3) intraocular surgery less than 3 months, and (4) choroidal neovascularization related to other disease than AMD.

2.3. Intervention and Observation Procedure. Measurement of Early Treatment Diabetic Retinopathy Study (ETDRS) best-corrected visual acuity (BCVA), intraocular pressure assessment, spectral-domain optical coherence tomography (SD-OCT), fluorescein angiography and indocyanine green angiography using a confocal laser scanning ophthalmoscope (HRA2; Heidelberg Engineering GmbH, Heidelberg, Germany) were performed at baseline. Visual acuity, adverse event monitoring, and SD-OCT were recorded at each visit. The SD-OCT-derived images had been obtained by using an eye-tracking system. Inverted images had also been routinely obtained by an enhanced depth imaging technique for the measurement of subfoveal choroidal thickness (EDI) [16]. Central retinal thickness (CRT) and macular thickness (MT) volume were computed automatically by the software (Heidelberg Eye Explorer, Heidelberg, Germany). Pigment Epithelial Detachment PED height and subfoveal choroidal thickness were manually measured. Analyses of OCT scans and variables measurements were conducted by 2 ophthalmologists (VR and YG) masked to the patient's characteristics. The presence of intraretinal fluid (IRF), subretinal fluid (SRF), hyper-reflective subretinal exudation (HSE), and disruption of ellipsoid zone (EZ) was defined as previously defined [17, 18].

2.4. Treatment Regimen. Participants were treated with a modified T&E regimen described previously [6] which consisted of three phases. (1) Induction phase with 3 doses of aflibercept injection (2 mg/0.05 ml) at 4-week intervals, (2) adaptation phase from week 12 to week 32, during which patients had to visit every 4 weeks and treated as needed to determine the recurrence interval, (3) after week 32, T&E was applied up to a maximum of 12-week interval during the first year and the second year. From year 2 to year 4, injection interval was extended up to 16 weeks and treatment was discontinued if there was no activity after 3 consecutive visits with injection. Once the treatment was discontinued, the monitoring protocol was monthly during the first year and then bimonthly thereafter.

If disease remained inactive through the 32-week period of observation, the patient continued the PRN dosing regimen at monthly or bimonthly visits. The retreatment criteria included recurrence of intra-/subretinal fluid or hemorrhages [19].

A treatment adherence was set up at the first visit. Explanations to patients and their relatives of importance of follow-up and treatment were given. Visits and injections were performed in the same appointments to reduce burden and fatigue. A sheet of scheduled appointments for a 6-month period was given to the patients and their family. They were requested to call in order replace a missed appointment within the week. Reimbursement for transportation was prescribed and obtained by the national healthcare system for patients if necessary. A message was sent to patients before the appointment, thanks to the reminder system set up by the hospital. When an appointment was missed, a nurse also called the patient to reschedule at the earliest a new appointment.

2.5. Data Collection. Data such as demographic characteristics, history of disease, history of ranibizumab treatment, and follow-up duration before and after the switch were collected from medical records and entered into an electronic file. ETDRS score, CRT, macular volume, subfoveal choroidal thickness, the maximum height of PED, the presence of intraretinal fluid (IRF), subretinal fluid (SRF), subretinal hyper reflective exudations (SHE), and disruption of the ellipsoid zone were collected. Data were collected monthly from baseline to 6 months, at 12 months, 24 months, 36 months, and 48 months. Window for data collection at the chosen annual time points was 2 months.

2.6. Study Outcome. The primary study outcome was change in mean VA over 48 months after initiating treatment. Secondary outcomes were change in the CRT, change in macular volume, change in subfoveal choroidal thickness, change in PED height, and mean number of injections, number of eyes with resolution of fluid, and qualitative description of OCT at different time points.

2.7. Statistical Analysis. Descriptive data are described as mean and 95% confidence interval or number (percentage). The statistical analysis was performed as paired comparisons between different time points using SPSS for Windows (version 20 SPSS, Chicago, IL). While we used results of survivors who completed four-year follow-up, data that included dropout patients were analyzed using last observation carried forward (LOCF) policy for the sensitivity analysis. The paired *t*-test was used for comparison between paired continuous variables. One way ANOVA was used to study the relationship between visual gain at year 4 as dependent factor and age, baseline visual acuity, baseline lesion size, and number of injections given as independent factors and four-year visual gain as dependent factor. Statistical significance was set at $P < 0.05$.

3. Results

3.1. Description of the Cohort. Baseline clinical characteristics of the study population (survivors and dropouts) are summarized in Table 1 and Figure 1. Forty-eight eyes of 38 patients were included. In our center, the reported rate of missed/changed appointments was 11% [6]. Dropout eyes were 17/48 (35%) after the 4-year follow-up. Overall, 31 achieved the 48-month end-point. In summary, dropout patients were older at inclusion (83.6 ± 1.9 years) than patients who have completed the study (78.3 ± 1.2 years, $P = 0.013$). We did not find any difference of baseline BCVA between the dropout eyes (53.1 ± 16.2 letters) and that of the eyes which achieved the 4-year follow-up (57.6 ± 16.4 letters; $P = 0.39$).

3.2. Visual Outcome. BCVA increased from 56.1 ± 16.3 letters at baseline to 57.7 ± 20.5 letters to month 3 with a gain of $+1.6 \pm 11.1$ letters ($P = 0.419$) (Figure 2). At 6 months, visual gain was $+5.0 \pm 11$ letters (61.1 ± 17.2 letters, $P = 0.017$). At 12 months and 24 months, visual gain was still significant: $+7.3 \pm 12.7$ letters (63.4 ± 14.8 letters, $P = 0.015$) and $+6.5 \pm 12.5$ letters (62.5 ± 19.3 letters, $P = 0.018$), respectively. At 36 and 48 months, we observed letters gain of $+5.2 \pm 16.9$ letters (61.3 ± 21 letters, $P = 0.224$) and $+6.2 \pm 18.6$ letters (62.3 ± 24.5 letters, $P = 0.162$), respectively, although this difference was not statistically significant. Vision gain at 4 years was correlated with that at 6 months ($r = 0.41$, $P = 0.04$) and at one year ($r = 0.42$, $P = 0.05$). There was correlation between visual gain at 4 years and baseline visual acuity, baseline lesion size, and number of aflibercept injection given.

At one year, all patients have gained or maintained vision. At 2 years, 33/35 eyes (94.3%) maintained vision (loss < 15 letters), while 8/35 eyes (22.9%) earned ≥ 15 letters. At four years, (28/31) 90% maintained vision while 8/31 (26%) earned ≥ 15 letters.

The proportion of eyes with VA ≥ 70 letters, allowing driving vision, increased from baseline (14/48, 29.1%) to 16/41 (39%) at 12 months, 15/35 (43%) at 24 months, 15/31 (48%) at 36 months, and 18/31 (58%) at 48 months.

Table 1: Baseline characteristics of the study population.

Number of patients (eyes)	38 (48)
Age, mean ± SD (years)	81 ± 8
Sex, *n*, male/female	
Male	12
Female	26
Bilateral disease	10
Baseline visual acuity, mean ± SD	56 ± 16
GLD, mean ± SD (mm)	2.2 ± 1.4
Surface area, mean ± SD (mm^2)	3.8 ± 3.9
CNV type, *n* (%)	
Type 1	26 (54)
Type 2	8 [17]
Type 3	12 [20]
Polypoidal choroïdal vasculopathy	2 [4]

GLD, greatest linear diameter; CNV: choroidal neovascularization; SD: standard deviation.

At the end of 4 years of follow-up, 8 eyes (26%) gained ≥ 15 letters ETDRS, 5 eyes (16%) gained 10–14 letters, 1 eye (3%) gained between 5 and 9 letters, 4 eyes (13%) gained between 0 and 4 letters, 10 eyes (32%) lost <15 letters, and 3 eyes (10%) lost ≥ 15 letters. Causes of loss of >15 letters was submacular hemorrhage in one case, foveal involved PED tear in one case, and foveal atrophy in one case.

3.3. Anatomical Response to Aflibercept. The central retinal thickness (CRT) decreased significantly from baseline ($410 \pm 131\ \mu m$) to month 3 ($282 \pm 71\ \mu m$, $P < 0.001$); to month 6 ($288 \pm 74\ \mu m$, $P = 0.001$); to month 12 ($294 \pm 75\ \mu m$, $P = 0.004$); to month 24 ($288 \pm 70\ \mu m$, $P = 0.05$), to month 36 ($289 \pm 80\ \mu m$, $P = 0.463$, and to month 48 (292 ± 110, $P = 0.365\ \mu m$) (Figure 2).

Macular volume (MV) decreased significantly from $8.97 \pm 1.21\ mm^3$ at baseline to $7.97 \pm 0.82\ mm^3$ ($P < 0.001$) at month 3; to $8.04 \pm 0.79\ mm^3$ ($P < 0.001$) at month 6; to $8.03 \pm 0.65\ mm^3$ ($P < 0.001$) at month 12; to $7.97 \pm 0.74\ mm^3$ ($P < 0.001$) at month 24; to $8.07 \pm 0.64\ mm^3$ ($P = 0.001$) at month 36, and $8.20 \pm 1.28\ mm^3$ ($P = 0.043$) at month 48.

The PED height decreased significantly from baseline to month 3 ($165 \pm 97\ \mu m$ to $129 \pm 80\ \mu m$, $P = 0.014$) at month 3; to $129 \pm 67\ \mu m$ ($P = 0.02$) to month 6; to $122 \pm 69\ \mu m$ ($P = 0.01$) at month 12, and to $141 \pm 107\ \mu m$ ($P = 0.045$) at month 24. After year 2, the difference in PED height from baseline was no longer significant: $140 \pm 85\ \mu m$ ($P = 0.147$) at month 36 and $147 \pm 107\ \mu m$ ($P = 0.516$) at month 48.

3.4. Subfoveal Choroidal Thickness. The subfoveal choroidal thickness was $192 \pm 91\ \mu m$ at baseline; $184 \pm 91\ \mu m$ at month 3; $185 \pm 86\ \mu m$ at month 6; $185 \pm 85\ \mu m$ at month 12; $184 \pm 93\ \mu m$ at month 24; $189 \pm 85\ \mu m$ at month 36, and $184 \pm 87\ \mu m$ at month 48. Change in subfoveal choroidal thickness was not significant over visits.

3.5. Distribution of Fluid and Qualitative SD-OCT Analysis. Distribution of fluid, subretinal hyper exudation, and EZ disruption on SD-OCT was summarized in Table 2. IRF and/or SRF were present in 45/48 (94%) eyes at the beginning of

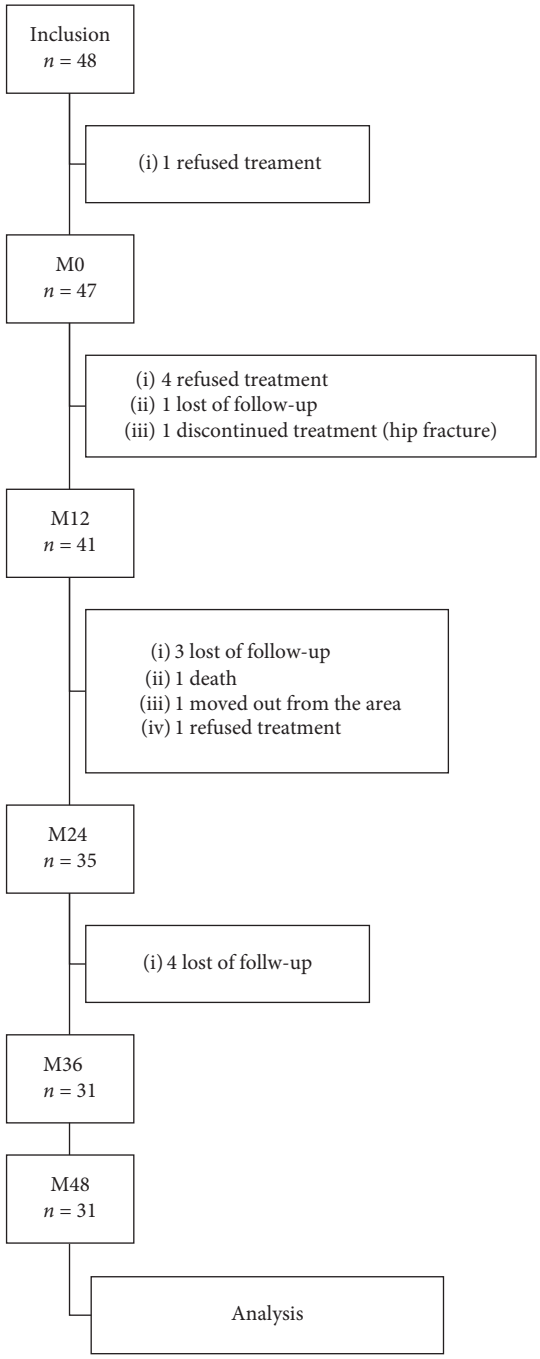

Figure 1: Flow chart of the cohort and survivors at year four.

the study. Complete resolution of fluid was obtained in 38/45 eyes (84%) after the induction phase, in 25/41 eyes (61%) at one year, and in 23/35 eyes (66%) at 2 years. At 48 months, 18/31 (58%) of the eyes had a complete resolution of fluid.

SHE was present in 27/48 eyes (56.2%) at baseline, in 16/45 eyes (35.6%) at month 3, in 8/41 (19.5%) at month 12, in 7/35 eyes (20%) at month 24, in 11/31 eyes (35%) at month 36, and in 10/31 eyes (32%) at month 48.

Ellipsoid zone disruption was observed in 44/48 (92%) eyes at baseline, 35/45 (78%) eyes at 3 months, in 34/41 (83%) at one year and in 31/35 (89%) at 2 years, in 27/31 eyes (87%) at month 36, and in 29/31 eyes (94%) at month 48.

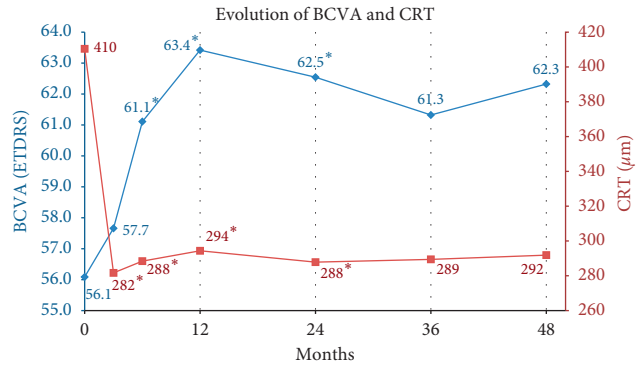

Figure 2: Best corrected visual acuity (BVCA -ETDRS score) and central retinal thickness (CRT) over visits. $^{*}P < 0.05$.

Over the 4 years of follow-up, 2/48 eyes (4%) displayed a PED tear and 3/48 eyes (6%) had a subretinal hemorrhage, and 10 eyes (32%) developed a macular atrophy.

3.6. Frequency of anti-VEGF Intravitreal Injection. Mean number of IAI was 5.7 ± 2 (median = 6, ranging from 3 to 11) during the first year, 2.9 ± 2.9 (median = 3) during the second year, 3.5 ± 3.3 (median = 3) IVT in year 3, and 4 ± 3.4 (median = 4) IVT in year 4. The average number of aflibercept injections received at the end of 4 years was 16 ± 10.6 IVT, ranging from 3 to 52 injections. There was a bimodal distribution: some patients did not require any injection after the loading phase, while 6 to 13% patients required injection every 4 weeks (Figure 3).

After the loading phase, 6 of 41 (14.6%) eyes did not have any activity through the first and second year. Among these, 2/6 were still inactive until month 48; 1/6 reactivated at the third year with maintained vision requiring 2 aflibercept injections, 1/6 died during the third year, and 2/6 were lost of follow-up. At the end of year 3, aflibercept was suspended in 7/31 (22.5%) eyes without any reactivation during year 4. At the end of year 4, suspending treatment was possible in 9/31 eyes (30%), whereas 70% others were receiving ongoing aflibercept treatment. No additional treatment was applied during this period.

Overall, treatment intervals of >8 weeks were found in 20/41 (48.7%) eyes during the first year and 32/35 (91.4%) during the second year. Proportion of eyes which needed interval injection ≥12 weeks increased with time, 39% at 2 years, 58% at 3 years, and 74% at 4 years (Figure 4). The maximum interval of 16 weeks was scheduled in 3 eyes and among these, 1 reactivated requiring shortened interval.

3.7. Adverse Events. During the 2-year study, 40/360 (11%) planned appointments had been changed or missed because of various causes (systemic disease, falls, hip fractures, stroke, and unavailability of accompanying person). Two of 7 patients who had interrupted monitoring and treatment during the first year came back to be treated during the second year. Two patients underwent cataract surgery during the 4-year follow-up. No other ocular adverse event

Table 2: Qualitative OCT results over visits. SRF (sub retinal fluid), IRF (intraretinal fluid), HRD (hyper-reflective dots), SHE (subretinal hyper exudation), and EZ (ellipsoid zone) disruption.

	Inclusion $n = 48$	3 months $n = 45$	6 months $n = 44$	12 months $n = 41$	24 months $n = 35$	36 months $n = 31$	48 months $n = 31$
SRF	29 (57%)	3 (7%)	8 (18%)	5 (12%)	6 (17%)	5 (16%)	6 (19%)
IRF	25 (53%)	7 (16%)	9 (20%)	8 (20%)	10 (29%)	9 (29%)	12 (39%)
NO FLUID	3 (6%)	38 (84%)	21 (48%)	25 (61%)	23 (66%)	21 (68%)	18 (58%)
HRD	43 (91%)	36 (80%)	28 (64%)	26 (63%)	15 (43%)	22 (71%)	23 (74%)
SHE	27 (57%)	16 (36%)	14 (32%)	8 (20%)	7 (20%)	11 (35%)	10 (32%)
EZ DISRUPTION	44 (94%)	35 (78%)	30 (68%)	34 (83%)	31 (89%)	27 (87%)	29 (94%)

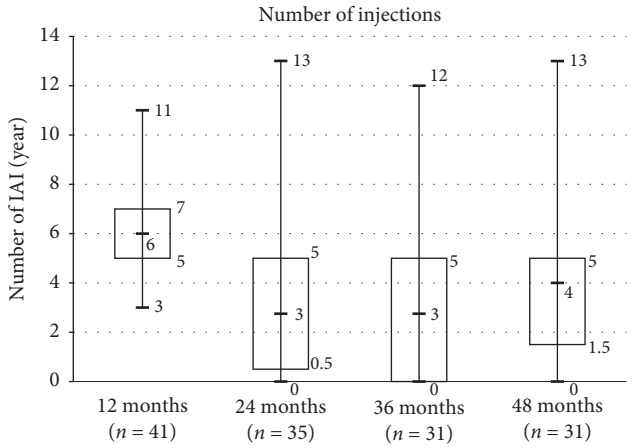

Figure 3: Box-plot of aflibercept injection number during the 4-year period.

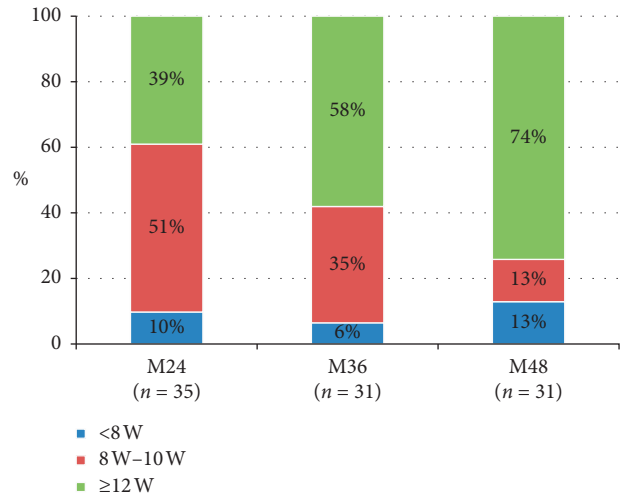

Figure 4: Proportion of interval treatment from year 2 to year 4.

(retinal detachment and glaucoma) occurred during the follow-up.

4. Discussion

In this study, we evaluated functional an anatomic response of 4-year outcome of aflibercept therapy naïve nAMD patients with a modified T&E dosing regimen in a real-life. The results showed favorable visual outcome with a mean gain of +7.3 letters at one year and of +6.5 letters at 2 years, compared with baseline. Visual gain was then described with survivors; however, the difference was not significant. The vision was maintained (losing <15 letters) in 90% eyes and most importantly, driving-vision (≥70 letters) was maintained in 58% of survivors at long term. Good anatomical response was also obtained with reduction of CRT, macular volume, and complete resolution of fluid in 58%. Two-thirds of eyes had complete resolution of fluid at 1 and 2 years and 58% of them at 4 years. Number of aflibercept injections varied widely among eyes, supporting for an individualized regimen. Additionally, we found that visual gain at 4 years was correlated with visual gain at 6 months.

Real-word clinical settings differ from clinical trial in several ways: patients were unselected and diverse; with range of comorbidity and a wider range of treatments, paradigms are implemented. It has been shown that functional stability is better in T&E compared with PRN with a 1.6 more injections but fewer clinical visits [21]. Real-world studies demonstrated that proactive dosing with aflibercept yields similar outcome to those observed in clinical trials and proactive TE-regimen is superior to PRN-regimen in clinical routine care of nAMD [22–24]. Our previous report of 2 years' results showed that aflibercept achieved similar anatomical and visual outcome using a modified T&E protocol, avoiding overtreatment in comparison with T&E real world observation registry [6].

Our real-life study also reported that accidents (fall and hip fracture), comorbidity, or relative constraints occurred 11% to 14% scheduled appointment per year, resulting in 35% missed data for the 4-year analysis in spite of effort to maximize adherence regimen. The rate of patients who dropped out was 31% in Eleftheriadou's study at 3 years [22] and 25% in Nishikawa et al.'s study at 4 years [25]. These factors can all impact on treatment outcomes [11].

The visual four-year outcome in our study is similar to Eleftheriadou's report at 3 years [22], which is to better than that of real-life studies reported by previous studies using aflibercept. We found that +6.2 letters gain was observed at 4 years and a mean number of 16 injections, though the difference was not statistically different. Eleftheriadou reported visual gain of +5.9 letters, +6.4 letters, and +6.6 letters at year 1, year 2, and year 3, respectively, with 15.6 injections at 3 years using 3 loading dose and bimonthly aflibercept injection followed by T&E regimen during year 2 and 3.

Nishikawa et al. [25] investigated four-year outcome of aflibercept for nAMD and polypoidal choroidal vasculopathy, using 3 loading doses, then bimonthly aflibercept injection during the first year, and then PRN during the subsequent three years and found that visual gain obtained in the first year is gradually lost in real-world clinical practice, but vision remained above baseline level and vision was maintained in 94.5% of patients with only 15 injections. Traine et al. described in a subgroup of newly diagnosed nAMD patients with 4-year follow-up using 3 aflibercept injections of an initial loading phase following a T&E regimen that vision was stable compared to baseline (−0.7 letters, $P = 0.35$) with a mean number of 7.7 injections during the first year and 4.4 injections per year from year 2 to year 4. The HORIZON study applied monthly ranibizumab injections during the first 2 years and then administered as needed in the following two years. This study showed that vision decreased. The HORIZON study showed that vision gain decreased to 2 letters and maintenance of vision was achieved in 80.4% at year four. The CATT study cohort examined the monthly bevacizumab or PRN with the switch from monthly to PRN. This study reported a loss of 3 letters at year 4 and a vision maintenance rate of 87.1%. Overall, there is a similar tendency that visual gain was no longer significant at four year, thus under different individualized regimens (3 + Q8 + PRN in Nishikawa's report, 3 + T&E in Traine's report). The 4-year data from a controlled clinical trial VIEW-1 extension, which applied a modified quarterly aflibercept injection schedule, followed by at least an every 8-week dosing through week 212, showed that vision gain maintained at 4 years with mean gain of +7.1 letters and mean number of injection 12.9 in the extension study.

Interestingly, in real-world studies, fewer numbers of injections were not associated with limited vision gain, as reported our study described in a previous study [9]. The presence of the external limiting membrane at baseline and at one year was associated with visual gain at 4 years [25]. The treatment interval extension ≥ 12 weeks was possible in half cases after year 2 and gradually increased with time up to 74% at 4 years [20] while 6% to 13% of cases need injections at ≤ 6 weeks of interval. Our modified T&E regimen with an observation period which allowed avoiding over- and undertreatment could be expected to produce good outcome with fewer injections while limiting number of visits and treatment burden on patients and caregivers.

Rate of good anatomic response defined as complete resolution of fluid was found in 58% in our study at 4 years, which was greater to that of previous reports showing persistence of fluid in 83% of eyes at 5 years using bevacizumab [8]. Rate of eyes with SHE, which represents the sign of active nAMD, was also reduced over visits. The proportion of EZ disruption and choroidal thickness reduction remained stable during the 4-year period.

The strength of our study is that (1) this is a real-world report on long-term results of aflibercept with at least 4 years of follow-up using a T&E regimen after an observation period, (2) patients were followed up and treated by the same physician ensuring the standardized personalized regimen, and (3) the set-up of the reminder system to avoid missed appointment. The limit of the study is the small number of included patients and the rate of loss of follow-up which may be responsible to a positive position leading to a better visual gain.

To conclude, in a real-world setting, treatment-naive patients with nAMD treated with aflibercept injection achieved good visual and anatomical outcome. Vision was maintained at 4 years for 90% of eyes, and 58% of eyes had VA of 20/40 or better, allowing driving-vision with an acceptable burden of the disease using an individualized regimen including observation phase and T&E regimen.

Data Availability

Data are available from the authors upon reasonable request and with permission of their institution.

Ethical Approval

The Institutional Review Board of Lille Catholic Hospitals acknowledged the study of this cohort.

Conflicts of Interest

The authors declare no conflicts of interest.

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Research Article

Anti-VEGF Treatment of Diabetic Macular Edema: Two-Year Visual Outcomes in Routine Clinical Practice

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Purpose. The purpose of this study was to evaluate 2-year visual outcomes in patients with diabetic macular edema (DME) treated with anti-VEGF agents in a routine clinical setting. *Methods*. The medical records of patients treated with ranibizumab or aflibercept due to DME at the Eye Hospital, University Medical Centre Ljubljana, Slovenia, between January 2016 and March 2019 were retrospectively reviewed. After applying inclusion and exclusion criteria, 123 patients (123 eyes) were included in the study. *Results*. Baseline visual acuity (VA) was 60.9 ± 15.2 letters (median 63; range 7–85). Baseline central retinal subfield thickness (CRT) was 440.7 ± 132.5 μm (median 430; range 114–1000). No significant change in VA over 2 years was found (mean change +2.1 ± 16.8 letters (median 2; range −53–52)). However, there was a significant change in VA in the subgroup with baseline VA <70 letters (mean change +5.7 ± 17.9 letters (median 5; range −52–52)). VA gains of ≥15 letters were achieved in 25 eyes (20.3%). Changes in CRT were significant over 2 years. Patients received 4.5 ± 2.1 (median 5, range 1–9) and 2.6 ± 2.3 (median 2, range 0–8) injections in the first and second years, respectively. *Conclusions*. The two-year visual outcomes in this retrospective analysis appear to be comparable to previously reported outcomes in routine clinical practice. Our analysis provides some information about the effectiveness of anti-VEGF treatment in routine clinical practice in Slovenia. More intensive treatment should be implemented in the management of patients in order to achieve better visual outcomes.

1. Introduction

Diabetic macular edema (DME) may affect up to 7% of patients with diabetes. This vision-threatening complication of diabetes can have a significant impact on patient quality of life. The risk factors for DME development are largely similar to those of diabetic retinopathy (DR) [1, 2].

Vascular endothelial growth factor (VEGF) has a crucial role in the complex pathogenesis of DME [3–5]. One of the most obvious effects of VEGF activity is the blood-retinal barrier breakdown [6]. Agents that block VEGF action restore the integrity of the blood-retinal barrier, resolve macular edema, and improve vision in most patients with DME [7]. Several randomized clinical trials (RCTs) have demonstrated the efficacy and safety of anti-VEGF agents in the treatment of DME, with greater improvements in visual acuity (VA) achieved by anti-VEGF treatment compared to laser therapy [8–12]. The introduction of anti-VEGF agents into clinical practice has considerably changed the management of patients with DME. Currently, intravitreal anti-VEGF agents are the preferred first-line treatment for DME [13]. Corticosteroids can also be used in the management of DME, mostly as a second-line treatment option [14–19].

RCTs, the gold standard for evaluating treatment outcomes, are research tools with strong internal validity but low generalizability to real-life conditions [20]. It is difficult to implement intensive RCT treatment protocols in routine clinical practice, where patient selection is not as rigorous and resources differ from those in RCTs [21]. In contrast to RCTs, real-life studies reflect the management of patients in routine clinical practice and provide insight into the real-life effectiveness of treatment [20]. Most real-life studies

evaluating the effectiveness of anti-VEGF treatment in DME have demonstrated lower VA gains in comparison with RCTs [22–28].

Anti-VEGF treatment of patients with DME in Slovenia started in 2011. There is a constant overload of patients needing anti-VEGF treatment. The difficulties in managing an increasing number of patients may have an impact on treatment results. The purpose of this study was to evaluate 2-year visual outcomes in patients with DME treated with anti-VEGF agents in a routine clinical setting at the Eye Hospital, University Medical Centre Ljubljana, Slovenia.

2. Methods

The medical records of all patients treated with an anti-VEGF agent (ranibizumab or aflibercept) for DME at the Eye Hospital, University Medical Centre Ljubljana between January 2016 and March 2019 were retrospectively reviewed. Data collected were age, history of previous treatment for DME, best-corrected VA at baseline and one year and two years of follow-up, central retinal subfield thickness (CRT) at baseline and one year and two years of follow-up, morphological type of the edema on optical coherence tomography imaging (OCT), presence of vitreomacular traction, stage of DR, prior laser treatment (laser treatment for macular edema and/or panretinal photocoagulation), number of visits and number of anti-VEGF injections in the first and second year, and adverse events.

The inclusion criteria were patients older than 18 years, a diagnosis of DME, availability of complete ophthalmological medical records, and a follow-up period of at least 2 years. The exclusion criteria were incomplete ophthalmological data, significant vitreomacular traction, other ocular conditions that could affect VA, laser treatment or treatment with steroids less than 6 months prior to anti-VEGF treatment and/or during the follow-up period, cataract surgery during the follow-up period and vitrectomy. If patients received treatment in both eyes, only one eye, randomly chosen, was included in the present analysis. Randomization was digitalized. The researchers who collected the data were not involved in the management of the patients.

Patients were managed according to routine clinical practice. A complete ophthalmological examination (VA testing, slit lamp and dilated fundus examinations, intraocular pressure measurement), OCT, fundus photography, and fluorescein angiography were performed at the first visit to evaluate DME and the stage of DR before any treatment decision. All patients signed informed consent to the treatment and to the use of their anonymized data for the purposes of clinical audit and research.

A pro re nata (PRN) treatment regimen was supposed to be implemented for anti-VEGF treatment after three to five monthly injections (depending on the drug that was used) as a loading phase. A complete ophthalmological examination, fundus photography, and OCT were performed at every follow-up visit. VA testing was performed using an ETDRS chart (4 meter 2000 series revised ETDRS chart (Precision Vision®, La Salle, USA)), and the best-corrected VA was recorded as the number of ETDRS letters. CRT was measured automatically by a SD-OCT machine 3D-OCT 1000 (Topcon Corp.®, Tokyo, Japan). Nurses trained in ETDRS visual acuity testing tested VA according to the international standards for ETDRS visual acuity testing. An OCT image of the macula was taken by a trained photographer. Nurses and photographers changed according to their work schedule, so each patient at each visit was randomly assigned to a certain nurse or photographer. Each patient was managed by the same physician at every visit.

The baseline characteristics of the patients were noted. The mean VA and mean CRT at 1 year and 2 years were compared to those of the baseline. The mean change in VA and mean change in CRT at 1 year and 2 years were calculated. The proportions of eyes with a VA gain or loss of ≥10 letters and ≥15 letters were also calculated. Eyes with a VA ≥70 letters and eyes with a complete resolution of edema were noted. The number of injections and the number of visits was noted as well.

Eyes were divided into two subgroups according to baseline VA (group 1 with baseline VA <70 letters, group 2 with baseline VA ≥70 letters). The mean VA and mean CRT at 1 year and 2 years were compared to those of the baseline for each group. The mean changes in VA, mean changes in CRT, and the proportions of eyes with a VA gain or loss of ≥10 letters and ≥15 letters were calculated for each group at 1 year and 2 years.

2.1. Statistical Analysis. Descriptive statistics included the mean with standard deviation and median with range (minimum and maximum value) for numerical variables. Since the data did not meet the normality assumption, nonparametric tests were used to assess the differences: the Friedman test and Wilcoxon signed-rank test were used for evaluating changes in the variables from baseline to 1 year and 2 years. The Mann–Whitney U test was used to test the differences in the data between the subgroups of eyes. Additionally, a repeated measures test was used to test the differences in VA and CRT over time and between the subgroups. The McNemar test was used to compare the proportions of eyes gaining or losing ≥10 letters and ≥15 letters. A p value less than 0.05 was considered statistically significant. Statistical analyses were performed using SPSS version 21 (SPSS IBM, New York, USA).

The study adhered to the tenets of the Declaration of Helsinki and was approved by the Slovenian National Medical Ethics Committee (National Medical Ethics Committee number 0120-604-2018).

3. Results

The medical records of all 228 patients (303 eyes) receiving anti-VEGF treatment for DME between January 2016 and March 2019 were reviewed. After applying the inclusion and exclusion criteria, 123 patients (123 eyes) were included in the study. There were 32 eyes treated with ranibizumab, 51 eyes treated with aflibercept, and 40 eyes that received both

Table 1: The VA at baseline, 1 year, and 2 years.

	VA, mean ± SD (median; range) (ETDRS letters)					
	Baseline	1 year	Change from baseline at 1 year	2 years	Change from baseline at 2 years	p value
All eyes ($n = 123$)	60.9 ± 15.2 (63; 7–85)	62.9 ± 15.3 (66; 13–85)	+2.2 ± 14.5 (1; −41–48)	62.9 ± 16.9 (65; 4–85)	+2.1 ± 16.8 (2; −53–52)	0.47
Eyes with baseline VA <70 letters ($n = 77$)	52.1 ± 12.3 (54; 7–69)	57.3 ± 16.0 (59; 13–85)	+5.3 ± 16.7 (4; −41–48)	57.6 ± 17.4 (60; 4–85)	+5.7 ± 17.9 (5; −52–52)	0.017
Eyes with baseline VA ≥70 letters ($n = 46$)	75.6 ± 4.6 (75; 70–85)	72.4 ± 7.6 (72.5; 58–85)	−2.9 ± 7.4 (−2; −21–10)	71.7 ± 11.9 (75; 32–85)	−3.9 ± 12.6 (−2; −53–11)	0.11

Legend: VA = visual acuity.

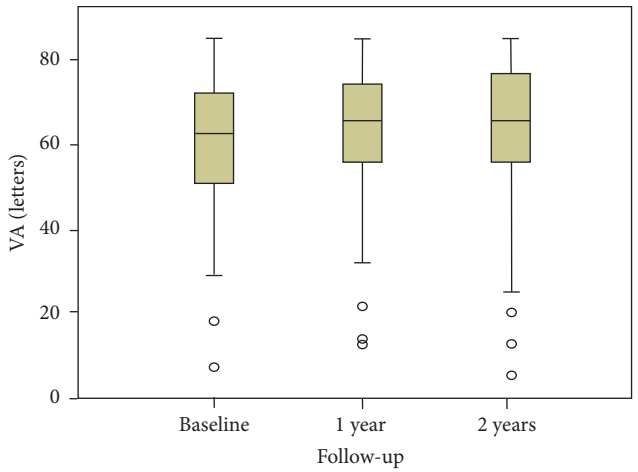

Figure 1: The VA at baseline, 1 year, and 2 years (all 123 eyes)—the changes were not significant (Friedman test: $p = 0.471$).

drugs during the 2-year period (at some time point, one drug was changed for the other).

3.1. Baseline Characteristics. The mean age of the patients was 67.5 ± 8.8 years, 80 were men (65%), and 43 were women (35%). OCT evaluation of the cases of DME showed diffuse edema in two eyes (1.6%), cystoid edema in 56 eyes (45.5%), and edema with a serous detachment in 65 eyes (52.8%). Mild to moderate nonproliferative DR was present in 21 eyes (17.1%), severe nonproliferative DR in 69 eyes (56.1%), and proliferative DR in 33 eyes (26.8%). Prior laser treatment of DME (laser photocoagulation or subthreshold micropulse laser treatment) was performed in 78 eyes (63.4%). Panretinal photocoagulation or some peripheral laser photocoagulation treatment was performed in 46 eyes (37.4%) before the start of DME treatment with an anti-VEGF agent. The baseline VA was 60.9 ± 15.2 letters (median 63; range 7–85). The baseline CRT was 440.7 ± 132.5 μm (median 430; range 114–1000).

3.2. VA. The VA at baseline, 1 year, and 2 years and the VA changes between baseline and 1 year and between baseline and 2 years are presented in Table 1. There was no statistically significant improvement in VA at 1 year or 2 years (Friedman test; $p = 0.471$, Figure 1). The proportions of eyes with a VA gain of ≥10 letters and a VA gain of ≥15 letters and the proportions of eyes with a VA loss of ≥10 letters and a VA loss of ≥15 letters are presented in Table 2. There were 22 eyes (17.8%) with a baseline VA ≤45 letters and 46 eyes (37.4%) with a VA ≥70 letters at baseline. The proportion of eyes with a VA ≥70 letters increased to 53 (43.1%) and 56 (45.5%) at 1 year and 2 years, respectively.

3.3. CRT. The CRT at baseline, 1 year, and 2 years and the CRT changes between baseline and 1 year and between baseline and 2 years are presented in Table 3. The change in CRT was statistically significant (Friedman test; $p < 0.0001$, Figure 2), and the Wilcoxon signed-rank test revealed significantly different changes between all observed time points ($p < 0.0001$). There were 70 eyes (56.9%) and 81 eyes (65.8%) with a CRT reduction of ≥10% at 1 year and 2 years, respectively. A CRT less than 250 μm was documented in 11 eyes (8.9%) at 1 year and in 18 eyes (14.6%) at 2 years.

3.4. Number of Visits and Injections. Patients had 6.7 ± 1.4 (median 7, range 4–11) visits in the first year and 6.5 ± 1.2 (median 6, range 4–10) in the second year (Wilcoxon signed-rank test: $p = 0.007$). The patients received 4.5 ± 2.1 injections (median 5, range 1–9) in the first year and 2.6 ± 2.3 (median 2, range 0–8) in the second year (Wilcoxon signed-rank test: $p < 0.0001$).

3.5. Analysis of Subgroups according to Baseline VA. Analysis of subgroups according to baseline VA showed no statistically significant changes in VA during the follow-up period in patients with baseline VA ≥70 letters (Friedman test: $p = 0.195$, Table 1). In contrast, there were statistically significant changes in VA during the follow-up period in the subgroup with baseline VA <70 letters (Friedman test: $p = 0.017$, Table 1): the changes were significant between baseline VA and VA at 1 year (Wilcoxon signed-rank test: $p = 0.015$) and between baseline VA and VA at 2 years (Wilcoxon signed-rank test: $p = 0.003$). Figure 3 shows the VA change over time for the subgroups divided according to baseline VA. The proportions of eyes with a VA gain of ≥10 letters and a VA gain of ≥15 letters and the proportions of eyes with a VA loss of ≥10 letters and a VA loss of ≥15 letters for both subgroups are presented in Table 2. There were statistically significant changes in CRT from baseline to 1 year and 2 years, respectively, in both subgroups according

Table 2: The proportions of eyes gaining or losing ≥10 letters and ≥15 letters.

	Number of eyes (percentage)											
	VA gain ≥10 letters			VA gain ≥15 letters			VA loss ≥10 letters			VA loss ≥15 letters		
	1 year	2 years	p value	1 year	2 years	p value	1 year	2 years	p value	1 year	2 years	p value
All eyes ($n = 123$)	29 (23.6%)	36 (29.3%)	0.21	20 (16.3%)	25 (20.3%)	0.18	23 (18.7%)	20 (16.3%)	0.81	10 (8.1%)	12 (9.7%)	0.51
Baseline VA <70 letters ($n = 77$)	28 (36.4%)	31 (40.3%)	0.77	20 (25.9%)	25 (32.5%)	0.18	14 (18.2%)	10 (12.9%)	0.51	6 (7.8%)	7 (9.1%)	0.62
Baseline VA ≥70 letters ($n = 46$)	1 (2.2%)	5 (10.9%)	0.12	0	0		9 (19.5%)	10 (21.7%)	1.0	4 (8.7%)	5 (10.9%)	1.0

Legend: VA = visual acuity.

Table 3: The CRT at baseline, 1 year, and 2 years.

	CRT, mean ± SD (median; range) (μm)					
	Baseline	1 year	Change from baseline at 1 year	2 years	Change from baseline at 2 years	p value
All eyes ($n = 123$)	440.7 ± 132.5 (430; 114–1000)	368.4 ± 138.21 (350; 50–1500)	−71.8 ± 159.9 (−64.5; −910–720)	350.4 ± 108.3 (332; 178–800)	−90.4 ± 131.1 (−85; −210–476)	<0.0001
Eyes with baseline VA <70 letters ($n = 77$)	464.2 ± 143.9 (460; 114–1000)	384.8 ± 164.6 (350; 50–1500)	−73.2 ± 185.9 (−62; −910–720)	363.5 ± 110.9 (340; 178–800)	−101 ± 136.8 (−90; −172–440	<0.0001
Eyes with baseline VA ≥70 letters ($n = 46$)	401.5 ± 100.5 (410; 207–665)	333 ± 82.8 (330; 186–700)	−68.2 ± 106.1 (−66.5; −97–479)	328.5 ± 100.9 (320; 186–770)	−72.4 ± 119.9 (−58; −210–476)	<0.0001

Legend: VA = visual acuity, CRT = central subfield retinal thickness.

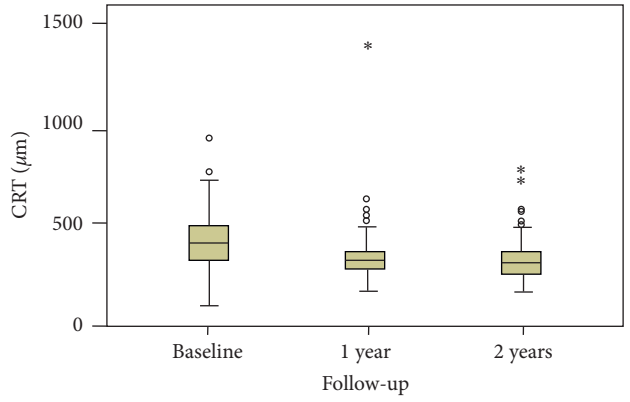

Figure 2: The CRT at baseline, 1 year, and 2 years (all 123 eyes)—the changes were significant (Friedman test: $p < 0.0001$), significantly different changes between all observed time points (Wilcoxon signed-rank test: $p < 0.0001$).

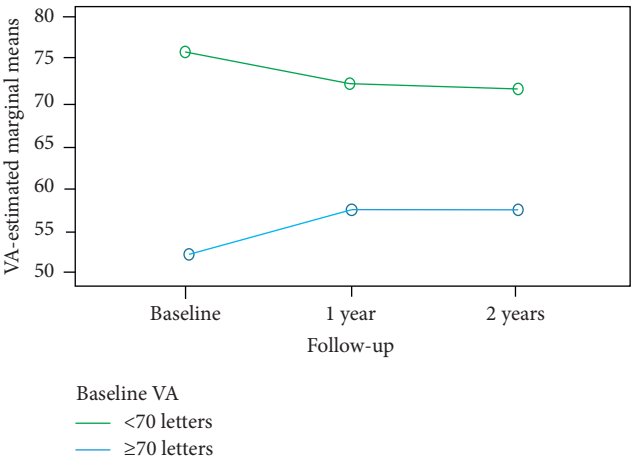

Figure 3: VA change over time for the subgroups divided according to baseline VA. The between-subgroups test was significant ($p < 0.0001$); the lines for the two subgroups are rather far apart in the graph. The within-subject test indicates that there was no overall significant time effect ($p = 0.579$). However, there was an interaction between the subgroups and time ($p = 0.002$): the line representing the subgroup with baseline VA <70 letters increases over time. In contrast, the line representing the subgroup with baseline VA ≥70 letters slightly decreases over time.

to baseline VA (Friedman test: $p < 0.0001$; Wilcoxon signed-rank test: $p < 0.0001$, Table 3). Figure 4 shows the CRT change over time for the subgroups divided according to baseline VA.

Eyes with a baseline VA <70 letters received 4.2 ± 1.9 injections (median 4, range 1–8) in the first year and 2.3 ± 2.3 (median 2, range 0–8) in the second year. Eyes with a baseline VA ≥70 letters received 5.1 ± 2.3 injections (median 5, range 1–9) in the first year and 3.1 ± 2.3 (median 3, range 0–8) in the second year. Eyes with a lower baseline VA received significantly fewer injections in the first year (Mann–Whitney U test: $p = 0.004$). There were no statistically significant differences in the number of injections between the groups in the second year (Mann–Whitney U test: $p = 0.26$).

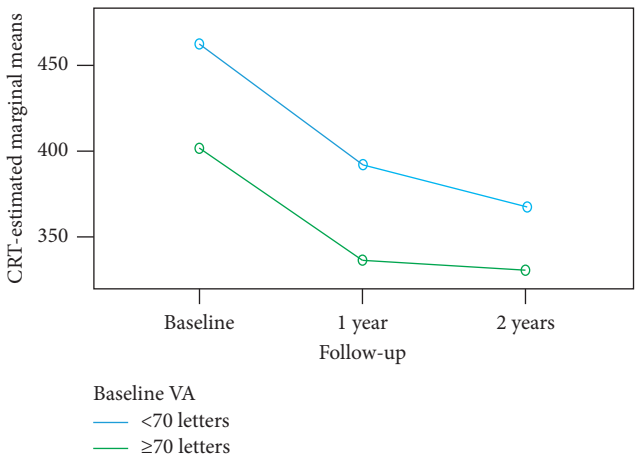

Figure 4: CRT change over time for the subgroups divided according to baseline VA. The between-subgroups test was significant ($p = 0.004$); the lines for the two subgroups are rather far apart. The within-subject test indicated a significant time effect ($p < 0.001$): CRT decreases over time. The interaction between the groups and time was not significant ($p = 0.272$): CRT similarly decreases over time in both subgroups.

3.6. Serious Adverse Events. No serious adverse events were noted during the follow-up period.

4. Discussion

Our retrospective analysis showed no significant change in VA over 2 years (mean change +2.1 ± 16.8 letters; median 2; range −53–52). However, there was a significant change in VA in the subgroup with a baseline VA <70 letters (mean change +5.7 ± 17.9 letters; median 5; range −52–52). VA gains of ≥15 letters were achieved in 25 eyes (20.3%). Changes in CRT were significant over 2 years in all eyes and in both subgroups divided according to baseline VA. These results were achieved with 4.5 ± 2.1 (median 5, range 1–9) and 2.6 ± 2.3 (median 2, range 0–8) injections in the first and second years, respectively.

The mean VA gain in our routine clinical practice was lower than the VA gains achieved in RCTs. Trials such as the RISE and RIDE, DRCR.net Protocol I, RESTORE, RESOLVE, VIVID, and VISTA, and Protocol *T* trials [8, 11, 29–32] demonstrated VA gains of +6.1 to +13.3 letters over 1 year. At 2 years, similar VA gains (+6.0 to +12.8 letters) were observed in the RISE and RIDE, DRCR.net Protocol I, RESTORE Extension Study, VIVID and VISTA, and Protocol *T* trials [10, 11, 29, 33, 34]. There could be several reasons for not achieving similarly high VA gains in our routine clinical practice. First, a large number of eyes had already undergone previous laser treatment for DME, which suggests the possibility of chronic DME, where anti-VEGF agents might not be very effective. Second, some eyes had very low baseline VA, suggesting possible morphological changes associated with permanent VA loss. On the other hand, 37.4% of eyes had baseline VAs better than 70 letters, which presumably had an impact on VA gain due to the ceiling effect. If these eyes were excluded from the analysis, the VA gain became significant, although still lower than in RCTs. Finally, and probably of crucial importance, our patients had fewer visits and received fewer injections during the observed period in comparison to the patients in the RCTs.

More than half of the eyes (63.4%) included in this retrospective review were not treatment naïve. Data regarding the duration of DME were incomplete and were not included in the present analysis. We do not know how many of these eyes had chronic edema, but we speculate that a significant number of treated eyes were poor responders to anti-VEGF treatment. In persistent DME not responding to anti-VEGF treatment, it is reasonable to switch to corticosteroids [13–19, 35, 36]. However, information about factors influencing the physician's decision to continue with anti-VEGF treatment in an individual case could not be found in our retrospective data. We can assume that the treatment response was good, but that the overall result of treatment was not optimal due to undertreatment.

Twenty-two eyes (17.8%) had baseline VAs ≤45 letters (equivalent to ≤20/125) in our retrospective analysis. Channa and coworkers analyzed factors affecting visual outcomes in patients with DME treated with ranibizumab and concluded that poor baseline VA (≤20/125) predicts poor visual outcome (≤20/100) after 2 years of treatment with ranibizumab and/or laser [37]. Similarly, Sophie and coworkers found that a low baseline VA was associated with poor visual outcome [38]. Low VA is often associated with chronic edema and permanent damage of the retina [39]. However, our retrospective analysis did not include analysis of possible correlations between OCT structural changes and VA. Therefore, the influence of eyes with low baseline VA on mean VA gain in this study remains unclear.

Eyes with good baseline VA have lower VA gain due to ceiling effect, which is evident from our results. Of the eyes with a VA <70 letters, 32.5% had a VA gain of ≥15 letters in our study, which might be comparable to RCTs such as the RISE and RIDE trials and the VIVID and VISTA trials [11, 29], despite the significantly higher number of injections administered in these trials. Patients eligible for the RISE and RIDE trials had VAs between 20/40–20/320 (20/40 ≈ 70 letters), and the proportions of patients gaining ≥15 letters at 2 years were 33.6–45.7% [29]. The VIVID and VISTA trials had the same VA enrolment criteria, and 31.1–38.3% of patients gained ≥15 letters at 100 weeks [11]. Our patients received 7.1 injections in 2 years in contrast to the 24 injections administered in the RISE and RIDE trials [29] or the 13.5–22.6 injections in the VIVID and VISTA trials [11]. Patients enrolled in the RESTORE Study had a baseline VA 79–39 letters, received on average 7 injections over a 1-year period and gained +6.8 letters in the ranibizumab monotherapy subgroup [8]. Notably, subgroup analysis in the same trial showed a VA gain of only +2.1 letters in patients with a baseline VA greater than 73 letters [8], which clearly indicates the importance of considering baseline VA when interpreting VA outcomes. In contrast to the RESTORE Study, where 19.8% of patients had a baseline VA >73 letters, 37.4% of patients had a baseline VA ≥70 letters in our retrospective analysis. The effect of baseline VA on VA gain was clearly demonstrated by Dugel and coworkers, who conducted a cross-trial comparison on data from nine

clinical trials and found that mean VA gain negatively correlated with baseline VA [40].

Kodjikian with coworkers analyzed 32 real-life studies evaluating the efficacy of anti-VEGF agents in the management of DME. The patients had a mean baseline VA of 57.3 letters (range 38–72 letters). The mean follow-up was 15.6 months (6–48 months). During follow-up, a mean VA gain of +4.7 letters (−5–+8.5 letters) was observed for a mean of 5.8 injections (1.3–17). The mean final VA was 62 letters (42–77.5 letters) [41]. These summarized results are in concordance with our results when considering only eyes with a baseline VA <70 letters, where mean VA gains of +5.3 letters and +5.7 letters at 1 year and 2 years, respectively, were observed. The mean number of injections in our analysis also tended to be similar to these summarized results. Similarly, a large prospective noninterventional OCEAN Study, which evaluated the use of ranibizumab in a routine clinical setting, demonstrated mean VA gains of +4 letters and +5.2 letters at 1 year and 2 years, respectively. Although the mean VA gains were lower in our analysis, similar proportions of patients gained ≥15 letters (23.5% in the OCEAN Study vs. 20.3% in our analysis) or lost ≥15 letters (7% vs. 9.7%) at 2 years [22].

Although fluctuations in VA and CRT were noticed during the follow-up period in our retrospective review, only the data at three time points (baseline, at 1 year and at 2 years) were included in the final analysis. In a retrospective study performed by Wecker and coworkers, the mean maximum VA gain during the first year was +6.2 letters. Maximum VA gain, however, occurred at different time points for each patient. As a result, the mean VA change for any given time point was less pronounced. By the end of the first year, the mean VA was -1.3 letters [42]. Our results might have been more favorable if the mean maximum VA gain had been considered.

Based on the comparison between RCTs and observational real-life studies evaluating anti-VEGF treatment, it appears that visual outcomes are strongly correlated with the number of injections. Patients treated with anti-VEGF injections in a routine clinical practice receive a substantially lower number of injections in comparison to patients included in RCTs [41]. The mean number of injections in a 2-year period in our analysis was 7.1 ± 3.6 injections (median 7, range 1–17), which is 2-3 times less than in RCTs [10, 11, 29, 34]. Furthermore, the mean number of visits in a 2-year period in our routine clinical setting was 13.4 ± 2.4 (median 13, range 8–20), which is not in accordance with Slovenian and European guidelines for the management of DME [13, 43]. Although the PRN regimen was the recommended protocol, patients were not followed on a monthly basis and consequently could not receive monthly injections if needed. Since only patients with 2 years of follow-up were included in our retrospective analysis, there were no patients lost to follow-up that could have influenced the final results. Some of the reasons for the low number of visits could be patient comorbidities or transportation problems. However, the most obvious reasons are the limited capabilities of the hospital to provide timely treatment for all patients.

Our analysis has some limitations, such as its retrospective nature, the inclusion of eyes with very low or very good baseline VA and the involvement of many physicians with different clinical experiences and sometimes variable retreatment criteria. However, the study provides information about the real-life effectiveness of anti-VEGF treatment, represents the first analysis of the effectiveness of anti-VEGF treatment in Slovenia, and can serve to improve the quality of management of our patients.

5. Conclusions

The two-year visual outcomes in this retrospective analysis appear to be less favorable compared to previously reported outcomes when considering only VA gain, although comparable proportions of eyes gaining ≥15 letters have been observed. A large proportion of our patients had a baseline VA ≥70 letters, which must be taken into account when interpreting the results. When only eyes with a VA <70 letters are considered, the results seem more comparable to the outcomes from other studies. Our analysis provides some information about the effectiveness of anti-VEGF treatment in routine clinical settings in Slovenia. Most importantly, this indicates that more intensive treatment should be implemented in the management of patients to achieve better visual outcomes.

Data Availability

Data used for the analysis are available from the corresponding author upon reasonable request.

Disclosure

Mojca Urbančič provided consultancy and received speaker honoraria from Allergan, Novartis, and Bayer.

Conflicts of Interest

Pia Klobučar, Matej Zupan, Katja Urbančič, and Alenka Lavrič have no conflicts of interest.

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Clinical Study

Systemic Factors Associated with Treatment Response in Diabetic Macular Edema

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Purpose. To identify systemic factors that may influence the response to anti-VEGF therapy in patients with diabetic macular edema (DME). *Methods*. 35 patients undergoing anti-VEGF injections for centre-involving DME were studied in this prospective observational study. The primary outcome was change in macular thickness one month after treatment, measured using spectral-domain optical coherence tomography (OCT). At baseline, information on various systemic factors was collected including glycosylated hemoglobin (HbA1c), serum VEGF levels, lipid profile and markers of renal function, and blood pressure. Thirty-three of the 35 patients were included in this study. Nonparametric statistical tests were used for the analysis of the data in view of the nonnormal distribution of the outcome variables. Multivariate analysis was performed using logistic regression. Stata 12.1 software was used for the analysis. *Main Outcome Measures*. Reduction in macular central subfield thickness (on spectral-domain OCT) and change in logMAR visual acuity at one month after injection. *Results*. Lower HbA1c levels (7% or less) were significantly associated with greater reduction in central macular subfield thickness at one month after injection of bevacizumab or ranibizumab on both univariate analysis ($p = 0.012$) and multivariate analysis ($p = 0.042$). *Conclusions*. Better glycemic control is associated with a greater reduction in central macular thickness after the first injection of bevacizumab or ranibizumab in diabetic macular edema. Patients with high levels of HbA1c and poor response to anti-VEGF may benefit from strict control of their blood glucose.

1. Introduction

Diabetic macular edema (DME) is a vision-threatening complication of diabetes. In DME, accumulation of fluid in the macula results in loss of central vision, which is important for facial recognition, reading, and driving. DME affects 1 in 15 people with diabetes [1] and is the leading cause of blindness in young adults in developed countries [2].

Intravitreal injections of antivascular endothelial growth factor (anti-VEGF) have revolutionized the treatment of patients with DME, causing visual impairment. Several landmark studies have demonstrated that anti-VEGF therapy, compared to laser photocoagulation, provides superior visual outcomes [3, 4]. In the Diabetic Retinopathy Clinical Research Network Protocol T, three commonly used anti-VEGF agents, bevacizumab, ranibizumab, and aflibercept, were shown in the randomized controlled trial to improve vision in centre-involving DME [5].

Despite the proven benefits of anti-VEGF therapy, a subgroup of patients has persistent DME after an initial course of anti-VEGF therapy. A secondary analysis of

Protocol T showed that after six monthly intravitreal anti-VEGF injections, persistent macular thickening was present in 65.6%, 41.5%, and 31.6% of eyes treated with bevacizumab, ranibizumab, and aflibercept, respectively [6]. The clinical challenge of predicting individual response to anti-VEGF therapy remains. Being able to do so will be invaluable for the physician to counsel patients and manage expectations.

The influence of systemic factors on the occurrence of diabetic retinopathy and other micro- and macrovascular complications has been well studied. Studies have shown that tight control of blood sugar and other associated systemic factors such as hypertension, serum cholesterol, and kidney function can significantly delay the onset of diabetic retinopathy [7–11]. However, it is not known if these systemic factors affect the anatomical and visual response to anti-VEGF intravitreal injections.

In this prospective study, we explored whether systemic factors, such as blood pressure, glucose control, cholesterol, triglyceride, and creatinine levels at the time of intravitreal anti-VEGF injection, affect the visual or anatomic response at one month after initiating the treatment.

2. Materials and Methods

2.1. Study Design. This prospective, single-centre, observational study was conducted with Institutional Review Board approval and adhered to the tenets of the Declaration of Helsinki. Informed consent was obtained from all study participants. Eligible participants had centre-involved DME confirmed on spectral-domain optical coherence tomography (OCT) (Spectralis HRA + OCT, Heidelberg Engineering, Heidelberg, Germany). Patients who had prior vitreoretinal surgery, laser, or anti-VEGF injections to the study eye within 2 months or were unable to come for review one month after the injection were excluded. The study recruited consecutive patients who required anti-VEGF for treatment of DME and were able to provide informed consent.

2.2. Assessment of Systemic and Metabolic Parameters. The following baseline clinical characteristics were recorded: age; gender; duration of diabetes; diabetic medications; and associated systemic conditions such as hypertension, nephropathy, and ischemic heart disease.

On the day of injection, blood was collected to check the glycosylated hemoglobin (HbA1c) and serum VEGF levels, lipid profile (triglyceride, total cholesterol, and fractions), and markers of renal function (estimated glomerular filtration rate (eGFR) and serum creatinine). The brachial systolic and diastolic blood pressures (BP) were recorded twice with a digital manometer, at intervals of 10 minutes, with the lower of the two recordings taken as the final value.

2.3. Assessment and Treatment of DME. The Snellen best corrected visual acuity (BCVA) was recorded. The central subfield thickness (CST) was measured on spectral-domain optical coherence tomography (OCT). The change in BCVA and CST, between baseline and one month after IVT anti-VEGF, was used to assess the functional and morphological response to treatment, respectively. Study participants received either intravitreal bevacizumab (1.25 mg in 0.05 ml) or ranibizumab (0.5 mg in 0.05 ml).

2.4. Statistical Analysis. The Snellen BCVA was converted to LogMAR units and the ETDRS letter score for statistical analysis.

Continuous variables were dichotomised as normal and abnormal. The value for dichotomisation was based on published literature (>140 mmHg for systolic BP [12]; >90 mm/hg for diastolic blood pressure [5]; >7.0% for HbA1c [13]; and >308 pg/mL for serum VEGF levels [14]) or the laboratory-specific reference range (>5.2 mmol/litre for cholesterol; >2.2 mmol/litre for triglycerides; >3.3 mmol/litre for LDL; <1 mmol/litre for HDL; >3.5 for total cholesterol : HDL ratio; >120 μmol/litre for serum creatinine; and <90 ml/min/1.73 m^2 for eGFR).

Univariate analysis was performed with nonparametric tests as the distribution of the outcome variables were significantly skewed to the right. Evaluation of the effect of each of the systemic factors (normal vs abnormal) on the change in CST and BCVA was performed with Mann–Whitney U test. Spearman correlation test was performed for testing correlation between linear variables such as visual acuity and central subfield thickness. Multivariate analysis was performed using logistic regression analysis and stepwise backward selection of variables to be included in the final model. The Strata 12.1 software was used for statistical analysis.

3. Results

3.1. Baseline Characteristics. Over a one-year period, 35 eyes of 35 participants received either intravitreal bevacizumab ($n = 25$, 71.4% of eyes) or ranibizumab ($n = 10$, 28.6% of eyes). Data were analyzed for 33 eyes that completed the one-month follow-up visit.

The baseline demographic and study eye characteristics are summarized in Table 1. The mean duration of diabetes for study participants was 11.8 ± 9.5 years. The mean baseline CST was 440.5 ± 136.3 microns. There was no statistically significant difference in the mean baseline CST of patients with HbA1c ≤7.0% and patients with HbA1c >7.0% ($p = 0.27$).

The systemic and metabolic factors at time of anti-VEGF treatment are shown in Table 2. The serum HbA1c was greater than 7.0% in 57.1% of participants.

No correlation was found between the baseline CST and BCVA (Spearman correlation test).

3.2. Effect of Treatment on Visual Acuity. The final visual acuity was 6/12 (70 letters) or better in 51.4%; >6/60 to <6/12 (36 to 69 letters) in 34.3%; and less than or equal to 6/60 (35 letters) in 8.6%. The visual acuity was unchanged in 12 eyes (36.4%). The visual acuity improved in 11 eyes (33.3%), with an increase in the visual-acuity letter score ranging from 3 to

Table 1: Patient demographics, clinical, and ocular characteristics ($n = 35$).

Parameter			Number (percentage)
Demographics	Gender	Male	17 (48.6)
		Female	18 (51.4)
	Age	Mean/SD	62.1 yrs/SD-7.4
		Range	50–80 yrs
Treatment for diabetes mellitus	Oral hypoglycemic agents		20 (57.14)
	Only insulin		4 (11.4)
	Insulin + oral hypoglycemic agents		11 (31.4)
Comorbidities	Hypertension		34 (97.1)
	Ischemic heart disease		11 (31.4)
	Nephropathy		17 (48.6)
	On renal dialysis		3 (8.6)
Ocular features	Snellen best corrected visual acuity	6/12 or better	21 (60)
		>6/60 to <6/12	11 (34)
		≤6/60	3 (8.6)
	Lens status	Minimal cataract	19 (54.3)
		Significant cataract	8 (22.9)
		Pseudophakia	8 (22.9)
	Proliferative diabetic retinopathy	2 (5.7)	
Prior treatment for diabetic retinopathy/maculopathy	Previous laser	PRP	18 (51.4)
		Macular	6 (17.1)
		Both	2 (5.7)
	Prior intravitreal anti-VEGF therapy		23 (65.7)

SD, standard deviation; PRP, pan retinal photocoagulation; anti-VEGF, antivascular endothelial growth factor.

Table 2: Prevalence of abnormal parameters related to systemic condition ($n = 35$).

S/N	Parameter	Number (percentage)
1	Systolic blood pressure >140 mm/hg	23 (65.7)
2	Diastolic blood pressure >90 mm/hg	4 (11.4)
3	Serum creatinine >120 μmol/litre	16 (45.7)
4	eGFR <90 ml/min/1.73 m^2	25 (71.4)
5	Serum total cholesterol >5.2 mmol/L	10 (28.6)
6	Serum triglycerides >2.2 mmol/L	13 (37.1)
7	Serum high density lipoproteins <1 mmol/L	6 (17.1)
8	Serum low-density lipoproteins >3.3 mmol/L	9 (25.7)
9	Ratio of LDL to total cholesterol >3.5	21 (60)
10	Serum HbA1c >7%	20 (57.1)
11	Serum VEGF levels >308 pg/mL	24 (68.6)

eGFR, estimated glomerular filtration rate; LDL, low-density lipoproteins; HbA1c, glycosylated hemoglobin; VEGF, vascular endothelial growth factor.

35 letters. An improvement of ≥15 letters was observed in 2 eyes (18.2%). The visual acuity worsened in 10 (30.3%) eyes, with 3 eyes (30%) having a ≥15 letters decline in the visual-acuity letter score.

3.3. Effect of Treatment on Retinal Thickening. At 4 weeks after injection, the CST decreased, on average by 82.03 ± 150.19 microns (range: $-519\,\mu$m to $+138\,\mu$m). By percentage (with reference to baseline) the change ranged from −65.6% to +28.9%. The Spearman correlation test did not reveal any correlation between the change in the level of vision and the change in CST.

3.4. Association of Systemic Factors with Anatomical and Visual Response. Tables 3 and 4 summarize the results of univariate and multivariate analysis of influence of various independent variables on the outcome variables.

On univariate analysis, only the HbA1c level was significantly associated with reduction of CST after anti-VEGF treatment ($p = 0.012$). The mean reduction in CST was 130 μm in the group with HbA1c ≤7.0% and 41.9 μm in the group with HbA1c >7.0%. On multivariate logistic regression analysis, the HbA1c level was associated with reduction in CST after anti-VEGF therapy (odds ratio −0.019, 95% confidence interval 0.042 to 0.944). The serum levels of VEGF had a moderate correlation with the reduction of CST, but this difference did not achieve statistical significance ($p = 0.1894$).

The change in BCVA after treatment did not have any correlation with the systemic factors that were tested.

4. Discussion

In the management of diabetic macular edema, following several landmark trials [3, 12, 13], anti-VEGF therapy has become the standard of care. However, a subgroup of patients lacks "good" visual or anatomical response for unclear reasons. Postulated factors include local factors, such as poor retinal pigment epithelium health. In this study, we hypothesized that systemic factors have an important role in the clinical response to anti-VEGF treatment.

4.1. Association of Systemic Factors with Anatomical Response after Treatment. Our study has identified that HbA1c levels of 7% or less, at the time of intravitreal anti-VEGF injection, is

Table 3: Association of various systemic factors with change in central subfield thickness (CST) and change in logMAR visual acuity ($N = 33$), (Mann–Whitney U test).

S/N	Systemic factor		Reduction in CST		p value	Change in logMAR visual acuity		p value
			Mean	SD		Mean	SD	
1	IHD	No ($n = 23$) Yes ($n = 10$)	98.43 44.3	165.38 105.23	0.3371	0.013 0.006	0.239 0.193	0.7479
2	On dialysis	No ($n = 30$) Yes ($n = 3$)	77.63 126	145.77 222.7	0.7542	0.006 0.06	0.234 0.053	0.2105
3	Systolic BP	≤140 ($n = 11$) >140 ($n = 22$)	71.73 87.18	180.23 137.18	0.4337	−3.05 0.016	0.29 0.192	0.09532
4	Diastolic BP	≤90 ($n = 29$) <90 ($n = 4$)	79.31 101.75	155.30 122.09	0.6994	0.283 −0.115	0.228 0.160	0.1492
5	Creatinine	≤120 (18) <120 ($n = 15$)	77.61 87.3	134.9 171.47	0.6255	−0.008 0.033	0.212 0.243	0.2582
6	eGFR	>90 ($n = 8$) <90 ($n = 25$)	82.13 82	172.0 146.44	0.8831	0.058 −0.004	0.267 0.212	0.7961
6	Total cholesterol	≤5.2 ($n = 24$) >5.2 ($n = 9$)	72.67 107.25	147.39 163.7	0.7464	−0.018 0.087	0.197 0.283	0.2905
7	Triglycerides	</ = 2.2 ($n = 22$) >2.2 ($n = 11$)	91.14 63.82	166.77 114.99	0.9239	0.054 −0.075	0.244 0.153	0.1645
8	HDL cholesterol	≥1 ($n = 27$) <1 ($n = 6$)	69.67 137.67	134.7 213.2	0.7794	0.002 0.05	0.208 0.307	0.6322
9	LDL cholesterol	</ = 3.3 ($n = 25$) >3.3 ($n = 8$)	69.76 120.38	145.02 169.67	0.5015	−0.017 0.098	0.192 0.301	0.2627
10	LDL: total cholesterol	≤3.5 ($n = 14$) >3.5 ($n = 19$)	41.86 111.63	75.49 183.86	0.8841	−0.054 0.059	0.157 0.256	0.5558
11	HbA1c	≤7 ($n = 15$) >7 ($n = 18$)	130.13 41.94	158.44 134.32	**0.012**	0.001 0.019	0.259 0.197	0.8821′
12	Serum VEGF	≤308 ($n = 10$) >308 ($n = 23$)	41.1 99.83	132.49 156.64	0.1894	0.008 0.012	0.065 0.267	0.6879

CST, central subfield thickness; IHD, ischemic heart disease; BP, blood pressure; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoproteins; HbA1c, glycosylated hemoglobin; VEGF, vascular endothelial growth factor.

Table 4: Multivariate logistic regression analysis using stepwise backward selection for influence of various factors on reduction in central macular thickness with anti-VEGF injection.

S/N	Parameter	Odds ratio	p value	Confidence interval	
				Lower	Upper
1	HbA1c	0.019	**0.042**	0.042	0.944
2	LDL: total cholesterol	3.19	0.172	0.603	16.83

Other factors were dropped during the stepwise backward selection.

associated with a better anatomical response, as assessed by the reduction in CST on OCT. This suggests that tight glucose control during the treatment period is important for good clinical outcome and is consistent with previous studies [14, 15].

We also hypothesized that serum VEGF levels might reflect intraocular VEGF levels and thus predict the anatomical response to intravitreal anti-VEGF injections. Although a statistically significant difference was not found ($p = 0.1894$), our results suggest a trend towards better anatomical response with lower serum VEGF levels.

An earlier study found serum creatinine and cholesterol levels to correlate with reduction in CST after treatment [16]. In this study, the serum creatinine and glomerular filtration rate (eGFR) did not show an association with CST after anti-VEGF therapy. Additionally, patients on dialysis did not show a preferential lack of response to treatment, although our study may not be sufficiently powered to address this.

4.2. Association of Systemic Factors with Visual Outcome after Treatment. Our study showed a significant association between lower HbA1c and CST reduction, but a similar association was not found for BCVA. However, changes in the CST and the visual acuity do not necessarily correlate. In the DRCR.net Protocol I, the CST and VA of eyes treated with laser had a modest correlation [17]. In the DRCR.net Protocol T, the change in CST at 12 weeks and visual acuity at 2 years did not have a strong association [18].

There is conflicting evidence on correlation of HbA1c and visual response to anti-VEGF from large phase 3 trials [19, 20]. An analysis of ranibizumab-treated patients from the RISE and RIDE trials did not find an association between mean change in BCVA at weeks 52 and 100, with the baseline HbA1c [19]. This is in contrast to an analysis of aflibercept-treated patients from the VISTA and VIVID

trials, which found that the mean improvement in VA at 2 years was dependent on HbA1c levels [21]. More recently, an exploratory analysis of DRCR.net Protocol T, in which participants were randomized to receive bevacizumab, ranibizumab, or aflibercept, similarly found the magnitude of vision improvement after anti-VEGF treatment to be associated with HbA1c levels [20].

One possible explanation for the discrepancy between studies is that patients with similar HbA1c levels can have marked differences in their daily glucose profiles, with variable frequency and duration of glucose excursions [22, 23]. Transient hyperglycemic spikes can be a HbA1c-independent risk factor for diabetes-related complications, due to transient episodes of oxidative stress [24]. Most studies have used HbA1c levels measured at the time of injection which reflects the blood glucose control in the previous 2 months and not prospectively after administering treatment. This could also be a limitation in understanding the correlation between HbA1c levels and response to anti-VEGF treatment.

4.3. Study Strengths and Limitations. The principal strength of this study is the prospective evaluation of the impact of other comorbidities on the short-term anatomical or visual response to anti-VEGF treatment. There are several limitations to this study, including the small sample size and inclusion of study participants receiving different anti-VEGF agents.

5. Conclusion

Although HbA1c has been demonstrated to be a marker and strong predictor of vascular complications in diabetic patients [7], its prognostic significance during treatment of DME and its effect on the efficacy is not clear. In our study, we identified that good glycemic control, as defined by an HbA1c level of less than 7%, in the period preceding anti-VEGF treatment, is associated with greater reduction in central subfield thickness on macular OCT. This has significant implications for our clinical management of DME patients with suboptimal response to initial anti-VEGF therapy. If the HbA1c levels are high in these patients, one can enforce rigid control of blood glucose, continue with the same therapy, and reassess, rather than switch to a different drug. This is because the initial lack of optimal response might be due to the lack of proper blood glucose control. Our results also will help with patient counselling and management of their expectations after their first intravitreal anti-VEGF injection.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

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Research Article

Three-Year Outcomes of Patients with Neovascular Age-Related Macular Degeneration Treated with Aflibercept under the National Health Insurance Program in Taiwan

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Purpose. To observe and analyze the long-term outcomes of patients with neovascular age-related macular degeneration (nAMD) treated with aflibercept monotherapy under the National Health Insurance (NHI) program in Taiwan. *Methods*. This retrospective observational study was conducted at Taipei Veterans General Hospital. Patients with naive nAMD who were treated with aflibercept and followed for more than 3 years were reviewed. The better eye was enrolled if both eyes were affected. Visual acuity (VA) and central macular thickness (CMT) were recorded for 3 years. The lost-to-follow-up rate, number of injections, and predictive factors for visual outcomes were analyzed. *Results*. Ninety-nine eyes in 99 patients were followed up for 3 years. The mean age at onset of nAMD was 82.8 ± 9.26 years, and 65% of the patients were male. Compared with initial visual acuity, 5 (5.1%) of our patients improved their vision for 3 or more lines after 3 years of follow-up, 11 (11.1%) of our patients improved for 1 to 3 lines, 62 (62.6%) patients remained their vision with 1 line or less changes, 15 (15.2%) patients lost their vision for 1 to 3 lines, and 6 (6%) patients lost their vision for 3 or more lines. The CMT was 359 ± 180 μm before treatment and 259 ± 98 after 3 years ($p < 0.001$). The mean number of injections was 4.63 ± 1.91 in the first year, 2.13 ± 2.2 in the second year, and 1.42 ± 1.79 in the third year. Multivariate analysis showed that final VA was significantly associated with VA at year 1, the presence of retinal pigment epithelial detachment at year 1, and receiving more than four injections in the first year. Final CMT was only significantly associated with CMT at year 1. *Conclusion*. After 3 years of treatment under the NHI program in Taiwan, 21.2% of the patients with nAMD still had a visual decline despite good anatomical outcomes. More aggressive treatment or other strategies should be used for patients who may have a poor prognosis.

1. Introduction

Neovascular age-related macular degeneration (nAMD) was a leading cause of visual impairment without optimal treatment in developed countries for decades [1]. However, the introduction of intravitreal injections of antivascular endothelial growth factor (anti-VEGF) agents has shown promising results in recent years. Patients in previous clinical trials have been treated with ranibizumab or aflibercept based on a fixed monthly or bimonthly dosing protocol in the first 2 years, which is impractical in a real-world setting [2–5]. To balance the burden of frequent clinic visits for injections and costs/benefits of the treatment, regimens including pro re nata (PRN), treat-and-extend (T&E), and observe-and-plan have been proposed in recent years or used in real-world clinical practice [6–11].

However, nAMD treatment is a continuous process. In long-term results, a decline in VA to worse than baseline has

been reported after a few years during the extension phase of previous trials, such as the MARINA study and CATT trials [12, 13] and a database observational study (Fight Retinal Blindness! Registry (FRB) and AURA study) [14, 15] in patients treated with ranibizumab. In the FRB study, a mean decline of 2.6 letters in the Early Treatment Diabetic Retinopathy Study (ETDRS) at the end of 7 years was noted, which treated patients with six injections in the first year followed by five injections annually in consecutive years [12]. In the AURA study, VA improved by +2.4 and +0.6 EDTRS letters with a mean of 5.0 and 2.2 injections in the first and second years, respectively [15]. The visual outcomes of real-world data have been noninferior to these trials if the patients received more injections during the observation periods [16].

The government in Taiwan launched the National Health Insurance (NHI) program in 1995, and currently it covers more than 99% of residents and health care utilities in Taiwan. The Bureau of NHI approved ranibizumab and aflibercept to treat nAMD in 2011 and 2014, respectively. Copayments are not required; however, a limited number of doses are reimbursed and switching agents are not permitted [17]. The aim of this study was to investigate the results of long-term outcomes of patients with nAMD treated with aflibercept under the NHI program in Taiwan.

2. Materials and Methods

2.1. Study Design, Patient Selection, and Treatment Intervention. This retrospective study was approved by the Institutional Review Board of Taipei Veterans General Hospital in Taiwan, and all research studies followed the tenets of the Declaration of Helsinki. We reviewed medical records of all patients who visited Taipei Veterans General Hospital from 2014 to 2019 with a diagnosis of treatment-naïve nAMD and who were eligible to receive intravitreal injections of aflibercept under the NHI program. The inclusion and exclusion criteria were as follows [17]:

(1) Age ≥50 years and diagnosed with nAMD based on fundus photography, fluorescence angiography, and optical coherence tomography.

(2) Best-corrected VA between 20/40 and 20/400, as tested by Snellen equivalent.

(3) Patients with choroidal neovascularization due to etiologies other than nAMD (such as high myopia or uveitis) or advanced macular scarring, subretinal fibrosis, and geographic atrophy were excluded.

(4) Three doses of anti-VEGF agents were allowed for the first application, with an additional four doses permitted if the disease activity responded to the treatments. For each eye, a lifetime maximum of seven doses could be reimbursed.

(5) Changing or switching between the two anti-VEGF agents was not permitted.

(6) All patients had to pay for the anti-VEGF medication if their application was not approved or if they had already received seven reimbursed injections.

If both eyes of the same patient were successfully covered by the NHI program, we only enrolled the eye which was diagnosed first. All enrolled patients were followed up for 3 years after the first aflibercept injection. Patients who withdrew and were followed up for less than 3 years were recorded, but excluded from the final analysis.

2.2. Treatment Protocol. Most of the patients in this study received 3 consecutive monthly injections during the initial loading phase. The treatment regimens were decided by doctors based on patients' clinical presentations. Most of them received injections under a PRN regimen in which they received treatment when their visual acuity dropped for more than 2 lines in a Snellen chart compared with the previous visit without developing other ocular diseases, or presenting any intraretinal or subretinal fluid in optical coherence tomography (OCT) exam. All patients paid for full amount of medications and treatments after they depleting the injections reimbursed by NHI. The follow-up frequency of each patient was decided by a doctor individually based on their clinical presentation and response to the treatment.

2.3. Outcome Measurements. The primary outcome in this study was the final VA 3 years after the initial injection. The best corrected VA was converted to logMAR (logarithm of the minimum angle of resolution). We also analyzed the difference in VA before and after treatment. Central macula thickness (CMT) was also measured after the initial injection. To record CMT, an OCT scanner, Avanti RTVue XR (OptoVue, Fremont, CA, USA), was used for this study. Fluorescence angiographies were checked for all patients to confirm the diagnosis and activity of nAMD before initiation of therapy. Repeated fluorescence angiography was checked after 3 anti-VEGF injections if the doctor thought it was necessary. Indocyanine green angiographies were done for those patients with suspicious signs of polypoidal choroidal vasculopathy (e.g., double-layer sign, high elevated RPED, massive subretinal or subretinal pigment, epithelial hemorrhage, etc.).

Visual outcomes were categorized into 5 groups: vision improved for 3 or more lines in Snellen chart after 3 years of follow-up, improved for 1 to 3 lines, stable as vision changes between final and initial tests were within 1 line, lost their vision for 1 to 3 lines, and lost their vision for 3 or more lines.

2.4. Associated Factor Analysis. The presence of subretinal fluid (SRF), intraretinal cyst (IRC), and retinal pigment epithelial detachment (RPED) at baseline and each follow-up visit was documented in the medical records and reconfirmed independently by two investigators (K.J. Lo and D.K. Hwang).

2.5. Statistical Analysis. Statistical analysis was performed using SPSS software version 22.0 (SPSS, Inc., Chicago, Illinois, USA). A p value less than 0.05 was considered to be statistically significant in all analyses. VA and CMT

measurements between baseline and follow-up visits were analyzed using the paired Student's *t*-test. To evaluate the potential predictive factors for visual outcomes and CMT at the third year, independent variables including age, sex, VA, and CMT at baseline, month 3, year 1, and year 2; SRF, IRC, and RPED at baseline and year 1; total number of injections at year 1 and year 3 were analyzed in a stepwise multiple linear regression model. Youden's index was used to calculate the ideal total number of injections at year 1, 2, and 3 in the patients who improved by 3 or more lines in Snellen chart at year 3.

3. Results

3.1. Patients' Characteristics. A total of 180 eyes of 180 patients were identified initially. Among them, 37 (21%), 30 (17%), and 14 (7%) patients were lost to follow-up before the first, second, and third years, respectively. Of the 99 patients who completed all 3 years of follow-up, 65 were male and 34 were female, with a mean age of 82.77 ± 9.26 years. The total number of clinics in 3-year follow-up ranged from 20 to 34 times, with a median of 25 times. Among these patients, 27 patients were subclassified as classic CNV (choroidal neovascularization), with 46, 14, and 10 patients were subclassified as occult CNV, RAP (retinal angiomatous proliferation), and PCV (polypoidal choroidal vasculopathy), respectively. The remaining 2 patients could not be subclassified clearly due to the poor quality of fluorescence angiography before enrolling.

3.2. Visual Outcomes. The visual outcomes of the patients who completed 3 years of follow-up and in those lost to follow-up are shown in Figure 1(a). The average follow-up periods were 5.1 ± 2.8, 17.1 ± 3.4, and 26.2 ± 2.1 months in those lost to follow-up before the first, second, and third years, respectively. All of the patients who were lost to follow-up had stabilized vision initially and then gradually decreased until they dropped out. A better baseline VA and relatively flatter decline slope were noted in those who completed 3 years of follow-up. The average VA in logMAR was 0.78 ± 0.44 at baseline and 0.99 ± 0.61 after 3 years of follow-up. Comparing with the initial visual acuity, 5 (5.1%) of our patients improved their vision for 3 or more lines after 3 years of follow-up, 11 (11.1%) of our patients improved for 1 to 3 lines, 62 (62.6%) patients remained their vision with 1 line or less changes, 15 (15.2%) patients lost their vision for 1 to 3 lines, and 6 (6.1%) patients lost their vision for 3 or more lines (Figure 1(b)). In addition, 4% of patients improved for more than 0.3 in logMAR.

No patients experienced ocular (e.g., endophthalmitis, retinal detachment, and enlargement of significantly geographic atrophy) and systemic (e.g., cerebrovascular accidents or cardiovascular diseases) side effect during the follow-up period.

3.3. CMT Outcome. The CMT values in those who completed 3 years of follow-up and those lost to follow-up are shown in Figure 2. A significant decrease in CMT in the treated eyes was noted, with an average thickness of $359 \pm 180\,\mu$m at baseline and $234 \pm 59\,\mu$m at the third year ($p < 0.001$).

3.4. Number of Injections. The number of injections and percentage of patients who received a different number of injections in each year in those who completed 3 years of follow-up are shown in Figure 3. The average numbers of injections were 4.63 ± 1.91, 2.13 ± 2.12, and 1.42 ± 1.79 in the first, second, and third years, respectively. An average total of 8.16 ± 4.57 doses were given over 3 years. Overall, 37% of the patients received over six doses, and 27% of the patients received three doses in the first year. In the second year, only 10% to 15% received one to five doses and 3% (3/99) received over six doses. The distribution of the number of injections in the third year was totally different compared with the previous two years, and almost half (49%) of the patients did not receive any further injections, and 75% received fewer than two doses.

3.5. Predictive Factors for Visual Outcome. The predictive factors which affected the third-year visual outcomes in those who completed 3 years of follow-up are shown in Table 1. In univariate analysis, younger age ($p = 0.003$), better VA at baseline ($p < 0.001$), at month 3 ($p < 0.001$), at year 1 ($p < 0.001$), and at year 2 ($p < 0.001$) and absence of IRC at baseline ($p = 0.004$), a greater number of injections in the first year ($p = 0.029$), and within three years ($p < 0.003$) were associated with a better visual outcome at the third year. However, after stepwise multivariate analysis, only better VA at year 1 ($p < 0.001$), absence of RPED at year 1 ($p = 0.011$), and receiving more than four injections ($p < 0.001$) at year 1 were significantly associated with a better visual prognosis at the third year.

To identify the factors associated with a better visual outcome at 3 years, the patients who had an improvement in VA by more than two lines in the Snellen chart compared to baseline VA were analyzed. We analyzed the number of injections in each year of this group and used Youden's index to calculate the cutoff value for a better visual outcome. We found that the patients who received more than 4.5 ($p < 0.05$), 3.5 ($p = 0.494$), and 4.5 ($p < 0.001$) doses in the first, second, and third years, respectively, achieved better visual outcomes (Figure 4 shows clinical pictures of patients before and after 3 years of follow-up).

3.6. Predictive Factors for CMT. The predictive factors for CMT at 3 years in those who completed 3 years of follow-up are shown in Table 2. A thinner CMT at month 3, year 1 and year 2, and the absence of IRC at year 1 were associated with a thinner CMT at year 3 after univariate analysis. In stepwise multivariate analysis, a thinner CMT at year 1 was the only predictive factor for a thinner CMT at the third year.

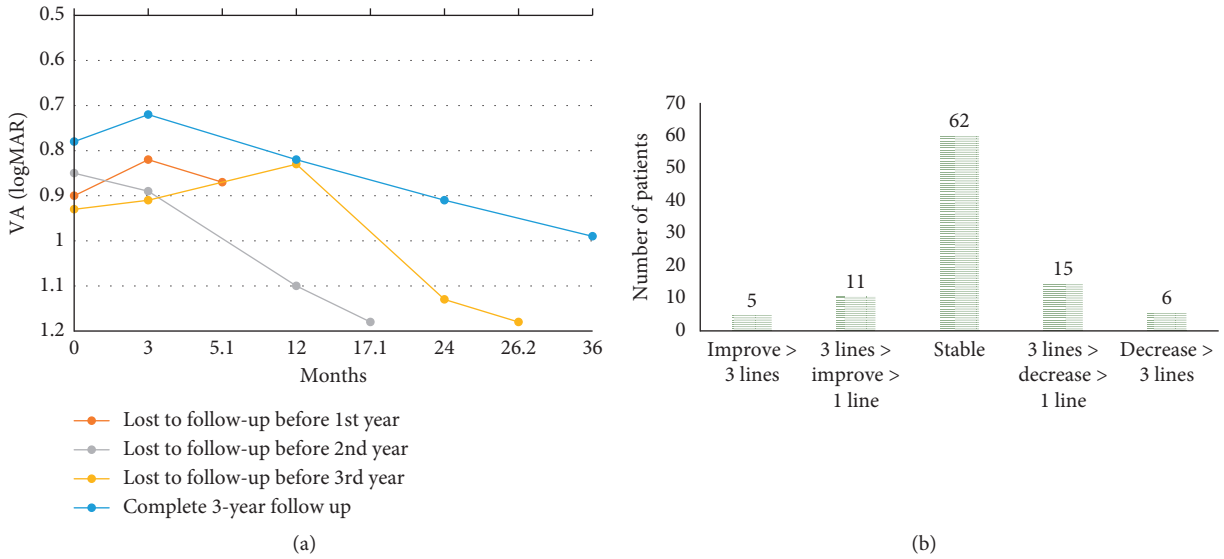

Figure 1: (a) Visual outcome at month 3, year 1, year 2, and year 3 in lost-to-follow-up before year 1, year 2, and year 3 and complete 3-year follow-up groups. (b) The third-year visual outcome compared to baseline in the complete 3-year follow-up group.

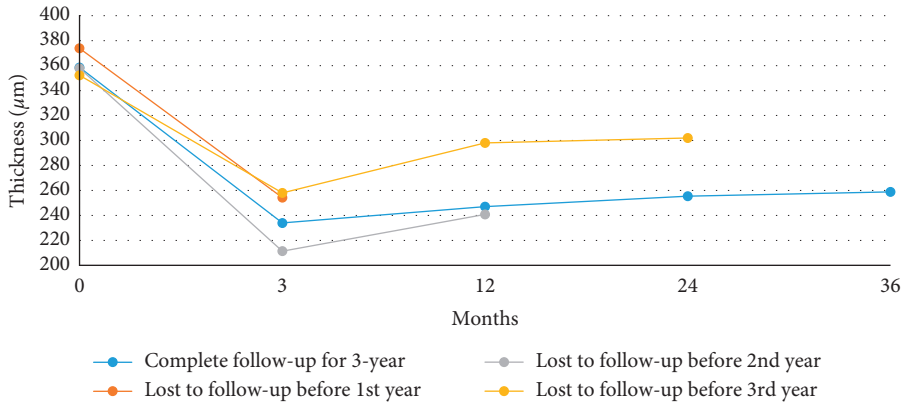

Figure 2: Central macula thickness at month 3, year 1, year 2, and year 3 in lost to follow-up before year 1, year 2, and year 3 and complete 3-year follow-up groups.

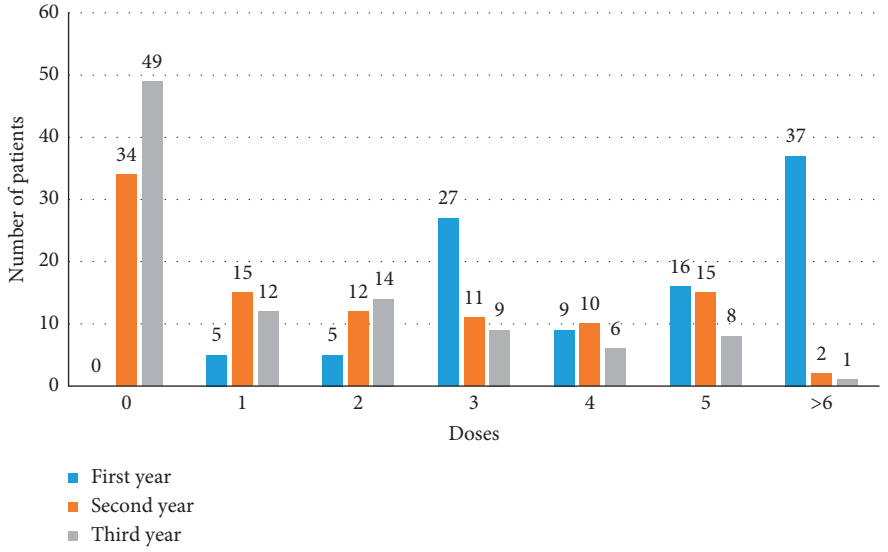

Figure 3: Number of injections at years 1, 2, and 3 in the complete 3-year follow-up group.

Table 1: Univariate and multivariate analysis for visual outcome at the third year in the complete 3-year follow-up group ($n = 99$).

$n = 99$	Univariate analysis		Multivariate analysis	
	β	p value	β	p value
Age	0.292	0.003*	−0.046	0.469
Sex	0.133	0.189	0.104	0.085
Visual acuity				
Baseline	0.62	<0.001*		
3rd month	0.686	<0.001*		
1st year	0.765	<0.001*	0.717	<0.001*
2nd year	0.89	<0.001*		
Central macular thickness (CMT)				
Baseline	0.094	0.395		
3rd month	−0.148	0.204		
1st year	−0.027	0.807	−0.04	0.626
2nd year	−0.053	0.628		
Others				
SRF at baseline	−0.074	0.493		
SRF at 1st year	−0.044	0.691	−0.047	0.425
IRC at baseline	0.306	0.004*		
IRC at 1st year	−0.028	0.802	−0.08	0.284
RPED at baseline	0.067	0.538		
RPED at 1st year	−0.02	0.855	0.166	0.011*
Number of injections				
1st year	−0.219	0.029*		
>4 in 1st year	−0.533	<0.001*	−0.301	<0.001*
Total	−0.293	0.003*		

*Statistically significant. SRF, subretinal fluid; IRC, intraretinal cyst; RPED, retinal pigment epithelial detachment.

4. Discussion

This study demonstrated the real-world situation of treating nAMD with anti-VEGF monotherapy under the NHI program in Taiwan. In this study, 99 patients completed 3 years of follow-up. Sixteen patients had improved VA by over one line in the Snellen chart, while the vision in 62 patients remained stable and 21 patients experienced a decline in VA by over one line in the Snellen chart at the end of the third year. The mean VA improved from baseline (0.78 ± 0.44 in logMAR) after three loading doses (0.72 ± 0.49 in logMAR), followed by a deterioration in visual outcome from year 1 to year 3 (0.82 ± 0.53, 0.91 ± 0.57, and 0.99 ± 0.61 in logMAR at the end of years 1, 2, and 3, respectively). The mean CMT decreased from baseline ($359 \pm 180\,\mu$m) and maintained a stable thickness ($234 \pm 59\,\mu$m, $247 \pm 87\,\mu$m, $255 \pm 88\,\mu$m, and $259 \pm 98\,\mu$m at the end of month 3, year 1, year 2, and year 3, respectively) throughout the 3 years. Although 79% of the patients had stable or improved vision, the average VA was still worse at the end of the third year.

Eleftheriadou et al. reported 3-year outcomes of treating nAMD with aflibercept [18]. In their study, VA improved from 54.4 ± 16.6 ETDRS letters to 61 ± 16.6 ETDRS letters and VA improved by 15 letters or more in 30.5% of the patients at the end of the third year. They administered 7.2 ± 1.8 injections in the first year, with a total of 15.9 ± 6.1 doses at the end of the third year. Traine et al. followed up nAMD patients treated with aflibercept for 4 years [19]. In their study, VA improved from 59.8 ± 16.9 letters to 64.2 ± 19.4 letters at the third year and 63.4 ± 20.4 letters at the fourth year, and they administered 7.7 ± 1.2 injections in the first year, followed by on average 4.4 ± 1.9 injections during the second to fourth years. Nishikawa et al. reported the 4-year outcomes of nAMD patients treated with aflibercept, and their results showed visual gains (logMAR) of 0.14, 0.13, 0.07, and 0.06 in years 1, 2, 3, and 4, respectively [20]. On average, these patients received 7.0 and 2.5 injections in the first and second years, respectively, followed by 2.7 injections each in the third and fourth years. The worse VA at the end of the third year in our study may mainly be attributed to an insufficient number of injections during the 3-year period. An average total of 8.16 ± 4.57 doses was given within 3 years, with an average of 4.63 ± 1.91, 2.13 ± 2.12, and 1.42 ± 1.79 injections in the first, second, and third years, respectively. Most of our patients paid for extra anti-VEGF doses after they had used all seven reimbursed aflibercept injections under the NHI program. The number of treatments was relatively few and visual outcomes were relatively poor in our patients. We hypothesized that there were two main factors influenced by the health insurance policy in Taiwan. Firstly, the reimbursement of anti-VEGF therapy required an approval of administrative application before the first injection, which usually took 2 to 3 weeks. This delaying of treatment may result in relatively poor visual outcome, thus, decreased patients' compliance to the therapy. Secondly, although many studies have shown that the aggressive therapeutic protocol such as fixed-dose or T&E regimen results in a better outcome than PRN regimen, ophthalmologists and patients tended to adopt the as-needed schedule with a limitation of reimbursing dosed (seven per eye). Besides, patients would not get the reimbursement if their vision was better than 20/40, worse than 20/400, or had a large macular scar.

Besides the number of injections, older age and worse baseline VA also influenced the final visual outcome. The mean age of our patients (around 83 years) was older than in other real-world nAMD studies (<80 years) [18–22]. Although age played a minor role in the final VA, other studies have reported that older age may be related to a poor visual outcome [23, 24]. The baseline VA (0.78 logMAR) in our study was inferior than in other real-world studies (around 60 EDTRS letters, equal to 0.5 logMAR) [18–22]. Adrian et al. reported out that a better initial VA may result in a better visual outcome [25]. This may partially explain why our visual prognosis was not as good as in other studies [18–22].

To further investigate the predictive factors that affected the visual outcome and CMT at the end of year 3, we analyzed age, sex, visual acuity, CMT, OCT characteristics of nAMD (presence of SRF, IRC, and RPED), and number of injections received in each year using a stepwise multiple linear regression model. Surprisingly, the final visual outcome was related to VA at the first year instead of baseline. This may explain why the patients who received over four injections in the first year had a better visual outcome in our study, which is consistent with other studies [18–20].

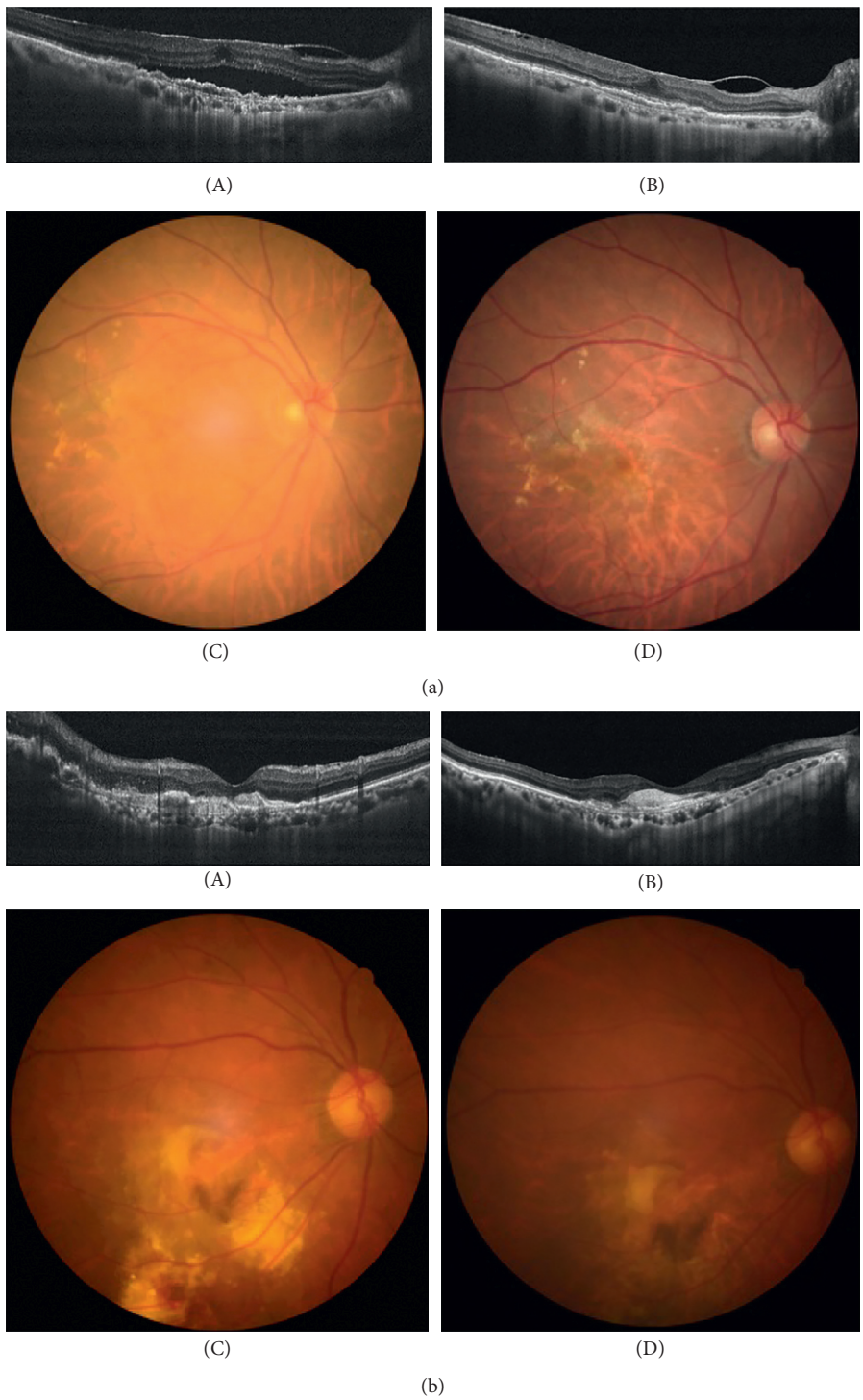

Figure 4: (a) An 80-year-old female who was diagnosed nAMD during her first visit. After receiving 7 doses (6 doses in the first year) of aflibercept injections within three years, her vision improved from 0.52 to 0.10 in logMAR. Fundus photography and OCT before treatment (A, C) and three years after treatment (B, D). (b) An 87-year-old female who was diagnosed nAMD during her first visit. After receiving 3 doses (3 doses in the first year) of aflibercept injections within three years, her vision decreased from 1 in logMAR to hand motion. Fundus photography and OCT before treatment (A, B) and three years after treatment (C, D).

Kim et al. published a meta-analysis which included studies of patients treated with ranibizumab for nAMD [26]. Their results showed a mean change in VA of +1.1 in ETDRS letters at the end of the third year, with a mean of 6.3, 4.4, and 3.3 doses in the first, second, and third years, respectively. We also analyzed the number of injections in each year in the patients who had a visual improvement by more than three lines in the Snellen chart and used Youden's index

Table 2: Univariate and multivariate analysis for central macular thickness at the third year in the complete 3-year follow-up group ($n = 99$).

$n = 99$	Univariate analysis		Multivariate analysis	
	β	p value	β	p value
Age	−0.032	0.765	−0.029	0.799
Sex	−0.044	0.685	0.004	0.969
Visual acuity				
Baseline	−0.062	0.567		
3rd month	0.028	0.803		
1st year	−0.092	0.401	−0.128	0.276
2nd year	0	0.999		
Central macular thickness (CMT)				
Baseline	0.028	0.799		
3rd month	0.306	0.008*		
1st year	0.258	0.031*	0.341	0.034*
2nd year	0.434	<0.001*		
3rd year	0.589	<0.001*		
Others				
SRF at baseline	0.152	0.187		
SRF at 1st year	0.038	0.738	−0.130	−0.238
IRC at baseline	0.175	0.128		
IRC at 1st year	0.374	0.001*	0.161	0.275
RPED at baseline	−0.081	0.484		
RPED at 1st year	0.210	0.066	0.021	0.857
Number of injections				
1st year	−0.06	0.578	−0.034	0.765
Total	−0.059	0.586		

*Statistically significant. SRF, subretinal fluid; IRC, intraretinal cyst; RPED, retinal pigment epithelial detachment.

to identify the number of doses associated with an improved final vision. We found that the patients who received over 4.5, 3.5, 4.5, and 12.5 injections in years 1, 2, and 3 and within 3 years, respectively, had a better visual prognosis. Previous studies have reported that the presence of RPED and IRC at baseline were related to worse VA outcomes [27, 28]. Lai et al. also reported that the presence of RPED and IRC at month 12 was related to final visual outcome in their 1-year follow-up study of anti-VEGF therapy in nAMD patients [29]. In our study, we found that the presence of RPED at year 1 may have been related to a worse visual outcome at the third year. In contrast to visual outcome, the third year CMT was only related to CMT at year 1.

The drop-out rates were 21%, 17%, and 7% before the first, second year, and third years, respectively. Mehta et al. analyzed the lost to follow-up rate in observational studies of anti-VEGF therapy in nAMD patients and reported a rate ranging from 17% to 34% at year 1 to 54% at year 5 [14]. Long-term outcomes of the FRB study showed a <10% drop-out rate in the first 2 years, increasing to 46% at the end of year 5 [16]. The lost-to-follow-up rate was 45% at the end of year 3 in our study; comparing with real-world studies in other countries, we have a relatively higher lost-to-follow-up rate. We found that there was a relatively higher lost-to-follow-up rate in patients with worse initial visual acuity, more systemic comorbidities, and poor treatment response to anti-VEGF therapy. This is not only a limitation of our study but also a barrier for achieving patients' optimal visual outcome in the real-world setting in Taiwan.

Furthermore, there are some limitations to this study. First, we only enrolled patients treated with aflibercept; therefore, we may have missed patients treated with ranibizumab. Second, the small sample size is another limitation as we only enrolled patients from a single referral hospital. Third, the high lost-to-follow-up rate may have led to bias in better visual prognosis since these patients may have had a poor visual prognosis and were not taken into consideration in the final outcome.

5. Conclusions

After 3 years of treatment under the NHI program in Taiwan, 21.2% of the patients with nAMD still had a visual decline despite good anatomical outcomes. To achieve better visual outcomes, more intensive treatment and more injections would definitely have been needed over the 3 years. Better best-corrected VA at year 1, absence of RPED at year 1, and receiving more than four injections at year 1 were good prognostic indicators for a better visual outcome at the third year.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

Authors' Contributions

De-Kuang Hwang and Shih-Jen Chen were responsible for the study design. Kang-Jung Lo, Jin-Yu Chang, and Hsin-Yi Chang performed the literature search. Kang-Jung Lo, Hsin-Yi Chang, and Shih-Hwa Chiou interpreted the data. Kang-Jung Lo, Jin-Yu Chang, Hsin-Yi Chang, De-Kuang Hwang, and Shih-Jen Chen wrote the manuscript.

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Research Article

Seven-Year Visual and Anatomical Outcomes of Intravitreal Vascular Endothelial Growth Factor Inhibition for Neovascular Age-Related Macular Degeneration

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Purpose. To evaluate 7-year visual and anatomical outcomes of intravitreal injections (IVI) with antivascular endothelial growth factor (anti-VEGF) for neovascular age-related macular degeneration (nAMD) based on a personalized pro re nata (PRN) regimen. *Methods*. Anonymized data of 124 consecutive eyes in 121 patients with treatment-naïve nAMD were initially collected in 2010. Of those, 45 received anti-VEGF IVI at least every 6months until 2017 in one single center in Austria and hence were retrospectively analyzed. All eyes had been initiated on a loading dose of 3 monthly IVI with different anti-VEGF agents followed by a PRN regimen in the first year. At year 2, monitoring as well as therapeutic intervention could be prolonged every 2weeks up to intervals of 3months without capping treatment. Primary outcome measure was the change of visual acuity (VA) assessed by Early Treatment Diabetic Retinopathy Study charts at 4 meters (ETDRS) in letters—counting every correctly read letter—and converted to Snellen. Secondary outcome measures were number of injections and change of central retinal thickness (CMT) from baseline. *Results*. Mean baseline VA was 20/63 + 1 (0.63 ± 0.26 ETDRS) and declined to 20/100 + 2 (0.45 ± 0.33) with an overall loss of 9 letters ETDRS after 7years ($p = 0.001$). An average of 3.5 ± 1.9 IVI was given per year and eye. Mean CMT at baseline was 322 ± 95 μm, decreased by 52 μm to 270 ± 70 μm within the first year, and remained below baseline at year 7 (271 ± 106 μm; $p < 0.001$). *Conclusions*. Our data confirm an absolute vision loss in eyes compromised by nAMD after 7 years of continuous VEGF inhibition. The visual decline was significantly related to baseline VA as well as the number of injections. We suggest following patients thoroughly independent of the initial VA and a greater incentive for the physician to treat.

1. Introduction

Late-stage age-related macular degeneration (AMD) is a substantial burden for patients and doctors in developed countries [1]. The projected number of patients with age-related macular degeneration in 2020 is 196 million, increasing to 288 million in 2040 [2]. Its neovascular entity accounts for only 10–20% of cases but is responsible for 80–90% of severe visual loss and progresses rapidly if left untreated [3, 4].

Large multicenter clinical trials have proven the efficacy of monthly intravitreal antivascular endothelial growth factor (anti-VEGF) therapy in treating neovascular (*n*)AMD for at least 2years [5, 6]. New drugs with prolonged injection intervals have become available in the past years [7]. Considering the excessive costs for health care systems, restricted capacity in clinical practice and risk for patients, alternative approaches like treatment as needed (pro re nata; PRN), or certain retreatment while extending intervals (treat and extend; TAE) have been explored [8–11]. Short-term

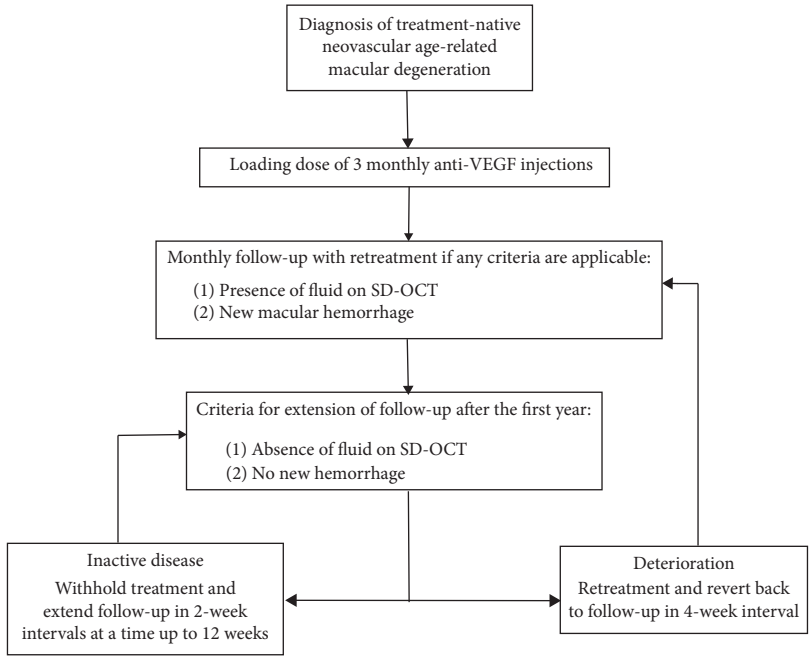

Figure 1: Personalized pro re nata treatment algorithm.

clinical trials have shown similar visual outcomes for all applied strategies [12–17]. A few prolonged studies have been published in the past years with varying results [18–20]. Real-world long-term data of different treatment strategies are needed to reflect maintenance of efficacy and safety over time.

In the light of the above, we analyzed 7year visual and anatomical outcomes of a personalized PRN treatment regimen with anti-VEGF for nAMD from one treatment center in Austria.

2. Materials and Methods

This was a retrospective, observational, cross-sectional data analysis. The study protocol adhered to the tenets of the Declaration of Helsinki.

2.1. Patients. Data of 127 eyes with treatment-naïve nAMD in 124 patients were initially collected in a consecutive manner. Of those, 124 eyes were eligible for enrollment. Forty-five eyes in 45 patients who commenced therapy with intravitreal anti-VEGF in 2010 at our tertiary eye care center (Medical Retina Unit, Department of Ophthalmology, Rudolf Foundation Hospital, Vienna) and who received intravitreal injections (IVI) for at least 7years could be analyzed. Patients with injection-free intervals of more than 6 months were excluded from analysis. Cataract surgery during follow-up was not an exclusion criterion.

2.2. Baseline Assessment. All patients underwent a complete ophthalmic examination including best-corrected visual acuity (BCVA) using the Early Treatment Diabetic Retinopathy Study charts at 4 meters (ETDRS)—counting every correctly read letter—as well as by indirect slit-lamp biomicroscopy (Haag-Streit AG, Switzerland) with dilated pupils using 0.5% tropicamide (Mydriaticum®, Agepha Pharmaceuticals, Vienna, Austria) and 2.5% phenylephrine drops. The diagnosis of nAMD was confirmed by dye-based angiography (Spectralis HRA-OCT Confocal Scanning Laser Ophthalmoscope and Angiography; Heidelberg Engineering, Heidelberg, Germany). The follow-up and further procedures regarding decision-making were regularly based on BCVA, slit-lamp biomicroscopy, and spectral domain-optical coherence tomography (SD-OCT; Cirrus HD 4000, Carl Zeiss Meditec AG, Germany). The central macular thickness (CMT) was measured by a SD-OCT B-scan within the central 1 mm zone.

2.3. Treatment Protocol and Follow-Up. Consenting patients received three consecutive monthly intravitreal anti-VEGF injections with different agents (aflibercept 2 mg, bevacizumab 1.25 mg, ranibizumab 0.5 mg). All patients continued on a PRN regimen with monthly visits and injections as needed within 5 working days in the first year. A medical retina fellow or senior evaluated the further treatment at each follow-up based on previously established criteria (Figure 1).

After year 1, monitoring visits were extended every 2weeks to a maximum of 3 months if the disease was inactive, but injections could be withheld for longer periods without capping. We considered 6 months of inactivity as stable disease and as a consequence excluded the eye from analysis. In other words, eyes had to be treated at least twice a year to be eligible for participation. Switching the anti-VEGF agent was left to the surveilling ophthalmologist but did not change treatment intervals. The occurrence of systemic cerebrovascular, cardiovascular, and ocular adverse events (AE) was documented and did not necessarily postpone the anti-VEGF treatment.

Table 1: Mean VA development for the respective cohort from baseline to each year in total, separated in baseline VA and amount of intravitreal injections/year in Snellen.

Years	VA (n)	≥20/50 (n)	20/50–20/114 (n)	≤20/114 (n)	<3 IVI/year (n)	34 IVI/year (n)	>4 IVI/year (n)
0	20/63 + 1 (124)	20/40 + 1 (65)	20/80 + 2 (37)	20/160–1 (22)	20/63 (50)	20/63 + 2 (31)	20/63 + 2 (43)
1	20/50 + 1 (119)	20/40 + 1 (62)	20/63–1 (33)	20/100 (20)	20/63–1 (43)	20/50 (31)	20/40–2 (44)
2	20/50–2 (119)	20/40 (64)	20/80 (32)	20/100 (20)	20/63–2 (43)	20/50 (32)	20/50 + 1 (44)
3	20/63 + 1 (119)	20/40–2 (64)	20/100 + 2 (32)	20/100 (20)	20/63–1 (42)	20/63 + 1 (33)	20/63 + 2 (44)
4	20/63–1 (119)	20/50 + 1 (64)	20/100 (33)	20/100–1 (19)	20/80 + 1 (42)	20/63 + 2 (33)	20/63–1 (44)
5	20/63–1 (119)	20/50 (63)	20/100 + 1 (34)	20/100–1 (20)	20/80 (42)	20/63–1 (33)	20/63 + 1 (44)
6	20/80 + 1 (87)	20/63 + 1 (51)	20/100 + 2 (22)	20/125 (13)	20/100 + 2 (32)	20/80 + 2 (23)	20/63–1 (32)
7	20/100 + 2 (45)	20/80–2 (25)	20/100 (15)	20/80–1 (5)	20/125 + 1 (13)	20/100 (12)	20/63–2 (20)
Letters*	−9	−18	−6	+14	−19	−11	−4

VA = visual acuity; n = number of eyes; IVI = intravitreal injection; *change in letters ETDRS = Early treatment diabetic retinopathy study chart at 4 meters.

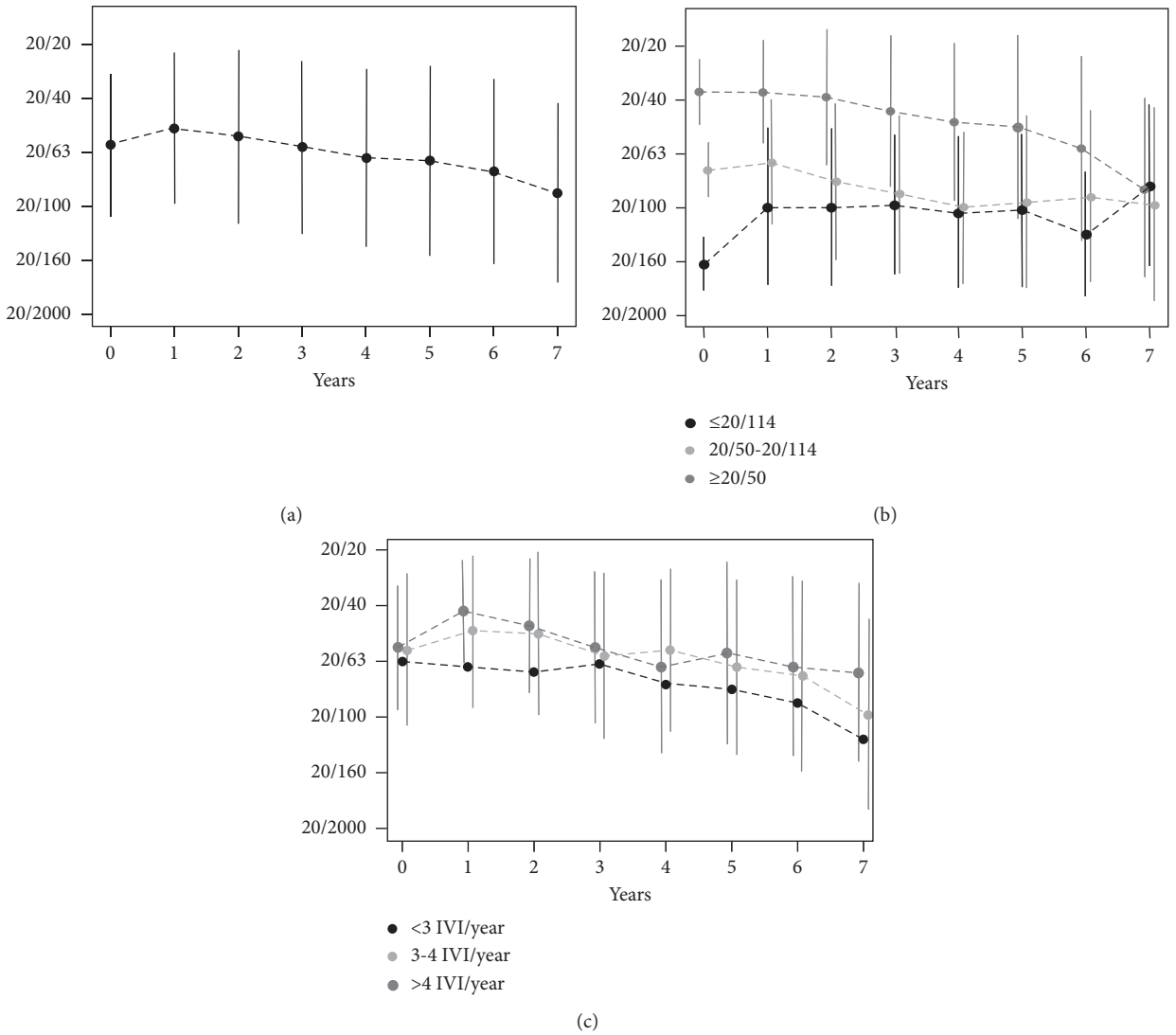

Figure 2: Mean visual acuity (VA) measured by Early Treatment Diabetic Retinopathy Study (ETDRS) charts at 4 meters and converted to Snellen over 7 years. (a) Mean change of VA for all eyes. (b) Mean change of VA separated in eyes with good baseline VA ≥ 20/50 (0.7 ETDRS), intermediate VA 20/50–20/114 (0.7–0.35 ETDRS), and minor VA ≤ 20/114 (0.35 ETDRS). (c) Mean change of VA subdivided into three groups based on the average numbers of intravitreal injections per year.

2.4. Data and Statistical Analysis. Patient charts were reviewed for BCVA, CMT, numbers of IVI, and the incidence of AE. The analysis was performed using SAS version 9.4 (SAS Institute Cary NC, USA), Microsoft Excel 2007 (12.0.4518.1014), and R release 3.2.1. Univariate regression models were calculated to investigate the influence of time,

eye, age at baseline, the average number of IVI, and the occurrence of AE on main outcome measures. All potential influencing significant factors in the univariate analysis were re-evaluated in a multivariable model. Continuous baseline variables were compared between eyes with 7 years of observation period using ANOVA. Categorical (laterality, sex, AE, and time) baseline variables were compared using Chi-squared tests. A p value <0.05 was rated statistically significant.

3. Results

The mean patient's age at initial presentation was 76 ± 7.5 years with a female preponderance (77%) and an evenly distributed laterality. Overall, baseline mean VA was 20/63 + 1 (0.63 ± 0.26 ETDRS). Forty-five (37%) eyes with nAMD were eligible for enrollment after 7 years. The baseline data of this population were comparable with a slightly higher age (77.7 ± 6.1 years), also a female dominance (85%) but more right eyes (57%), while the initial mean VA was 20/63 + 3 (0.66 ± 0.24 ETDRS). In total, mean VA raised significantly within the first year to 20/50–1 (0.69 ± 0.28 ETDRS; $p = 0.044$ (95% CI: 0.001; 0.09)). No difference was found between baseline mean VA and the second or the third year. A significant mean visual loss became evident in the following years 4–6. Mean VA declined to 20/100 + 2 (0.45 ± 0.33 ETDRS) in year 7 (Table 1; Figure 2(a); $p < 0.001$ (95% CI: −0.23; −0.11)).

In a subanalysis, 65 of 124 (52%) eyes had a VA ≥ 20/50 (0.7 ETDRS) at the baseline, 37 of 124 (30%) eyes had an intermediate VA between 20/50 (0.7 ETDRS) and 20/114 (0.35 ETDRS), while 22 of 124 (18%) eyes had an initial VA ≤ 20/114 (0.35 ETDRS) (Figure 2(b); $p < 0.001$ (95% CI: −0.23; −0.11)). Regarding the VA at 7 years, comparable relative numbers in 25 of 45 (56%) eyes with good initial VA lost 18 letters, 15 of 45 (33%) eyes with intermediate VA lost 6 letters, while 5 of 45 (11%) eyes with minor initial VA gained 14 letters. A significant difference between good VA and minor VA at baseline ($p < 0.001$ (95% CI: −0.5; −0.28)) as well as intermediate VA and good VA at baseline could be detected after 7years (Figure 2(b); $p < 0.001$ (95% CI: −0.36; −0.19)). Overall, 3.5 ± 1.9 IVI per eye and year was given. The number of IVI administered over time was significantly related to the outcome of VA ($p = 0.011$ (95% CI: 0.01; 0.05)). For further analysis, the eyes were subdivided into 3 groups (<3IVI/year; 3–4 IVI/year; >4 IVI/year) based on the average number of IVI given per year. Eyes with a follow-up of 7 years had more IVI/year (4.0 ± 2.0) than the average number administered in total. After 7 years, 13 of 45 (29%) eyes with less than 3 IVI/year lost 19 letters on an average, and 12 of 45 (27%) eyes with 3 to 4 IVI/year lost 11 letters, while 20 of 45 (44%) eyes treated with more than 4 IVI/year lost 4 letters (Figure 2(c)). Neither age nor sex, laterality nor the occurrence of adverse events (AE) had an impact on VA.

The mean CMT was $322 \pm 95\,\mu$m at the baseline. For the 7-year subgroup, a comparable CMT of $325 \pm 59\,\mu$m was evident. A significant thinning compared with the baseline was measured at all time points ($p < 0.001$ (95% CI: −83.84; −33.90)). A reduction of $52\,\mu$m became apparent within the first year, declined to $246 \pm 56\,\mu$m after 4years, and remained at $271 \pm 106\,\mu$m on average in year 7 (Figure 3).

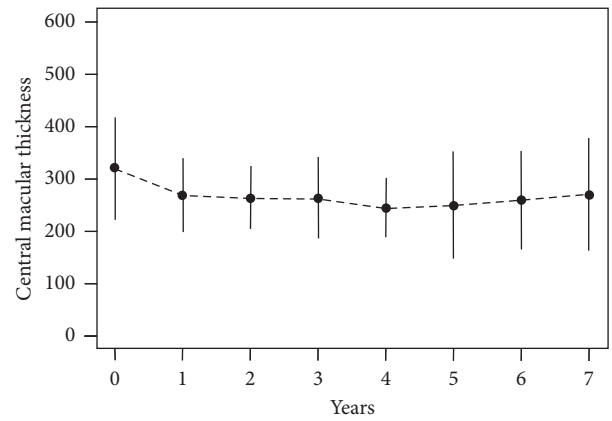

Figure 3: Mean change of central macular thickness for all eyes measured by spectral domain-optical coherence tomography B-scans over time.

Neither VA at baseline nor age, sex, laterality, nor the number of IVI was significantly related to a change in CMT ($p = 0.308$).

Severe ocular events AE were documented in 2 (1.6%) eyes (retinal tear, elevated IOP >30 mmHg), and no cases of endophthalmitis were reported. Nine patients had an episode of stroke or myocardial infarction during the observation period. These eyes were not included in the 7-year data analysis.

4. Discussion

In this retrospective data analysis, we evaluated a representative number of eyes complicated by nAMD and treated with a personalized PRN regimen at least every 6 months for 7 years. A visual decline of nearly 2 lines of ETDRS became evident with a low number of 3.5 IVI/year based on our protocol, which relies on empiric variable intervals for each patient and was published in 2019 [21]. It mixes advantages of both, PRN and TAE, as it combines a fairly low injection rate with an acceptable clinical effort, a limited risk besides minimum undertreatment.

A few studies on long-term anti-VEGF treatment for nAMD have been published yet. Gillies et al. extracted heterogeneous data of 1212 eyes from a multicentered registry, of which 131 were being followed for 7 years [22]. The multicenter SEVEN-UP study reported on 65 patients treated with intravitreal ranibizumab and different regimens for a mean of 7.3years with a decline of 8.6 letters [19]. Patients were treated either monthly or PRN for 24 months before entering a quarterly PRN protocol for another 2 years. An average of 6.8 IVI was given in the last 3.4 years after the exit from HARBOR protocol, resulting in 1.6 IVI/year and study eye. This low number was partially attributed to the study design. The authors did not exclude eyes without treatment in the last years, while our cohort reflects only eyes with the need of at least 2 injections per year. It seems difficult to acquire representative data of a homogeneous

cohort for an interpretation over an extended time period. In our study, a uniform data collection was possible with the help of continuous observation and minimum diversity in respect of the medical staff including 2 medical retina specialists as well as a single center setting in an urban environment. Our low number of average IVI/year is most likely related to a compensation for a higher number of injections in the first years and a low number due to less burden for treatment in the latter years.

Although an absolute visual loss became evident in the total number of eyes, their separation based on baseline VA led to interesting findings: the better BCVA at baseline, the more letters were lost after 7years. Our results were concordant with those of other authors as well as the UK Age-Related Macular Degeneration EMR Users Group, who previously described similar effects [23, 24]. "Ceiling" is referred to as the limited potential gain in vision simply due to a relatively good BCVA at the baseline. The terminus "floor" was used in initially poor vision where loosing was unlikely but gaining an option. It looks like this phenomenon was true for all eyes compromised by nAMD with long-term treatment, independent of the underlying modality.

In general, 3 different regimens have been established in the past years. Fixed continuous dosing could rarely be prolonged and was never practical because of certain overtreatment besides cost and burden to patients as well as clinicians. Reality led to an interest in different therapeutic approaches with encouraging visual results in short-term studies [12, 25]. PRN with fixed visits and variable injection intervals based on the disease activity included the advantages of fewer burden to the patient with more cost-effective management in the long-term [26]. TAE was introduced as injection and extended by Spaide in 2007 and was based on the strategy of minimizing recurrences by retreating even without signs of activity while expanding the intervals [11, 27]. This protocol reduced the number of visits and tests but increased the potential of overtreatment. Lately, it was widely adopted in centers across the U.S. Considerably good 8-year TAE outcomes were published recently by a Scandinavian group [20]. Nevertheless, noninferior VA could only be achieved by a relatively large number of IVI. We also investigated the effect of the numbers of injections given per year and found significant differences. A fair loss of 1-line ETDRS in 7 years could be established with only 1 more injection on average per year. Considering the rising number of elderly patients affected by this chronic disease as well as the associated financial and social burden, it should be our primary goal to limit the number of IVI/year but at the same time to sustain an acceptable visual outcome for our patients to conquer their daily routine.

CMT measurements were collected as a secondary outcome. The significant macular thinning in OCT B-scans within the first year has been proposed by various 1-year registration trials [8–11]. In our study cohort, the reduction at year 1 could be preserved throughout the 7-year observation period, independent of the number of IVI.

This paper has several limitations. Its retrospective design questions many variables likely to be evaluated in a prospective study. No endpoints at predetermined time intervals were set. Eyes submitted to cataract surgery were included and likely to demonstrate considerably higher BCVA. Recent data from the CATT Research Group, who investigated the development of geographic atrophy (GA) in eyes complicated by nAMD, showed an incidence of 38% among these 5 years after initiating therapy [28]. Potential GA as a source of the visual decline was not assessed in our study. The three predominantly administered intravitreal medications were exchanged randomly if eyes seemed to respond inadequately. The switch was not investigated separately due to the retrospective data collection. Thus, our findings reflect real-life outcomes. This study's strength is its long observation period and data recording by means of well-established repeatable methods and personnel for a reasonably large number of eyes.

5. Conclusions

In conclusion, our real-world data confirm an absolute visual loss of 9 ETDRS letters with a reasonably low number of injections per year enabled by a personalized PRN regimen over a time period of 7 years. The response to treatment needs to be addressed thoroughly regardless of chronicity or baseline VA. Retreatment should be considered in doubt to largely avoid undertreatment. The initial submacular thinning in the first year could be preserved over time. Many questions are still to be answered in a prospective manner. Reliable data of long-term treatment effects following VEGF inhibition are mandatory to conquer this disease in the future.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Disclosure

This research was performed as part of the employment of the authors, namely, the Rudolf Foundation Hospital and the Karl Landsteiner Institute for Retinal Research and Imaging.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this article.

Authors' Contributions

All authors contributed equally to this work. Each author certifies that he or she has made substantial contribution to

the work reported in this manuscript to all of the following: (1) conception and design, acquisition of data, and analysis and interpretation of data, (2) drafting the article and revising it critically for important intellectual content, (3) final approval of the version to be published, and (4) agreement to be accountable for all aspects of the work in ensuring that all questions related to the accuracy and integrity of the work are appropriately investigated and resolved.

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Research Article

Intravitreal Injections for Macular Edema Secondary to Retinal Vein Occlusion: Long-Term Functional and Anatomic Outcomes

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Purpose. To report the long-term visual and anatomic outcomes of intravitreal injections for macular edema (ME) secondary to retinal vein occlusion (RVO) in a real-life clinical setting. *Design*. Retrospective interventional case series. *Methods*. A total of 223 consecutive eyes with ME secondary to RVO, treated with the first three intravitreal Ranibizumab or dexamethasone injections between August 2008 and September 2018, were enrolled in the study. Subsequent retreatment was guided by best-corrected visual acuity (BCVA) and central macular thickness (CMT) measurements, aimed at achieving macular fluid regression and BCVA stability. BCVA and CMT were recorded at baseline and at subsequent annual time points. The mean number of injections administered each year and the incidence of adverse events were recorded. *Results*. The mean BCVA and CMT at baseline were 0.79 logMar (SD 0.71) and 615.7 μm (SD 257.5), respectively. The mean follow-up (FU) period was 47.8 months (min 12–max 120). At 12 months, the mean BCVA and CMT had significantly improved to 0.62 logMar (SD 0.68; $p < 0.0001$) and 401.04 μm (SD 183.8; $p < 0.0001$). Improvements remained significant at the final FU visit. Eyes with BRVO and nonischemic RVO showed significantly better visual outcomes when compared to eyes with CRVO and ischemic RVO, over the entire FU period. An average of 4.08 (SD 2.1) Ranibizumab and 1.5 (SD 0.6) Ozurdex injections were administered over the first 12 months. The number of injections decreased thereafter progressively. One eye with CRVO developed endophthalmitis and one with BRVO developed an intraocular pressure increase that was refractory to topical medications and ultimately treated with trabeculectomy. *Conclusion*. Intravitreal Ranibizumab and/or dexamethasone injections were found to be effective at inducing a long-lasting improvement of BCVA and CMT in a real-life clinical setting. A safety profile similar to that already well-established in Ranibizumab and dexamethasone treatment was observed, as well as a steady decrease in the number of intraocular injections required. The results support intravitreal treatments for BRVO and CRVO in patient populations with similar characteristics in similar settings.

1. Introduction

Retinal vein occlusion (RVO) is the second most common cause of vision loss due to retinal vascular disease, after diabetic retinopathy [1]. Macular edema (ME) is a frequent and sight-threatening complication of both central (CRVO) and branch (BRVO) retinal vein occlusion [2, 3].

In the past, treatment options for ME secondary to RVO were limited. The CRVO study group [4] demonstrated that grid laser photocoagulation is not effective in cases of visual impairment due to CRVO-related ME, while the BRVO study group [5] reported its efficacy in treating ME secondary to BRVO. Since the publication of those two reports, the standard of care for BRVO-related ME became grid laser photocoagulation and for CRVO-related ME was observation. However, evidence from subsequent randomized controlled trials has demonstrated significant visual and anatomic improvements among patients with either CRVO- or BRVO-related ME who were treated with intravitreal injections of vascular endothelial growth factor (VEGF) inhibitors or with corticosteroids.

In particular, the Geneva study group [6], in a randomized, sham-controlled, clinical trial conducted on 1267 patients, found significantly greater improvement in the

mean best-corrected visual acuity (BCVA) of eyes treated with dexamethasone intravitreal implant (DEX implant; Ozurdex®, Allergan, Inc., Irvine, CA, USA) compared to controls, with a good safety profile. Significant visual and anatomic improvements among patients receiving VEGF inhibitors have also been demonstrated in randomized clinical studies including COPERNICUS, GALILEO, BRAVO, CRUISE, and VIBRANT [7–11]. The CRUISE study reported a mean gain in BCVA of 13.9 letters in CRVO eyes at 12 months. The BRAVO study, with a similar design to CRUISE, demonstrated mean BCVA improvements by 16.4 and 18.3 letters in the 0.3 and 0.5 mg groups, respectively, among BRVO eyes, over the 12-month study period. Extension studies following BRAVO and CRUISE [12] have given some insight into the outcomes of anti-VEGF therapy for RVO up to 4 years after initiating treatment.

In light of these favourable results, patient and physician expectations in the visual outcomes with intravitreal injections for RVO-related ME have increased greatly. However, results from clinical trials might differ considerably from those found in real-world settings, given that the intensive treatment schedules and close monitoring, typically employed in clinical trials, are very difficult to replicate in real-life. Moreover, the strict eligibility criteria of trials may result in selected populations that do not represent those routinely found in clinical practice.

Although intravitreal injection therapy has now become the treatment of choice for RVO-related ME in many countries, there is very limited data available on the long-term outcomes in real-world settings.

The aim of this study was to investigate the long-term visual and anatomic outcomes in patients with ME secondary to RVO treated with intravitreal injections of Ranibizumab and/or dexamethasone in a real-world setting.

2. Methods

2.1. Study Design. This research is a retrospective interventional case series undertaken at a single tertiary referral center. It evaluated the long-term anatomic and functional outcomes of all consecutive eyes that were (a) diagnosed with recent onset, previously untreated ME secondary to RVO at the IRCCS Sacro Cuore Hospital, Negrar, Verona, Italy, and (b) treated with their first injection between August 2008 and September 2018.

The primary end point was the evaluation of any change in mean BCVA and central macular thickness (CMT) from baseline to the 12-month follow-up (FU) visit and at each subsequent annual FU visit thereafter.

Secondary endpoints were as follows:

(i) The number of injections received at the end of the first 12-month period and thereafter in the subsequent years of treatment

(ii) The relationship between BCVA and CMT throughout the study period

(iii) The incidence of adverse events

(iv) The influence of the following factors: age, sex, presence of ischemia, type of RVO (BRVO/CRVO), FU duration, and baseline BCVA on visual outcomes

This study complied with Declaration of Helsinki regulations. The IRCCS Sacro Cuore Hospital Institutional Review Board provided approval for the review of patient data.

2.2. Study Population

Inclusion criteria were

(i) age ≥18 years

(ii) ME involving the foveal center secondary to BRVO or CRVO

(iii) CMT ≥ 350 μm

(iv) ME treatment naïve

(v) recent onset of RVO (less than 6 months since diagnosis)

(vi) a minimum FU of 12 months

When both eyes of a patient met the eligibility criteria, they were both included in the study.

Exclusion criteria were

(i) any previous treatment with focal/grid laser macular treatment, anti-VEGF, or corticosteroids injection

(ii) the presence of concomitant diseases that could influence outcomes, such as high myopia (>6 D), uveitis history, diabetic retinopathy, and macular holes

(iii) a history of vitreoretinal surgery

(iv) inadequate imaging (i.e., severe media opacities, asteroid hyalosis, and synchysis scintillans)

(v) ME secondary to diseases other than RVO

2.3. Treatment Protocol and Evaluation Procedures. In accordance with the routine practice for patients treated with intravitreal injections at Sacro Cuore Hospital [13], at baseline all patients underwent a complete ophthalmologic examination, including medical history, BCVA evaluation, slit-lamp biomicroscopy, intraocular pressure (IOP) measurement, dilated fundus examination with a 90 diopters indirect lens, optical coherence tomography (spectral domain OCT-SLO Heidelberg Engineering, Heidelberg, Germany) and fluorescein angiography (FA) with the Heidelberg Retina Angiograph (HRA). BCVA was measured by Snellen visual charts and converted to logarithm of the minimum angle of resolution (logMAR) units for statistical analysis.

RVO was classified as nonischemic or ischemic at the initial visit; any conversion of status from nonischemic to ischemic was carefully monitored and evaluated during the FU. Eyes affected by ischemic RVO with evidence of neovascularization, or those at high risk of its development, underwent laser photocoagulation of the areas of peripheral retinal nonperfusion.

Eyes underwent a loading phase with three consecutive monthly intravitreal injections of Ranibizumab. The eyes were then periodically inspected through complete ophthalmological examinations to determine the need for pro re nata (PRN) injections. In particular, the FU examinations included BCVA evaluation, slit-lamp biomicroscopy, IOP evaluation, fundus examination, OCT, and, at the physician's discretion, FA. Retreatment criteria for PRN injections followed a BCVA- and OCT-driven regimen aimed at achieving complete macular fluid regression and BCVA stability. Upon reaching stability, patients were checked bimonthly or quarterly as per physician discretion. Treatment was then continued in the instance of a CMT increase or a BCVA decline due to recurring ME.

Beginning in January 2015, intravitreal dexamethasone implant (Ozurdex) has been at our disposal to treat ME secondary to RVO. Therefore, it was associated with intravitreal Ranibizumab injections in cases of incomplete response to anti-VEGF, as determined by the treating clinician. In general, eyes were considered incomplete responders in case they did not manifest improvement in CMT of at least 20% after a minimum number of six intravitreal anti-VEGF injections. Moreover, Ozurdex was used as a first therapeutic option in pseudophakic eyes with no glaucoma and with no history of IOP increase after topical therapy with corticosteroids. Focal/grid laser macular treatment was also associated with intravitreal injections in cases of incomplete response to anti-VEGF and/or to Ozurdex, as determined by the treating physician. Laser photocoagulation of areas of peripheral retinal nonperfusion and cataract surgery were allowed throughout the study period.

3. Statistics

Continuous data were expressed by mean, standard deviation, and min and max value. The two-sample *t*-test for unpaired data was used to compare the means for normal distributed data, while the correspondent nonparametric Wilcoxon rank-sum test was used for nonnormal data. The chi-square test was used to test the statistical association between two categorical variables, while the Pearson linear correlation index was used to evaluate the linear correlation between two continuous variables. A p value less than 0.05 was considered for the statistical significance.

Data were analyzed by STATA vers. 15 (StataCorp, 2017, Stata Statistical Software: Release 15, College Station, TX: StataCorp LLC).

4. Results

4.1. Study Population. A total of 223 eyes from 207 consecutive patients met the inclusion criteria and were enrolled in this study, 99 eyes with CRVO and 124 with BRVO. The mean time period since RVO diagnosis was 1.2 months (SD 2.01; min 0.5–max 6). The mean follow-up was 47.8 months (SD 27.3; min 12–max 120). The baseline characteristics of the study population are summarized in Table 1.

When comparing BRVO and CRVO subgroups at baseline, no significant differences were found in age, sex, or number of phakic/pseudophakic or ischemic/nonischemic eyes. On the contrary, mean BCVA and CMT differed significantly in the subgroups, being significantly worse in CRVO eyes (Table 1; p value <0.0001).

Furthermore, mean baseline BCVA and CMT also differed significantly in ischemic and nonischemic RVO eyes (mean baseline BCVA: 0.67 (SD 0.55) logMar for nonischemic versus 0.9 (SD 0.81) for ischemic RVO (p value: 0.0065); mean baseline CMT: 561.9 (SD 216.1) μm for nonischemic versus 659.4 (SD 280.2) for ischemic RVO (p value: 0.0018)).

4.2. Visual and Anatomic Outcomes after Treatment. The mean baseline BCVA in the whole population was 0.79 (SD 0.71). At the 12-month and 2-year FU visits, it significantly improved to 0.62 (SD 0.68; p value <0.0001) and 0.63 (SD 0.71; p value: 0.009), respectively. Mean BCVA and visual improvements at the subsequent annual time points are reported in Table 2. At each annual time point, the mean BCVA was found to be improved compared to that of baseline, although not statistically significantly so at the 3-year and 4-year follow-up visits. Improvement was significant, however, at subsequent follow-up visits and at the final visit.

Sex, FU duration, and phakic/pseudophakic status did not show any significant influence on visual outcome. On the contrary, greater visual improvement significantly correlated with better baseline BCVA (linear correlation coefficient 0.6226; p value <0.0001). Moreover, the presence of ischemia (p value = 0.004), older age (p value: 0.006), and the type of RVO (CRVO/BRVO) (p value: 0.003) was negatively associated with visual outcomes.

At the 12-month FU visit, 35 (15.7%) eyes gained ≥1 line, 170 (76.2%) were stable (less than 1-line gain or loss), 18 (8.1%) lost ≥1 line. The number of eyes gaining/losing ≥1 line at each subsequent annual FU visit is reported in Supplementary Material Table S1.

The mean baseline CMT was 615.7 μm (SD 257.5). It significantly improved to 401.04 μm (SD 183.8) and 376.4 μm (171.2) at the 12-month and 2-year FU visits, respectively. Improvements in CMT were significant over the entire study period up until the final FU visit (Table 2).

4.3. BCVA-CMT Correlation. The analysis of correlation between BCVA and CMT showed that a weak correlation was only detectable at baseline and at the first annual time point (at baseline: linear correlation coefficient 0.38; p value <0.0001), while no correlation was apparent over the subsequent FU period (at the 5-year FU visit: linear correlation coefficient 0.22; p value <0.06).

4.4. Comparison between BRVO versus CRVO Outcomes. At the 12-month FU visit, both BRVO and CRVO eyes improved significantly in BCVA and CMT (Figures 1(a) and 1(c)); however, a statistically significant difference in mean BCVA and CMT between the two groups was still detectable. Table 3 shows mean visual and anatomic outcomes at each time point in BRVO versus CRVO eyes. The mean BCVA

Table 1: Characteristics of the study population.

	Number eyes (%)	Age mean (SD)	Gender (%)	Phakic/ pseudophakic	Ischemic (%)	Baseline BCVA logMar-mean (SD)	Baseline CMT μm-mean (SD)
Whole population	223	68.2 (12.7)	116 M(52.0) 107 F (47.9)	184/39	123 (55.2%)	0.79 (0.71)	615.7 (257.5)
BRVO	124 (55.6%)	69.2 (10.6)	68 M (54.8) 56 F (45.2)	105/19	63 (50.8%)	0.60 (0.53)	536.9 (212.5)
CRVO	99 (44.4%)	66.9 (14.8)	48 M (48.5%) 51 F (51.5%)	79/20	60 (60.6%)	1.03 (0.84)	714.4 (275.4)

was found to be significantly better in BRVO eyes compared to CRVO over the entire FU period; mean CMT was significantly lower in BRVO eyes at the first annual time points, while up until the 5-year follow-up visit, no differences could be found in CMT between BRVO and CRVO eyes.

4.5. Ischemic versus Nonischemic RVO Outcomes. When comparing ischemic and nonischemic subgroups at baseline, no significant differences were found in age, sex, number of phakic/pseudophakic eyes, or FU duration. On the contrary, mean BCVA and CMT differed significantly, being worse in ischemic eyes (Figure 1(b); p value: 0.0065).

At the 12-month FU visit, mean BCVA significantly improved in both subgroups (Figure 1(b)). However, visual improvements in nonischemic BRVO eyes were significantly higher than those of ischemic eyes, throughout the entire FU period. On the contrary, no significant differences were found in visual outcome when comparing ischemic and nonischemic CRVO eyes (Supplementary Material Table S2). No significant difference in CMT improvement was found when comparing ischemic and nonischemic subgroups, both for BRVO and CRVO eyes, throughout the entire FU period (Supplementary Material Table S2).

4.6. Number of Injections. The mean number of injections administered in the first year was 4.08 (SD 2.1) for Ranibizumab and 1.5 (SD 0.6) for Ozurdex. The number of injections decreased to a mean number of 3.02 (SD 1.05) for Ranibizumab and 0.62 (SD 0.9) for Ozurdex in the second year. The number of injections administered up until the 6th year is reported in Supplementary Material Table S3. At the 7-year FU visit, only 11 eyes received additional Ranibizumab injections and 7 eyes received Ozurdex injections. At the 8-year FU visit, 1 eye was treated with Ranibizumab and 3 eyes with Ozurdex.

In the study population 184 eyes were phakic, while the remaining eyes were pseudophakic. Cataract surgery was performed on 81 eyes during the period of investigation. In addition, 82 eyes underwent laser photocoagulation of areas of peripheral retinal nonperfusion and 77 eyes underwent focal/grid macular laser treatment.

4.7. Adverse Events. Table 4 summarizes the adverse events that occurred in the study population through the treatment with intravitreal injections.

A transient increase in IOP was found in 65 (29.1%) eyes (min 20, max 38 mmHg); this was treated with topical IOP-lowering medication or kept under observation, with no need for additional procedures. One eye with BRVO developed an increase in IOP that was refractory to topical medications after two Ozurdex injections. It was therefore treated with trabeculectomy. IOP was 38 mmHg and reduced to 10 mmHg after surgery, remaining stable over the entire subsequent FU period. The baseline visual acuity in this eye was 1.01 logMar (20/250); at the end of the study period (43-month FU), BCVA improved to 0.6 logMar (20/80).

One patient with CRVO, a female aged 66 years, developed endophthalmitis two days after the second Ozurdex injection. She was treated with pars plana vitrectomy, phacoemulsification, and intravitreal injection of vancomycin and ceftazidime. The Ozurdex implant was not removed. The treatment resulted in the infection's regression, with no residual vitreous debris detectable upon subsequent examinations. The baseline visual acuity was 0.7 logMar (20/100). At the end of the study period, BCVA had decreased to 1.3 logMar (20/400) as a consequence of the endophthalmitis.

No additional serious adverse events were observed during the FU period, as is reported in Table 4.

5. Discussion

In the present study, intravitreal treatment with Ranibizumab and/or dexamethasone was found to effectively provide long-lasting visual and anatomic improvement to eyes affected by RVO that were treated in a real-life clinical setting. In particular, this analysis presents the clinical outcome over a mean FU period of almost 4 years, showing significant visual gains with a flexible dosing regimen and decreasing number of intraocular injections over the period of investigation.

The visual and anatomic outcomes that are achievable with intravitreal treatment for RVO have been described in several randomized clinical trials. However, limited data are

Table 2: Mean BCVA and CMT and their changes at each annual time point for the whole population and for BRVO/CRVO subgroups (results are reported until the eighth year; subsequent FU is not included because of the small sample size).

		Number of eyes	BCVA logMar-mean (SD)	BCVA improvement logMar-mean (SD)	p value	CMT μmmean (SD)	CMT improvement μm-mean (SD)	p value
Baseline	Whole population	223	0.79 (0.71)	—	—	615.7 (257.5)	—	—
	BRVO	124	0.60 (0.53)	—	—	536.9 (212.5)	—	—
	CRVO	99	1.03 (0.84)	—	—	714.4 (275.4)	—	—
1 year	Whole population	223	0.62 (0.68)	0.16 (0.61)	<0.0001	401.04 (183.8)	214.6 (269.6)	<0.0001
	BRVO	124	0.43 (0.51)	0.17 (0.50)	<0.0001	355.2 (135.0)	181.7 (211.5)	<0.0001
	CRVO	99	0.88 (0.78)	0.16 (0.72)	0.0169	458.5 (218.3)	255.9 (324.7)	<0.0001
2 years	Whole population	189	0.63 (0.71)	0.12 (0.68)	0.009	376.4 (171.2)	229.0 (289.1)	<0.0001
	BRVO	114	0.40 (0.47)	0.17 (0.51)	0.0002	348.7 (139.7)	183.3 (243.5)	<0.0001
	CRVO	75	0.99 (0.85)	0.03 (0.87)	0.3652	418.1 (203.9)	297.9 (336.9)	<0.0001
3 years	Whole population	147	0.65 (0.73)	0.04 (0.70)	0.2588	367.1 (171.1)	232.1 (288.6)	<0.0001
	BRVO	94	0.47 (0.55)	0.10 (0.60)	0.0522	337.9 (147.9)	193.1 (236.6)	<0.0001
	CRVO	53	0.96 (0.89)	−0.07 (0.95)	0.3089	419.9 (197.4)	302.6 (356.1)	<0.0001
4 years	Whole population	115	0.60 (0.75)	0.06 (0.74)	0.1761	379.8 (196.2)	215.9 (273.1)	<0.0001
	BRVO	73	0.39 (0.48)	0.16 (0.48)	0.0029	340.8 (158.6)	181.7 (239.2)	<0.0001
	CRVO	42	0.96 (0.97)	−0.09 (1.04)	0.2726	449.0 (236.2)	276.6 (319.1)	<0.0001
5 years	Whole population	80	0.48 (0.62)	0.14 (0.58)	0.0183	344.6 (156.4)	241.5 (251.2)	<0.0001
	BRVO	52	0.40 (0.63)	0.08 (0.51)	0.1338	330.2 (154.3)	170.8 (201.8)	<0.0001
	CRVO	28	0.61 (0.59)	0.25 (0.69)	0.0341	369.8 (159.5)	365.8 (283.1)	<0.0001
6 years	Whole population	61	0.46 (0.57)	0.19 (0.59)	0.0079	332.8 (154.0)	255.5 (255.9)	<0.0001
	BRVO	41	0.32 (0.48)	0.20 (0.48)	0.0068	313.2 (149.4)	223.6 (227.1)	<0.0001
	CRVO	20	0.76 (0.64)	0.17 (0.78)	0.1676	374.1 (159.4)	322.6 (303.6)	0.0001
7 years	Whole population	39	0.57 (0.80)	0.06 (0.78)	0.3264	306.9 (147.0)	239.2 (271)	<0.0001
	BRVO	28	0.31 (0.45)	0.21 (0.49)	0.0154	298.5 (159.1)	221.8 (241.3)	<0.0001
	CRVO	11	1.23 (1.09)	−0.34 (1.19)	0.1824	334.8 (98.9)	297 (364.4)	0.0201
8 years	Whole population	19	0.48 (0.71)	0.2 (0.52)	0.0562	270.5 (155.0)	305.1 (305.2)	0.0001
	BRVO	16	0.30 (0.51)	0.23 (0.56)	0.0616	267.2 (163.5)	257.9 (246.2)	0.0002
	CRVO	3	1.40 (0.98)	0.03 (0.06)	0.2113	300.5 (0.71)	729.5 (581.9)	0.1635
Final visit	Whole population	223	0.69 (0.80)	0.11 (0.76)	0.0175	355.6 (171.9)	260.1 (292.7)	<0.0001
	BRVO	124	0.42 (0.57)	0.19 (0.60)	0.0003	316.0 (137.1)	220.9 (246.6)	<0.0001
	CRVO	99	1.02 (0.91)	0.01 (0.91)	0.4634	405.1 (197.2)	309.3 (336.8)	<0.0001

available for real-world clinical experiences in large patient populations treated over long FU periods.

Spooner et al. [14] have recently reported their real-life experience with anti-VEGF for RVO-related ME, describing good long-term outcomes in 68 eyes over a 5-year FU period. In our population, the improvement in visual acuity was lower than that reported by Spooner et al. This may be related to the worse baseline visual acuity in our population (conversion to approximate ETDRS letter score [15]: 54.9 versus 61.4 for BRVO; 33.5 versus 54.1 for CRVO) and the greater number of ischemic RVO (55.2% versus 27.9%). This reflects a more difficult-to-treat population with a lower potential for visual recovery. Another real-life analysis over a long FU period (4 years) included only 28 eyes affected by BRVO. In that study, Rezar et al. [16] reported a slightly better outcome compared to that of our population, but, once again, there was a lower number of ischemic BRVO eyes as compared to our study (33% versus 50.8%). It is well known that visual gains after treatment may be strongly influenced by factors such as extent of ischemic macular damage, retinal pigment epithelium atrophic changes, and progressive apoptotic cell death. Accordingly, eyes with ischemic RVO and low baseline visual acuity might experience low or no visual improvement after treatment. However, these conditions are not uncommon in eyes affected by RVO; therefore, it is worthwhile investigating their

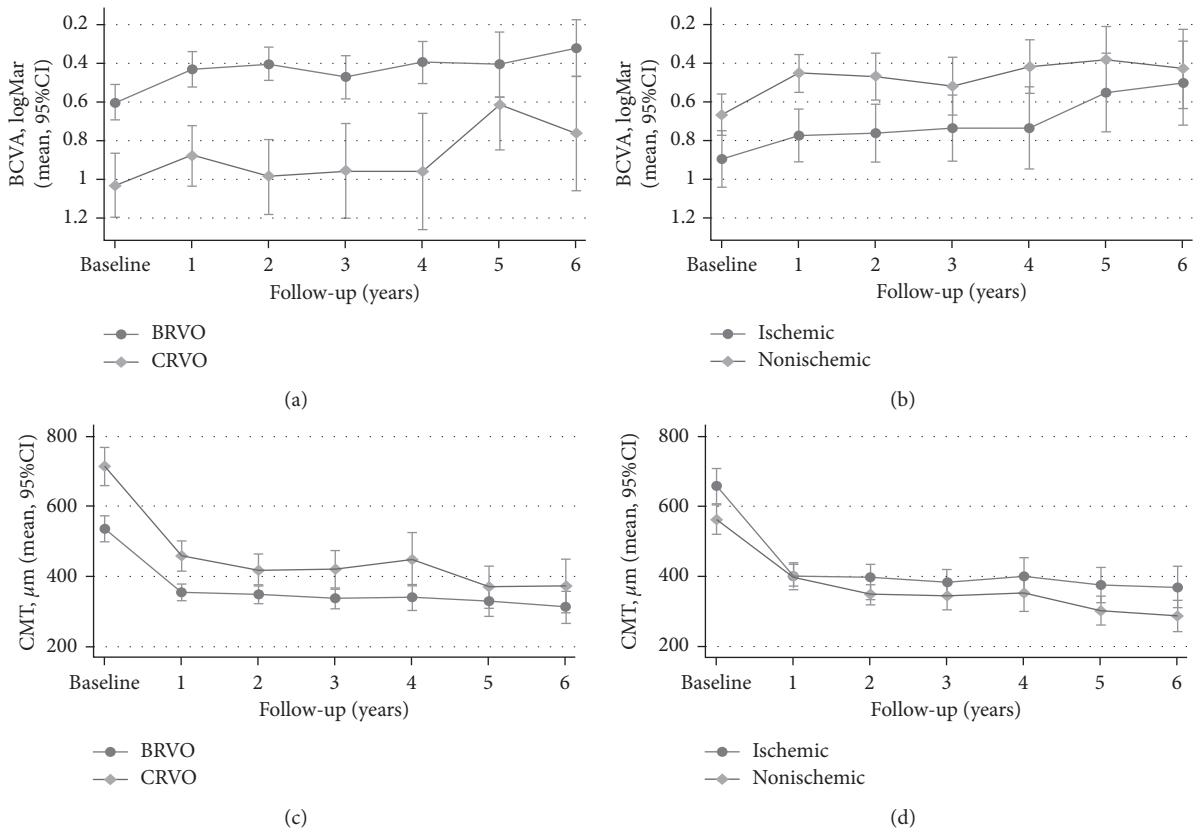

Figure 1: Changes in BCVA and CMT throughout the study period for each subgroup. (a) Changes in BCVA for BRVO/CRVO subgroups. (b) Changes in BCVA for ischemic/nonischemic subgroups. (c) Changes in CMT for BRVO/CRVO subgroups. (d) Changes in CMT for ischemic/nonischemic subgroups.

response to intravitreal treatment. Previous studies [17, 18] found that while a poor final visual acuity is recorded in these eyes if left untreated, significant improvement may be seen with intravitreal treatments over short FU periods. Our results show that significant visual gains are achievable also over longer periods of treatment, despite the more severe baseline condition. This represents an important finding as long-term efficacy is crucial in the treatment of RVO given that the mean age of onset is estimated to be <60 years in about 42% of patients and <70 years in about 72% [1].

The evaluation of possible predictive factors for better visual outcomes revealed only a weak correlation between visual improvement and CMT, which disappeared over the long-term FU period. This highlights that additional factors, other than macular thickness, such as photoreceptor damage and progressive retinal atrophy, may contribute to the impairment in visual acuity. In our population, ischemia and older age were found to be detrimental to visual acuity, while better visual outcomes were detected in eyes with a better baseline BCVA. Furthermore, better visual acuity was recorded in eyes with BRVO as compared to those with CRVO, at each time point. This confirms previous findings [17, 19] and emphasizes that considerably more severe retinal damage may be caused by a more extensive impairment in retinal vein circulation.

The adverse events found in our population were consistent with the well-established safety profile of Ranibizumab and dexamethasone. The percentage of transient increase in IOP (29.1%) was similar to that reported in the previous studies [6, 17, 20, 21]. Similarly, the surgery for glaucoma has been previously described after single or multiple Ozurdex injections [21, 22]. In our affected patient, the ocular hypertension completely and stably regressed after trabeculectomy, and considering the entire FU period of 43 months, intravitreal injections still resulted in a consistent improvement in visual acuity, suggesting that the treatment was beneficial despite the adverse event.

In our population, one patient developed endophthalmitis. This is a rare complication of Ozurdex injections, whose incidence is variable in the previous literature [6, 23, 24]. Stem et al. [25] reported that the endophthalmitis rate in 3593 Ozurdex injections, over a 3-year FU period, was 0.14% of injections and 0.4% of patients (5/1051 cases). One patient in their study developed

Table 3: Mean visual and anatomic outcomes at each time point in BRVO versus CRVO eyes.

		BRVO	CRVO	p value
Baseline	Number of eyes	124	99	
	$BCVA_{logMar\text{-}mean\text{-}(SD)}$	0.60 (0.53)	1.03 (0.84)	<0.0001
	$CMT_{\mu m\text{-}mean\text{-}(SD)}$	536.9 (212.5)	714.4 (275.4)	<0.0001
1 year	Number of eyes	124	99	
	$BCVA_{logMar\text{-}mean\text{-}(SD)}$	0.43 (0.51)	0.88 (0.08)	<0.0001
	$CMT_{\mu m\text{-}mean\text{-}(SD)}$	355.2 (135)	458.5 (218.3)	<0.0001
2 years	Number of eyes	114	75	
	$BCVA_{logMar\text{-}mean\text{-}(SD)}$	0.40 (0.47)	0.99 (0.85)	<0.0001
	$CMT_{\mu m\text{-}mean\text{-}(SD)}$	348.7 (139.7)	418.1 (203.9)	0.0057
3 years	Number of eyes	94	53	
	$BCVA_{logMar\text{-}mean\text{-}(SD)}$	0.47 (0.55)	0.96 (0.89)	0.0003
	$CMT_{\mu m\text{-}mean\text{-}(SD)}$	337.9 (147.9)	419.9 (197.3)	0.0052
4 years	Number of eyes	73	42	
	$BCVA_{logMar\text{-}mean\text{-}(SD)}$	0.39 (0.48)	0.96 (0.97)	0.0004
	$CMT_{\mu m\text{-}mean\text{-}(SD)}$	340.8 (158.6)	449 (236.2)	0.006
5 years	Number of eyes	52	28	
	$BCVA_{logMar\text{-}mean\text{-}(SD)}$	0.40 (0.63)	0.61 (0.59)	0.0729
	$CMT_{\mu m\text{-}mean\text{-}(SD)}$	330.2 (154.3)	369.8 (159.5)	0.1426
6 years	Number of eyes	41	20	
	$BCVA_{logMar\text{-}mean\text{-}(SD)}$	0.32 (0.48)	0.76 (0.64)	0.0051
	$CMT_{\mu m\text{-}mean\text{-}(SD)}$	313.2 (149.4)	374.1 (159.4)	0.0854
7 years	Number of eyes	28	11	
	$BCVA_{logMar\text{-}mean\text{-}(SD)}$	0.31 (0.45)	1.20 (1.09)	0.0098
	$CMT_{\mu m\text{-}mean\text{-}(SD)}$	298.5 (159.1)	334.8 (98.9)	0.2088
8 years	Number of eyes	16	3	
	$BCVA_{logMar\text{-}mean\text{-}(SD)}$	0.3 (0.51)	1.4 (0.98)	0.0841
	$CMT_{\mu m\text{-}mean\text{-}(SD)}$	267.2 (163.5)	300.5	0.1196

endophthalmitis twice; however, two patients continued to receive Ozurdex after the endophthalmitis with no additional adverse events. The authors concluded that endophthalmitis is an uncommon complication following Ozurdex injection that requires prompt treatment and suggested that vitrectomy with the removal of the dexamethasone implant may not be necessary in all patients. Our case confirms that there is not always a need for implant removal in order to reach a complete resolution of the infection.

The main strength of the present study is its reporting of long-term outcomes among a large patient cohort and its analysis of factors that may have an influence on visual recovery. However, a limitation of the study is its retrospective nature. In addition, the real-life clinical setting may have influenced the outcome and number of treatments as it did not allow for the strict exclusion criteria and scheduling of visits and treatments as in clinical trials. However, the aim of this study was to be representative of a typical real-world clinical experience. Although clinical trials support intravitreal therapy for RVO treatment, it is well known that visual outcomes may differ remarkably in a real-life setting. Intravitreal therapy may present a relevant burden to patients and healthcare professionals in routine clinical practice as intensive treatment and monitoring are required over long FU periods. Our findings of good long-term visual gains that are achievable in routine clinical practice among real-world individuals encourage the continuation of efforts to pursue better outcomes in the treatment of this debilitating retinal pathology.

In conclusion, the results of the present study show good long-term anatomic and functional responses to intravitreal therapy for RVO-related ME in a real-life clinical setting with a progressive reduction in the frequency of treatments. These findings support this treatment in populations with similar characteristics in similar settings.

Table 4: Adverse events in the study population throughout treatment with intravitreal injections.

Adverse event	n (%)
Endophthalmitis	
Whole sample	1–0.4
CRVO	1–1.0
BRVO	—
Elevation in intraocular pressure*	
Whole sample	65–29.1
CRVO	33–33.3-
BRVO	32–25.8
Surgery for refractory ocular hypertension**	
Whole sample	1–0.4
CRVO	—
BRVO	1–0.8
Vascular events***	
Whole sample	2–0.9
CRVO	2–2.0
BRVO	—
Request for emergency room service ****	
Whole sample	40–17.9
CRVO	14–14.1
BRVO	26–21.0

*Transient increase in IOP, requiring topical IOP-lowering medications; no additional procedures were required to reduce IOP. **Trabeculectomy for ocular hypertension refractory to topical medications. ***Nonfatal myocardial infarction or nonfatal stroke. ****Reasons for emergency room request: conjunctival hyperemia (n.5), floaters (n.2), feeling of a foreign body (n.2), and blurred vision (n.31).

Data Availability

The data used to support the findings of this study include patients' age, gender, and other demographic characteristics, visual acuity measurements, central macular thickness measurements, treatments administered, clinical details on diagnosis, and safety data. They are not included in the text in order to protect patients' privacy. The anonymized data are available from the corresponding author (emi_maggio@yahoo.it) upon request or, alternatively, from the Sacro Cuore Hospital Institutional Review Board (elvia.malo@sacrocuore.it), for researchers who meet the criteria for access to confidential data.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Supplementary Materials

The supplementary material section includes three tables. They report, respectively, the number of eyes gaining/losing ≥1 line at each annual time point, the comparison between ischemic and nonischemic RVO outcomes, and the number of injections until the 6th year of treatment. (*Supplementary Materials*)

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Research Article

Morphological and Functional Outcomes after Intravitreal Dexamethasone Injection for Macular Edema in Patients with Central Vein Occlusion at 48-Week Follow-Up

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Purpose. The purpose of the study was to assess the efficacy of intravitreal dexamethasone implant (IDI: Ozurdex®) injection in eyes with macular edema due to retinal vein occlusion. *Material and Method*. A retrospective, nonrandomized study was conducted in patients with macular edema (ME) due to retinal vein occlusion (RVO) who undertook intravitreal Ozurdex® as first-line treatment. We performed a complete ocular exam including macular OCT. *Results*. The mean BCVA (logMar) improved from $0.420.42 \pm 0.23$ logMar at baseline to 0.21 ± 0.23 logMar at 48 weeks in the BRVO group and from 0.72 ± 0.16 logMar at baseline to 0.31 ± 0.23 logMar at 48 weeks in the CRVO group. In both groups, CFT values decreased significantly compared to baseline ($p < 0.0001$ at each timepoint). Reinjection for recurrent macular edema after 18 weeks was indicated in five eyes (41.67%) in the BRVO group and in six eyes (25%) in the CRVO group. Cataract developed in two eyes (16.67%) in the BRVO group and in one eye (4.17%) in the CRVO group. The IOP was higher than 25 mmHg in two cases in the BRVO group (16.66%) and in three cases (8.33%) in the CRVO group. *Conclusion*. Ozurdex® injected intravitreally significantly improved the mean CFT and BCVA in eyes with macular edema due to retinal vein occlusion.

1. Introduction

Central retinal vein occlusion (CRVO) and branch retinal vein occlusion (BRVO) are between the most significant causes of decreased visual acuity due to the existence of macular edema (ME), whether the fovea is perfused or not [1]. ME is the result of increased intraluminal pressure, vascular endothelial damage, and impaired blood-retina barrier that results in leakage, relative ischemia, and low-grade inflammation [2]. For many years, the standard procedure for patients with ME has been grid laser photocoagulation [3, 4]. The Central Vein Occlusion Study not only confirmed its beneficial effects on ME but also showed that there was no statistical significant difference in visual acuity [5]. Over the last decade, the therapeutic options for ME associated with retinal vein occlusion (RVO) were revolutionized by intravitreal pharmacotherapy. Data revealed by clinical studies regarding treatment of ME due to retinal vein occlusion with intravitreal injection with antivascular endothelial growth factor (VEGF) and

dexamethasone showed substantial morphological and functional improvements in comparison to those obtained by laser therapy alone [1]. Ozurdex® was developed as a biodegradable vehicle for dexamethasone administered by intravitreal implant, which delivers a 700 μg dose of this drug to the retina and the vitreous. It was approved for use in the treatment of RVO in the United States of America (USA), Europe, and Switzerland. Several studies showed that intravitreal steroid injections have anti-inflammatory, antiangiogenic, and antivascular permeability characteristics and are effective for treating RVO-related ME [1, 2, 6–8].

Therefore, the purpose of the study was to evaluate the efficacy of intravitreal dexamethasone implant (IDI: Ozurdex®) injection in eyes with macular edema due to retinal vein occlusion.

2. Materials and Methods

2.1. Study Design. A retrospective, nonrandomized study was performed, based on the medical records of patients who had macular edema (ME) consequently to retinal vein occlusion (RVO) and had been treated as first-line treatment with Ozurdex intravitreal injection between September 2015 and December 2017 in Oculens Clinic, Cluj-Napoca, Romania. The study began after obtaining approval from the Clinical Ethics Committee.

2.2. Subjects. Newly diagnosed naïve RVO patients who had macular edema under 3 months at first presentation with a baseline central foveae thickness (CFT) of >300μ and visual acuity of +0.3 logarithm of the minimum angle of resolution (logMar) or worse were included. The exclusion criteria were coexisting retinal disease (such as diabetic retinopathy, age related macular degeneration, vitreomacular traction, or epiretinal membrane), or media opacities (cataract) that could decrease visual acuity (VA), and pregnancy. Patients who had previously received treatment for ME (anti-VEGF, steroids, and laser), with a history of ocular surgery (except cataract) and trauma, were excluded. All patients underwent standardized examination including measurement of best-corrected visual acuity (BCVA) using a projection chart at 5 m, slit-lamp biomicroscopy, fundus examination using a postdilation +90 diopter lens and a three mirror contact lens, measurement of intraocular pressure (IOP) via applanation tonometry, and color fundus photography. Fluorescein angiography (FA) (HRA-2; Heidelberg Engineering, Heidelberg, Germany) and optical coherence tomography (OCT) imaging (Triton, Topcon, Japan) of the macula were performed prior to treatment initiation. At each visit, the aforementioned examinations were performed, with exception of FA. Macular optical coherence tomography (OCT) was used to measure central foveae thickness (CFT), which was defined as mean thickness of the neurosensory retina in central 1 mm diameter region, and was computed via OCT mapping software provided with the device. Fluorescein angiography was performed in order to establish capillary dropout zones at the fovea and peripheral retina, and for leakage, as causes of ME.

Written informed consent for treatment was obtained from all patients, and the study complied with the principles of the Declaration of Helsinki (1964) and its amendments (Tokyo 1975, Venice 1983, and Hong Kong 1989).

2.3. Study Protocol. All injections were performed under sterile conditions in the operating room, after application of topical anesthesia (Benoxi–Oxybuprocaini Hydrochloridum, Unimed Pharma LTD., Slovakia) and of 10% povidone-iodine solution (Betadine Egis Pharmaceuticals PLC, Hungary); scrub was used on the lids and lashes, and 5% povidone-iodine was administered in the conjunctival sac. Intravitreal Ozurdex® 0.7 mg (Ozurdex®, Allergan Inc., Irvine, CA, USA) was injected through the pars plana into the vitreous, at 3.5 mm posterior to the limbus with a customized, single-use 22-gauge applicator. After the injection, each patient was prescribed steroids and antibiotics five times a day for one week. Patients were instructed to return to the hospital if they experienced decreased vision, eye pain, or any new symptoms.

2.4. Safety Evaluation. All the patients were followed up for 48 weeks. During the study period, the patients were monitored for adverse effects (IOP measurement; lens transparency). In the first year, the patients were examined the day after injection and 4 weeks, 8 weeks, 12 weeks, 24 weeks, and 48 weeks after injection.

Panretinal or sectorial photocoagulation was applied to the patients who showed any kind of neovascularization during the follow-up. Panretinal photocoagulation was applied to the CRVO patients who showed neovascularization of the iris or on optic disc. Sectorial laser photocoagulation was applied to the BRVO patients who showed any kind of neovascularization, and the treatment area covered the entire ischemic area that was detected via FA.

2.5. Data Collection. Data collected from patients' records included age, gender, type of RVO, ischemic status, types of RVO, associated risk factors, complications after injection, BCVA (converted to logarithm of the minimum angle of resolution, logMar), intraocular pressure, and CFT. Visual acuity and CFT were measured at all timepoints (baseline, 4 weeks, 8 weeks, 12 weeks, and 48 weeks).

2.6. Statistical Analysis. Visual acuity and the CFT values between baseline and the other timepoints were assessed with repeated measurement tests. Categorical variables were compared using the chi-square test. A p value <0.05 was considered statistically significant.

3. Results

3.1. Demographics. Thirty-six eyes of 36 patients were included. The average age of the patients was 59.33 ± 15.74 years (range 22–89). Twenty-four of the patients (66.67%) had nonischemic CRVO, while 12 (33.33%) had

nonischemic BRVO and received IDI injection as the first-line treatment for ME. No significant difference was seen between the two groups with respect to age and gender ($p = 0.33$). The follow-up period was 48 weeks. Demographic characteristics of the patients are shown in Table 1.

Systemic comorbidities included diabetes mellitus in 9% of the patients, atherosclerosis (9%), ischemic heart disease (9%), and hypertension (19%). Primary open angle glaucoma was present in two cases of BRVO (16.66%) and in four cases of CRVO (16.66%). All these patients followed a topical treatment with fixed combination (timolol 0.5% and dorzolamide) or prostaglandin analogue, with well-controlled IOP. Small hyperopia was present in 16 cases (44.44%).

In the CRVO group, the mean BCVA (logMar) value was 0.72 ± 0.16 logMar at baseline and improved to 0.45 ± 0.19 logMar after 4 weeks, 0.36 ± 0.18 logMar after 8 weeks, 0.35 ± 0.24 logMar after 12 weeks, 0.33 ± 0.24 logMar after 24 weeks, and 0.31 ± 0.23 logMar at 48 weeks (see Figure 1). In the CRVO group, the difference between the baseline and postinjection follow-up BCVA values was statistically significant. BCVA values at each control visit improved significantly compared to baseline ($p = 0.0012$ after 4 weeks; $p < 0.0001$ at 8 weeks, 12 weeks, 24 weeks, and 48 weeks).

In the BRVO group, the mean BCVA (logMar) value was 0.42 ± 0.23 logMar at baseline and improved to 0.26 ± 0.26 logMar after 4 weeks, 0.24 ± 0.23 logMar after 8 weeks, 0.22 ± 0.21 logMar after 12 weeks, 0.22 ± 0.22 logMar after 24 weeks, and 0.21 ± 0.23 logMar at 48 weeks (see Figure 1). In the BRVO group the difference between the baseline and postinjection follow-up BCVA values was statistically significant. BCVA values at each control visit improved significantly compared to baseline ($p = 0.0017$ after 4 weeks; <0.0001 at 8 weeks, 12 weeks, 24 weeks, and 48 weeks).

The difference between the two groups regarding BCVA was statistically significant at baseline ($p = 0.0057$), at 4 weeks ($p = 0.038$), at 8 weeks ($p = 0.0248$), at 12 weeks ($p = 0.0336$), and at 24 weeks ($p = 0.0448$), but there was no statistically significant difference at 48 weeks ($p = 0.1152$) (see Figure 1).

In the CRVO group, the mean CFT value was $504.38 \pm 112.91\,\mu$m at baseline and decreased to $366.58 \pm 109.58\,\mu$m after 4 weeks, $322.13 \pm 76.80\,\mu$m after 8 weeks, $288.25 \pm 96.89\,\mu$m after 12 weeks, $277.92 \pm 96.27\,\mu$m after 24 weeks, and 255.50 ± 67.86 at 48 weeks (see Figure 2). CFT values at each control visit improved significantly compared with baseline CFT values ($p < 0.0001$ at each timepoint).

In the BRVO group, the mean CFT value was $430.25 \pm 100.5\,\mu$m at baseline and decreased to $301.25 \pm 66.30\,\mu$m after 4 weeks, $314.08 \pm 102.30\,\mu$m after 8 weeks, $271.33 \pm 59.78\,\mu$m after 12 weeks, $251.08 \pm 64.85\,\mu$m after 24 weeks, and 250.80 ± 84.65 after 48 weeks (see Figure 2). CFT values at each control visit improved significantly compared with baseline CFT values ($p = 0.012$ at 4 weeks, $p = 0.0103$ at 8 weeks, $p < 0.0001$ at 12 weeks, 24 weeks, and 48 weeks).

The difference between the two groups regarding CFT values was not statistically significant at any control visits ($p = 0.0629$ at baseline visit, $p = 0.0671$ at 4 weeks, $p = 0.7929$ at 8 weeks, $p = 0.5844$ at 12 weeks, $p = 0.5519$ at 24 weeks, and $p = 0.9393$ at 48 weeks) (see Figure 2).

Table 1: Demographic characteristics of patients included in the study.

Present pathology	Mean age	Males (%)	Females (%)
CRVO	61.17 ± 15.43	66.67	33.33
BRVO	55.67 ± 16.37	50	50

Reinjection for recurrence of CFT elevation demonstrated by the macular OCT at 18 weeks was indicated in 6 cases (25%) in the CRVO group and in 5 cases in the BRVO group (41.67%). These cases presented for a check-up at 18 weeks (even it was not the check-up timepoint) because they observed a significantly visual acuity decrease. These cases were treated using a second injection of anti-VEGF such as bevacizumab (Avastin). The switch had a good rationale due to the different mode of action of these agents (Ozurdex versus Becacizumab) and also because of financial reasons. In Romania, the intravitreal injection with Ozurdex is not covered by the National Health Care System.

Intraocular pressure was measured in both groups in the first week after the injection. In the CRVO group and the BRVO group, the mean IOP value in the first week was 19.08 ± 2.95 mmHg and 18.75 ± 2.90 mmHg, respectively. The IOP was higher than 25 mmHg in three cases (8.33%) in the CRVO group and in two cases (16.66%) in the BRVO group two months after the intravitreal injection. IOP higher than 10 mmHg was present in 2 eyes (4.8%) in the CRVO group and in one eye (1.2%) in the BRVO group. Topical antiglaucomatous drugs were required in all these cases. Topical timolol 0.5% combined with dorzolamide in fixed combination was administered twice per day. Moreover, no statistical significant difference was shown between IOP values in the third and fourth month and baseline values ($p = 0.332$ in the CRVO group and $p = 0.673$ in the BRVO group). One patient required surgical treatment such as trabeculectomy.

Cataract developed in one eye (4.17%) in the CRVO group and in two eyes (16.67%) in the BRVO group and required phacoemulsification with intraocular artificial lens implantation. Conjunctival hemorrhages occurred in five patients (13.8%). None of the patients developed endophthalmitis, vitreous hemorrhage, or retinal detachment.

4. Discussions

Ozurdex® (dexamethasone intravitreal implant) is an intravitreal implant containing 0.7 mg (700 μg) dexamethasone in the Novadur solid polymer drug delivery system (Allergan Inc., Irvine, CA, USA). It is a potent corticosteroid, which suppresses inflammation by inhibiting multiple inflammatory cytokines resulting in decreased edema, fibrin deposition, capillary leakage, and migration of inflammatory cells [9]. The National Institute for Health and Care Excellence recommends the dexamethasone 0.7 mg intravitreal implant as an option for the treatment of ME following CRVO and BCVO when treatment with laser photocoagulation has not been beneficial or was not considered because of the extent of the hemorrhage [10]. The rationale for the use of steroids for ME is that steroids lessen retinal

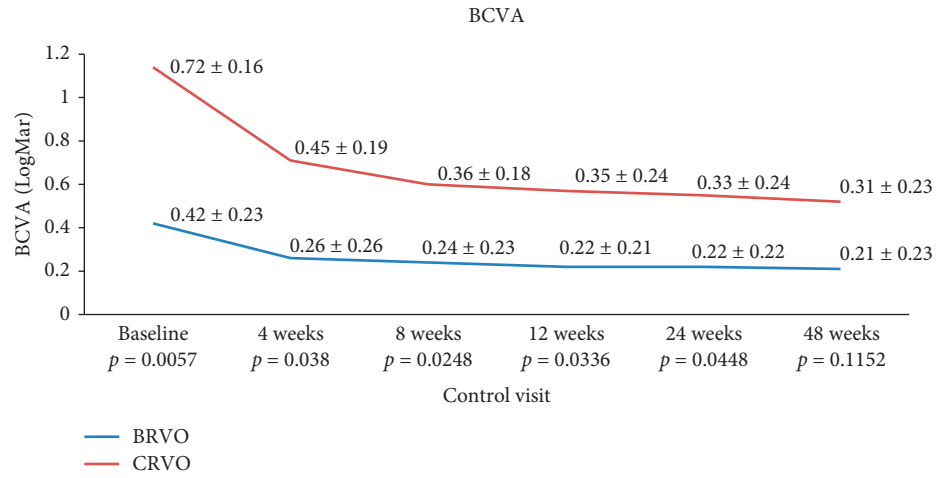

Figure 1: Mean BCVA values from baseline to follow-up visits after intravitreal dexamethasone injection in the two groups and the p values between the groups.

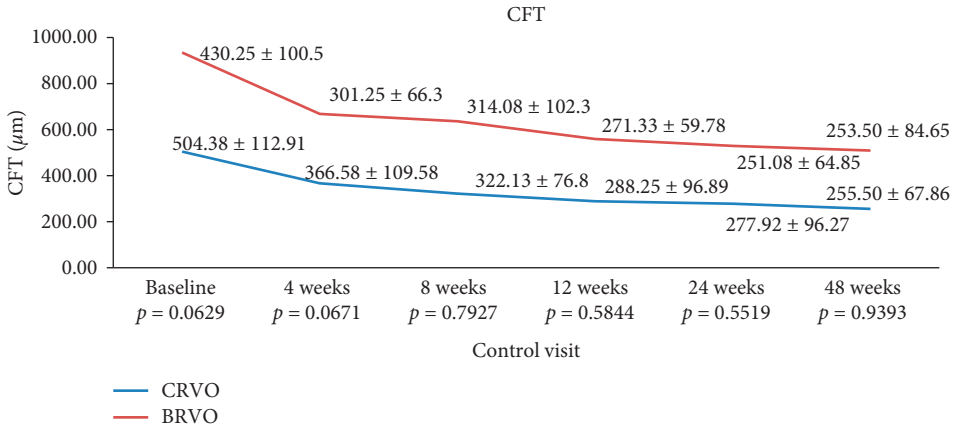

Figure 2: The difference between the baseline and postinjection follow-up CFT values in both groups and p values between the groups.

capillary permeability and stop the expression of the VEGF gene and the metabolic pathway of VEGF.

Demographic data from our study were similar with those showed in a recent study [11], which evaluated the efficacy and safety of intravitreal steroids for ME secondary to retinal vein occlusion.

Functional results from our study showed a statistical significant improvement in BCVA in both groups at each timepoint comparing with baseline ($p < 0.005$). The results were similar to those of previous studies. In the GENEVA study, the improvement in BCVA by 15 letters or more was 29% at 60 days and 22% at 180 days [4, 12]. In the COBALT study, 65% of the patients gained more than 15 letters at the EDTRS logMar chart at 6 months and 56% at 12 months [13]. The results of recent studies revealed that treatment of BRVO as early as 2 weeks after onset of ME enhanced visual outcomes [14]. In the SOLO study, the improvement in BCVA in the BRVO group was from 0.6 to 0.45 logMar after 24 weeks after the treatment, and in the CRVO group, VA increased from 0.7 to 0.52 logMar after 24 weeks [15]. Simsek et al. [10] showed in their study that BCVA improved significantly compared with baseline ($p = <0.001$) after the second injection of Ozurdex intravitreal implant. Mayer et al. [16] demonstrated an improvement in BCVA by 6.6 ± 1.7 letters in the CRVO group and by 7.8 ± 2.9 letters in the BRVO group.

Mean reduction in central macular thickness in our study was significant in both groups at each time point ($p < 0.005$) and was comparable with other studies. In the GENEVA study, it was shown a mean reduction of 119 μm at 180 days following treatment [13]. Singer et al. [17] showed a reduction in CFT of 195 μm. Shahina et al. [9] demonstrated in their study a mean reduction in CFT of 181.3 ± 210.92 μm. Simsek et al. [10] showed a statistically significant improvement ($p < 0.001$) of CFT 4 months after intravitreal dexamethasone injection. Moreover, they observed the recurrence of CFT elevation in 65.3% of patients in the BRVO group and in 68.1% in the CRVO group 4 months after the second injection of intravitreal dexamethasone implant. In the present study, the recurrence after the first injection was present in 41.67% patients with BRVO and in 25% patients with CRVO. Bezatis et al. [11] reported that the mean CFT

maintained was significantly reduced ($p < 0.001$) compared with the baseline at each follow-up visit.

In the current study, the recurrence of ME appeared in six eyes (25%) in the CRVO group and in five eyes (41.67%) in the BRVO group at 4.5 months from baseline. Published reports in which reinjections have been made after shorter intervals on an "as needed" basis are now available [18, 19]. In an earlier published retrospective assessment of 33 RVO-afflicted eyes, retreatment with dexamethasone was necessary at 4.7 ± 1.1 months after the first injection and at 5.1 ± 1.5 months after the second one in order to sustain a significant improvement in the best-corrected visual acuity and in the central retinal thickness [16]. Considering the results of the aforementioned studies, it is clear that the effects of intravitreal-administered dexamethasone can be sustained for 4 months (range: 3 to 7 months) irrespective of the patient's clinical background. A retreatment initiation on an "as needed" basis would require injection intervals of substantially less than 6 months for the vast majority of eyes [6, 15, 18, 20]. Moreover, frequent and repeated treatments with Ozurdex enlarge the risk of ocular side effects such as raised IOP and cataract formation. That is why in our study we preferred to use as a second injection an anti-VEGF medication.

In this study, cataract that decreased VA appeared in one eye (4.17%) in the CRVO group patients and in two eyes (16.67%) in the BRVO group during the follow-up. The results are similar with others studies [17]. Cataract may form because of long-term steroid secretion after single injection. The risk for cataract is higher after two injections of dexamethasone intravitreal implant [21]. Ozkaya et al. [8] reported a rate of cataract of 4.4% after a single intravitreal dexamethasone injection. The COBALT study showed a progression in lens opacities in 36% of patients [13]. Mayer et al. [16] reported a rate of 50% of eyes with cataract after three Ozurdex injections. Reid et al. [22] showed that the risk of cataract formation is higher in patients receiving multiple IDI injections. Nevertheless, cataract may form because of long-term steroid secretion after a single injection [10]. Meyer and Schönfeld did not reveal any cataract progression at 6 months after intravitreal injection of Ozurdex [23]. There are some conflicting studies that reported no cataract progression even after accidental intralenticular Ozurdex implant administration [24, 25]. In addition, many authors have revealed a resolution of the ME with an intralenticular implant [24, 26–29].

In our study, intraocular pressure increased in three eyes (8.33%) in the CRVO group and in two eyes (16.66%) in the BRVO group. In 2 eyes in the CRVO group, the IOP increased more than 10 mmHg. These results were lower in comparison to those revealed by Schmitz et al. [19]. In their retrospective study on 342 retinal vein occlusions, the IOP increased in 20% afflicted eyes after intravitreal injections of dexamethasone. In the Shasta trial [30], in 32.6% of the CRVO- and BRVO-afflicted eyes, an IOP increase of ≥10 mm Hg was reported. Intraocular pressure-lowering medication was given in 29.1% of the patients, while in 1.7%, incisional glaucoma surgery was performed. Mayer and Schönfeld [23] described an elevated IOP (>5 mmHg) in 40% of patients. Joshi et al. [31] reported an increase in IOP in 27% of the eyes, which needed to be medically controlled. In the GENEVA study [7], the authors showed an elevation of 25% of IOP at 6 months after intravitreal injection. On the contrary, Meyer and Schönfeld [23] did not notice any increase in IOP 6 months after the treatment. The increased IOP after Ozurdex intravitreal injection appears as a result of the steroid intravitreal injection. Dot et al. showed that steroid-induced glaucoma is the most common side effect associated with the dexamethasone intravitreal injection. We believe that each patient from our study who developed ocular hypertension was steroid responder [32]. Several pathogenetical mechanisms have been proposed for steroid-induced IOP elevation as a result from biochemical and structural changes in the trabecular meshwork (TM). Inhibition of extracellular matrix material degradation with the accumulation of fibronectin, glycosaminoglycan, laminin, and elastin in the TM, reduced phagocytotic capacity, decreased activity of protease, increased DNA content and nuclear size, reorganization of the TM cytoskeleton (which is unclear), formation of intercellular junctions, and rearrangement of specific protein synthesis are the main effects of steroids on the TM activity http://ghrnet.org/index.php/IJOR/article/view/2513/2894 [33–36]. François [37] and Armaly [38] suggested that the increased IOP is due to the alteration of the mucopolysaccarides, leading to their accumulation in the TM. Experimental studies have reported that steroids significantly increase expression of different genes in human TM [39–41].

In our study, we did not have any endophthalmitis after Ozurdex intravitreal implantation. The results are similar with previous studies [42, 43].

In our study, one eye (8.33%) with BRVO received a sectorial photocoagulation after 12 weeks and three eyes (12.5%) with CRVO received a panretinal laser photocoagulation 12 weeks after injection. In these cases, 12 weeks after the intravitreal treatment, the patients developed new vessels on the optic disc as a sign of ischemic form of retinal vein obstruction, even if they had a nonischemic form at the beginning of the study. The goal of the treatment was to decrease neovascular changes and prevent the development of neovascular glaucoma. There are studies that revealed that 30% of eyes with nonischemic CRVO at first may convert to ischemic type [44–47]. Trombosis of the retinal veins give rise to an increase in retinal capillary pressure with a higher capillary permeability and leakage of fluid and blood into the retina. Once the ischemia appears, the production of vascular endothelial growth factor (VEGF) is facilitated and promotes the retinal capillary permeability and leakage into the extracellular space ending in development of ME [48].

The present study has some limitation regarding the small sample size, the short period of follow-up and the absence of a control group. To our knowledge, this is the first Romanian study regarding the efficacy of intravitreal Ozurdex injection for ME after retinal vein occlusion. Nonetheless, further studies with active controls are needed to completely understand the efficacy and safety of intravitreal dexamethasone implant injection.

5. Conclusions

Intravitreal Ozurdex® injection significantly improved mean BCVA and reduced CFT in eyes with macular edema due to retinal vein occlusion. The treatment is safe and effective. Cataract formation and increasing IOP demands regular visits in patients treated with intravitreal Ozurdex.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declared that there are no conflicts of interest.

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Research Article

Sustained Intraocular Pressure Rise after the Treat and Extend Regimen at 3 Years: Aflibercept versus Ranibizumab

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Purpose. To determine the risk factors associated with sustained intraocular pressure (IOP) rise in patients enrolled in the treat and extend (T&E) protocol receiving aflibercept/ranibizumab therapy for 3 years. *Design*. Retrospective, observational chart review. *Setting*. Multicentric. *Patients*. 789 patients (1021 eyes; 602 males) enrolled in T&E using aflibercept/ranibizumab for diabetic macular edema (DME), wet age-related macular degeneration (AMD), or macular edema in retinal vein occlusion (RVO). *Intervention*. The history, examination (clinical and special investigations), and treatment records were thoroughly scrutinized. Sustained IOP rise was defined as a rise in IOP above baseline by ≥6 mmHg and/or >24 mmHg on 2 or more consecutive visits. The Wilk–Shapiro test was used for confirming normality of data. The Mantel–Haenszel test and generalized estimating equations were used to analyse multicentric data as well as to analyse data from both eyes of the same patients in the event that both eyes were under therapy. The relative risk, chi-square test (with and without Yates' correction), and univariate and multivariate analysis were used wherever appropriate. Statistical significance was set at $P < 0.05$. The primary outcome measure was the determination of risk factors for sustained IOP rise with ranibizumab/aflibercept therapy. Secondary outcome measures included determining the incidence of IOP rise (short term and sustained), visual field, and retinal nerve fibre layer (RNFL) changes. *Results*. The mean follow-up was 42.4 months. Male gender, South Asian ethnicity, older age, presence of AMD and vein occlusion, use of ranibizumab, higher number of injections, narrow angles, switch to bevacizumab/ranibizumab, and preexisting glaucoma were associated with sustained IOP rise. No significant visual field and RNFL changes were seen. The overall incidence was 8.91%. No patient required filtering surgery. No patient with IOP rise returned to baseline. *Conclusion*. IOP rise is an important consideration as the chronicity of the condition can eventually lead to glaucomatous changes in eyes with already compromised vision. Follow-ups and use of appropriate therapy can be determined correspondingly.

1. Introduction

Sustained intraocular pressure rise following intravitreal anti-VEGF injections is a known phenomenon, with several publications addressing this issue in part or whole [1–5]. There is a certain measure of discrepancy in reporting insofar as the potential risk factors as well as definitions of intraocular pressure (IOP) rise are concerned [6–8]. With numerous publications on the subject, it is only natural that contrasting outcomes are noted in studies conducted across the globe [1–8], the most disputed amongst risk factors for IOP rise being the number of injections administered and the treatment interval [2] between consecutive injections. When one factor in the indication, the anti-VEGF agent

used, the phakic status, the anterior chamber angle status, family history of glaucoma, and other characteristics [1, 2], it is evident that the condition (IOP rise) and analysis thereof is a complex phenomenon.

Despite a plethora of literature on the subject, a recently published review [1] highlights the lack of readily identifiable risk factors for IOP rise following intravitreal injections. Additionally, a literature search on PubMed, Scopus, and the Cochrane Database on 11th May 2019 using the key words "anti-VEGF agents, diabetic macular edema, retinal vein occlusion, age-related macular degeneration, choroidal neovascular membrane, intraocular pressure rise, ocular hypertension, ethnicity, anti-VEGF drug volume, short-term intraocular pressure rise, treat and extend regimen, aflibercept, ranibizumab, bevacizumab, dexamethasone implant, therapy switch, glaucoma progression, RNFL thickness, visual fields and optic disc changes" revealed a paucity of data on a comprehensive overview and hazard analysis of risk factors and IOP rise, especially between ranibizumab and aflibercept. We undertook this study with the aim of concurrently analysing all probable risk factors for sustained IOP rise following anti-VEGF injections under one complete regression model on patients enrolled under the treat and extend protocol and under follow-up for at least 3 years.

2. Methods

A retrospective, database search was conducted for patients who received the treat and extend protocol for wet age-related macular degeneration (wAMD), diabetic macular edema (DME), and macular edema secondary to retinal vein occlusion (RVO), and who were followed up for at least 3 years. Patients recruited had been treated at the Alphavision Augenzentrum, Bremerhaven, Germany, between January 2013 and June 2016; and the Indian centres of Raghudeep Eye Hospital, Ahmedabad; and MS Sudhalkar Medical Research Foundation, Baroda, The study adhered to the tenets of Helsinki. Informed consent about possible use of data for research had been obtained from all patients at the time of the first consultation. The chart review adhered to guidelines set out for the retrospective review process.

2.1. Patient Data

2.1.1. Inclusion Criteria. For inclusion, patients were required to have been enrolled in the treat and extend protocol of anti-VEGF injections for one of the aforementioned conditions (diabetic macular edema, macular edema associated with vein occlusion, or age-related macular degeneration) and to have had a follow-up for 3 years at least.

2.1.2. Data Chart Analysis. Data collected included a thorough history, demographics, the ethnicity of the patient, the indication for injection, the number of injections, the treatment interval, the type of anti-VEGF agent used, the volume of drug injected, therapy switch (if any), the status of the crystalline lens, the axial length, the anterior chamber angle status (per the Shaffer system; grade 2 or less was considered narrow), the relation between short-term IOP rise (measured 2 minutes after injection) and sustained IOP rise, and whether the patient was a preexisting patient of glaucoma or if the patient had a family history of glaucoma. We also noted the concentration of ranibizumab injected (0.5 mg or 0.3 mg). In India, the Drugs Controller General of India (DCGI) has approved both 0.3 mg and 0.5 mg concentrations for all three aforementioned indications, including 2 mg/0.05 ml for treatment-resistant cases [9].

2.1.3. Injection Procedure. Patients received a preemptive combination of brimonidine and timolol twice daily [10], starting 24 hours prior to the day of injection followed by one drop in the morning at least 2 hours prior to the injection. Additionally, we performed ocular decompression using the technique described by Gregori and associates [11] if there was no light perception after injection on table as assessed by asking the patient to look directly into the microscope light.

The injections had been administered under antiseptic conditions and topical anesthesia using a standardized technique in the inferotemporal quadrant. Preoperative preparation was conducted with povidone-iodine. Light perception and finger counting were confirmed on table after injection. No topical/systemic antibiotics were prescribed postoperatively. The IOP was measured with the Goldmann Applanation Tonometer 2 minutes after the injection in each patient to look for short-term IOP rise. The patients were followed up after injection on days 1, 10, and 30 and later as per the treat and extend regime. The treat and extend regime was strictly followed in all patients.

2.1.4. Therapy Switch and Treatment Details. Patients were advised a therapy switch based on standardized protocols. Bevacizumab could be administered to patients with neovascular AMD if therapy with ranibizumab and aflibercept was not effective; patients were required to have a minimum of 6 injections each before any switch was attempted. Patients with DME or macular edema secondary to RVO could receive the dexamethasone implant as therapy if treatment with ranibizumab and aflibercept was not effective. For DME and RVO patients, bevacizumab was permitted only if the patient showed no response to the implant or if the implant was contraindicated in a particular patient. Overall, at least 6 monthly injections of either ranibizumab or aflibercept were necessary followed by at least 6 monthly injections of the other drug before the dexamethasone implant or bevacizumab could be administered, regardless of the indication as per the protocol for treat and extend regime set by the *Deutsche Ophthalmologische Gesellschaft*, *Deutsche Retinologische Gesellschaft*, and *Berufsverband für Augenärzte* [12]. These associations also set out guidelines for patient examination (clinical examination) and follow-ups and are compulsory for receiving reimbursement [12]. Our centres in India followed the treat and extend regimen as well. It is also of note that some patients in our centres in India received 0.3 mg ranibizumab as approved of by the Drugs

Controller General of India. The treat and extend protocol was, however, strictly followed as already stated. We also noted the effect of therapy switch to either bevacizumab, dexamethasone implant, or from aflibercept to ranibizumab or vice versa on IOP of patients who had been treated with either ranibizumab or aflibercept. This was done to note the influence, if any, of switching to a particular drug from a particular drug.

2.1.5. Sustained IOP Rise. We defined sustained IOP rise as a rise in IOP above baseline by ≥6 mmHg and/or an IOP elevation to >24 mmHg on 2 or more consecutive visits beyond month 1 (i.e., IOP spike sustained beyond day 30) as suggested and published by Al-Abdullah and coauthors. The rise was to have been sustained for at least 6 months after first documentation of IOP rise.

2.1.6. Monitoring for Glaucoma. Eyes with preexisting glaucoma received quarterly visual field assessments in accordance with the guidelines set out [12]. Nonglaucomatous eyes received annual visual field evaluations unless they developed ocular hypertension, in which case they received semiannual visual field examinations in accordance with guidelines [12]. Patients with unreliable visual fields were excluded from the analysis.

2.1.7. Statistical Analysis. Descriptive statistics was used to analyze categorical variables in size (absolute frequencies) and percentage (relative frequencies). The Wilk–Shapiro test was used to confirm the normality of the data distribution. The chi-square test was used, with and without Yates' correction, wherever appropriate. The relative risk ratio was deduced for eyes receiving injections versus fellow eyes which acted as controls. The paired *t*-test was used to compare variables before and after the studied events. The Cochran–Mantel– Haenszel model for binary outcomes and generalized estimating equations were used to assimilate data from different centres as well as to analyze data from both eyes in patients who had bilateral treatment and to produce an overall result. Univariate analysis was performed to determine the association between various independent variables (such as age, indication, lens status, and number of injections) and IOP rise (dependent variable). Those variables which returned a significant association ($P = -0.05$) on univariate analysis were included in a multiple logistic regression model to determine the influence of one variable on IOP spikes after having factored in other characteristics which are known to influence the IOP. Correlation coefficients were derived to determine the strength of association between a said variable and the development of IOP rise. The results of these tests were presented as adjusted and unadjusted odds ratio, confidence intervals, and their *P* values. An odds ratio value that is greater than one indicates a higher risk of development of OHT. Fisher's exact test (with Benjamini–Hochberg adjustments of *P* value for pairwise comparisons, wherever applicable) was used to compare categorical variables between groups of various indications. A *P* value of 0.05 was considered statistically significant.

2.1.8. Outcome Measures. The primary outcome measure was the determination of risk factors associated with sustained IOP rise in patients enrolled in the treat and extend protocol. The secondary outcome measures included determining the incidence of sustained IOP rise, changes in visual field defects (especially mean deviation) as noted at final follow-up from baseline, and the changes in RNFL thickness from baseline to final follow-up.

3. Results

3.1. Demographics and Characteristics. A total of 839 patients (1021 eyes; 431 males) were analyzed. The mean follow-up was 42.4 months (SD: 2.5 months; range 36–52 months). Table 1 provides a detailed breakup of patients classified per anti-VEGF agent with reference to age, sex, indication, ethnicity, axial length, number of injections, the treatment interval, details of therapy switch, and other previously enumerated factors.

3.2. Transient IOP Rise. 133 (13.02%) eyes were documented to have a short-term rise in IOP 2 minutes after the injection procedure at some point in time during the follow-up period. 7/133 eyes were later documented to have sustained IOP rise. 5 out of these 7 eyes had wet AMD while one each had DME and RVO. 7 eyes needed ocular decompression immediately after injection.

3.3. Sustained IOP Rise. Overall, 91 eyes (8.91%) demonstrated a sustained IOP rise. 14 out of 1602 untreated eyes (of the same patients) developed sustained IOP rise over the said period. All 14 eyes had dry AMD, while the fellow eye in these patients had wet AMD. Multivariate analyses demonstrated a significant association of IOP rise with male gender, younger age (<70 years), South Asian ethnicity, ranibizumab therapy, patients with AMD, vein occlusion, narrow anterior chamber angle at baseline, the number of injections administered, therapy switch to bevacizumab, and switch from aflibercept to ranibizumab. Preexisting open-angle glaucoma was also associated with sustained IOP rise, necessitating an increase in therapy. 5.33% of 1444 eyes developed ocular hypertension, giving us a relative risk of 6.95 (95% CI 3.97–12.17, *Z*-statistic 6.78, $P < 0.0001$, number needed to treat for harm 19.38; 95% CI 25.61) at one year.

3.4. Other Factors. Sustained IOP rise was not associated independently with the treatment interval, short-term IOP rise, axial length, female gender, therapy switch from ranibizumab to aflibercept, and choice of anti-VEGF agent prior to switch to bevacizumab. DME did not correlate well with IOP rise either and neither did a family history of glaucoma.

Table 1: Univariate and multivariate analysis of characteristics associated with IOP spikes after antivascular endothelial growth factor agents in the treat and extend regimen.

Characteristics	Univariate analysis			Multivariate analysis		
	Odds ratio	95% CI	*P* value	Adjusted OR	CI	*P* value
Age (years)						
>70	Ref					
<70	3.34	1.32–5.72	0.012	3.72	1.72–4.63	0.015
Gender						
Female	Ref					
Male	2.83	1.02–4.76	0.024	2.94	1.1–4.89	0.018
Lens status						
Pseudophakic	Ref					
Phakic	1.04	0.84–1.46	0.21			
Etiology						
DME	Ref					
AMD	3.31	1.34–4.28	0.01	2.40	1.43–4.57	0.009
RVO	1.47	1.23–2.12	0.28			
Anti-VEGF agent						
Aflibercept	Ref					
Ranibizumab	6.62	2.95–8.89	0.001	5.85	2.07–7.24	0.001
Ac angle						
TM seen	Ref					
TM not seen	4.27	3.17–5.94	0.002	3.15	1.87–5.34	0.017
Ethnicity						
German	Ref					
South Asian	2.89	1.76–5.13	0.023	3.14	1.87–4.32	0.013
Turkish	1.57	1.33–2.19	0.22			
Arab	1.42	1.32–1.89	0.19			
Short-term IOP rise						
No	Ref					
Yes	2.31	2.12–4.33	0.24			
Baseline IOP						
<14 mm Hg	Ref					
14 mm or higher	2.17	1.27–5.32	0.12			
Ranibizumab volume (ml)						
0.03						
0.05	4.31	2.18–6.75	0.001	3.78	1.32–5.75	0.001
Treatment interval (weeks)						
4	Ref					
>4	2.31	2.09–4.12	0.11			
Number of injections						
3 or less	Ref					
3–6	3.35	1.67–3.87	0.07			
>6	3.24	2.09–5.08	0.012	4.11	1.83–5.39	0.001
Therapy switch						
To aflibercept	Ref					
To ranibizumab	4.13	2.29–6.03	0.003	3.78	2.10–4.78	0.002
To DEXI	3.11	2.87–5.4	0.09			
To avastin	5.12	2.56–7.25	0.011	4.55	2.17–6.78	0.002
Glaucoma						
No glaucoma	Ref					
Preexisting	3.11	2.78–5.97	0.013	4.13	3.12–5.89	0.001
F/H glaucoma						
No	Ref					
Yes	1.57	1.33–4.21	0.14			
Axial length (mm)						
23.0–25.0	Ref					
<23.0	2.34	1.42–5.22	0.13			
>25.0	1.85	1.2–3.98	0.10			

CI: confidence interval, DME: diabetic macular edema, OR: odds ratio, $P = p$ value, AMD: age-related macular degeneration, RVO: retinal vein occlusion, TM: trabecular meshwork, DEXI: dexamethasone implant. "Ref" is short for "Reference for statistical comparison of independent variables with more than one possible outcome during multivariate analysis.

3.5. Injections and IOP Rise. IOP rise was noted after a mean of 7.2 injections with ranibizumab and 10.8 injections with aflibercept. The difference tended towards but did not attain statistical significance ($P = 0.1$). The mean rise in IOP was 8.8 mmHg (range 6–19 mmHg). 43/87 patients demonstrated an IOP >28 mmHg at some point in time during the follow-up period. 10 patients were managed efficiently with monotherapy and 31 patients required 2 antiglaucoma medications while 9 required triple local therapy for IOP control. The most commonly used antiglaucoma medicine was a combination of brimonidine tartrate and timolol maleate (61 eyes).

3.6. Therapy Switch to the Dexamethasone Implant. 134 eyes required a switch to the dexamethasone implant for DME or RVO; 78 had chronic DME and the remaining 56 had macular edema secondary to retinal vein occlusion. 4/134 patients were diagnosed to have sustained IOP rise prior to therapy switch. 14/134 eyes developed ocular hypertension secondary to dexamethasone implant injection; none of these 14 eyes had any evidence of sustained IOP rise with anti-VEGF therapy. The mean number of injections prior to switch was 14.25 (SD: 2.25) for ranibizumab and 16.14 (SD: 2.8) for aflibercept. Regardless of primary therapy (aflibercept or ranibizumab), switch to the implant was not associated with an increased propensity towards sustained IOP rise (chi-square value: 0.069. $P = 0.79$; chi-square value with Yates' Correction: 0.0043. $P = 0.94$).

3.7. Therapy Switch to Bevacizumab. 87 eyes required a switch to bevacizumab therapy for wet AMD after ranibizumab/aflibercept therapy. The mean number of injections prior to the switch was 17.42 (SD 3.14) for ranibizumab and 15.46 (SD: 2.78) for aflibercept. 14/87 (16.09%) eyes developed IOP rise after a mean 6.27 injections of bevacizumab therapy.

3.8. Sustained IOP Rise. All patients continued with topical therapy and with injections for IOP rise during the course of follow-up. 80/87 patients required no additional therapy than what was instituted at the time the IOP rise was first detected. 7 patients required additional IOP lowering topical therapy after a mean of 5.24 injections (SD: 1.58) after topical therapy for IOP control was first instituted. 4/7 patients were under therapy with aflibercept while 3/7 patients were under therapy with ranibizumab.

3.9. Preexisting Glaucoma. A total of 107 eyes had preexisting glaucoma. 11/107 eyes demonstrated a worsening of IOP control during the course of follow-up and required additional therapy. 2 patients were on 3 drugs while 9 were on two drugs for glaucoma control. All 11 patients continued to do well with additional topical therapy and did not require surgical intervention.

None of the patients demonstrated visual field worsening during the follow-up period. None of the patients with preexisting glaucoma demonstrated significant visual field progression: The mean deviation for glaucomatous eyes was -2.6 ± 1.2 dB at baseline and 2.72 ± 1.06 dB at 3 years ($P = 0.09$).

The mean RNFL thickness in normal patients in our analysis was 109.7 ± 7.32 microns at baseline and 108.1 ± 6.89 microns at 3 years ($P = 0.06$). The mean RNFL thickness in glaucomatous eyes changed from 91.32 ± 8.11 microns at baseline to 90.02 ± 7.57 microns at 3 years ($P = 0.083$). 20 patients were excluded from the analysis because of unreliable fields.

4. Discussion

We demonstrate an association between sustained IOP rise and the following: older age, male sex, South Asian ethnicity, narrow angles, preexisting glaucoma, >6 injections, AMD and RVO, use of ranibizumab, concentration of ranibizumab injected, and switch to ranibizumab or bevacizumab. All patients had well-controlled IOP (with local therapy) till the end of the follow-up period. None of the patients demonstrated optic nerve head changes or visual field worsening till the end of the follow-up period. RNFL thinning was demonstrated in our study but it did not reach statistically significant proportions. All patients continued to require IOP lowering medication until the end of the follow-up period. 11 patients with preexisting glaucoma required additional IOP lowering topical therapy. Not a single patient required filtering surgery till the end of the follow-up period. Patients who had a short-term IOP rise were not necessarily predisposed to develop sustained IOP rise. Patients who had sustained IOP rise with anti-VEGF therapy were not predisposed to develop IOP rise with the dexamethasone implant. Although a rise of 6 mm or 20% rise in IOP may not necessarily be detrimental to the eye in general, we chose these definitions in line with past literature for ease of interpretation, considering the fact that this may artificially inflate the number of patients who do demonstrate an IOP rise without detriment. This is so because the purpose of this study was primarily to document IOP rise and not necessarily the damage to visual fields and/or RNFL.

Male gender and South Asian ethnicity were two demographic factors associated with an increased chance of sustained IOP rise after repeated intravitreal injection. Males were represented in greater number in our study probably because of the fact that diabetes mellitus and hypertension (and their consequent complications such as macular edema and vein occlusion) were found to be higher in several of the studied ethnic groups (Turks, Indians, and Germans). Additionally, we included several ethnic groups wherein males were more likely to present for therapy as well as comply with follow-up for 3 years as was required because of cultural issues which often tend to unfortunately sideline female patients and their visual needs (Turks, Arabs, and different Indian ethnolinguistic groups). We can only speculate at this point in time that this probably has something to do with an influence of these two factors on reduced microparticle clearance of degradation products of the anti-VEGF agent through the trabecular meshwork as suggested in earlier publications. The South Asian population in general and the

Indian population in particular does not seem to have a higher incidence of glaucoma, but the chances of undetected glaucoma is higher than the Caucasian population [13, 14]. However, this does not seem to be a consideration in our study since all patients were comprehensively examined prior to therapy.

Sustained IOP rise with aflibercept and ranibizumab use for AMD has been documented and studied [15]; studies have thrown up conflicting reports as regards the risk factors studied for IOP rise. Indeed, some studies do not report of any sustained IOP rise following anti-VEGF injections [1, 2, 6, 8]. The most oft studied and documented risk factors are the number of injections and the treatment interval, followed by lens status, presence of vein occlusion [2], preexisting glaucomatous disease, and angle chamber depth. Additionally, most studies that do report IOP rise are ones that follow patients over a mean of 84 weeks. This is consistent with our findings in that most patients developed an IOP spike after a mean of 7–10 injections had been administered. AMD was a risk factor for IOP rise independent of number of injections in our study. Also, the potential role of vein occlusions in IOP rise has been suggested in past analyses [1, 2].

Pretreatment [10, 11, 16] with IOP lowering medications or ocular massage has been suggested for short-term IOP rise; the long-term effect of this measure is unknown. RNFL thinning [17] has been suggested as a short-term consequence of acute IOP fluctuations. Also, vitreous reflux [18] is said to play a role in reducing immediate rise in IOP. We determine through multivariate analysis that short-term IOP rise did not correlate significantly with long-term IOP rise. A large proportion of patients in our series did not manifest an acute IOP spike. This is probably influenced by our prophylactic control of short-term IOP rise using topical therapy and globe decompression. Most studies that advise preemptive lowering of IOP did not look at the long-term consequences of these measures on sustained IOP rise [1]. This suggests that the cause for RNFL thinning as described by Martinez de la Casa and associates is probably short-term IOP rise. We did not notice significant RNFL thinning. The prophylactic use of IOP lowering medication and ocular decompression probably prevented short-term IOP fluctuations, and thus we avoided its detrimental effect on the RNFL layer.

The treatment interval in our study did not influence IOP rise unlike the findings of Mathalone et al. They reported an incidence of sustained IOP rise of 11% (comparable to our study). Overall 22 patients in their series were noted to have IOP rise. It is possible that the lower numbers (a fourth of the total number of patients we report to have sustained IOP rise) influenced the outcomes [2]. Even if we exclusively consider wet AMD patients in our series, the number of eyes under consideration is much higher than what has been reported in the study by Mathalone and associates.

The anti-VEGF agent used has generated considerable interest, with reasonably consistent findings reported from various studies. Bevacizumab [1, 2, 14, 19] has been noted by most authors to lead to sustained IOP rise followed by ranibizumab [1, 2]. Our data corroborates with past literature in that ranibizumab has a higher probability of causing sustained IOP rise when compared to aflibercept [1, 2, 19]; only one study (with insufficient numbers) reports that ranibizumab is not associated with IOP rise [8]. We also determine in our study through multivariate analysis that switching to ranibizumab or bevacizumab increases the chances of the patient developing sustained IOP rise, whereas switching to aflibercept does not [7]. This agrees well with past reports and may have something to do with the structure of ranibizumab. Also, per our analysis, switching to the dexamethasone implant after primary therapy with anti-VEGF agents does not increase the probability of IOP rise, regardless of the agent used (ranibizumab or aflibercept). This finding is somewhat in conflict with the discussion by Dedania and associates [2] based on past reports.

The outcome of research on the number of injections and its influence on long-term IOP rise is mixed; some studies suggest that this is a consideration [20], while other authors reject this theory [21, 22]. Even the average number of injections to IOP rise fluctuates between 6 [23] and 24 [24, 25].

The concentration of the injected drug, a consideration only with ranibizumab in the South Asian region in our study (given that aflibercept is only used in a dose of 0.5 mg), seems to correlate positively and independently with sustained IOP rise. A literature search using the key words "anti-VEGF agent, intraocular pressure, ranibizumab, drug volume, 0.3 mg, 0.5 mg ml, age-related macular degeneration, macular edema, sustained IOP rise, long-term IOP rise" on PubMed, Scopus, and the Cochrane Database on 11th May 2019 failed to reveal any study that looks at the volume of injected ranibizumab and IOP rise; logically, a higher volume would mean a great probability of short-term IOP spikes, but we demonstrate courtesy multivariate analysis that this influences long-term IOP rise too. This has probably something to do with greater probability of trabecular meshwork obstruction with higher drug concentrations.

Whereas a narrow anterior chamber angle predisposed the patient to sustained IOP rise in our study, the axial length seemingly did not. Short-term IOP rise has been associated with short eyes and narrow chambers [23], but its influence on long-term IOP rise does not seem to have been adequately addressed.

Preexisting glaucoma and sustained IOP rise seem to have a controversial association [1, 2], with some studies reporting a strong correlation and another reporting none. Studies that report no influence of preexisting glaucoma on long-term IOP rise generally have small numbers [1]. A family history of glaucoma was reported to be a risk factor by Hoang and associates [20]; Dedania et al. [2] suggest that their exclusion of 3 patients with glaucoma might have confounded the results. Whereas one study reports the average time to IOP rise to be 39 weeks in glaucoma patients [23], we noted the time to be 25 weeks on an average in our analysis. Whereas preexisting glaucoma appeared to be a risk factor for sustained IOP rise in our study, a family history of glaucoma did not seem to predispose a patient to long-term

IOP rise. Unlike the findings of Kim and associates [5], a low baseline IOP did not seem to predispose the patient to sustained IOP rise. AMD and RVO, however, were strongly associated with sustained IOP rise. Patients with AMD in our study tended to receive on an average a greater number of injections probably leading to a greater buildup of degradation microparticles and causing a rise in IOP.

None of the patients in our study received topical or peribulbar steroids; the use of the implant after therapy switch in our analysis did not seem to independently alter the IOP profile of the patient till the end of the follow-up period. Past literature reports that patients with a history of ocular or systemic corticosteroid use had a rapid and greater increase in IOP [2, 20]. Our prophylactic treatment probably influenced this. The hypothesis that alteration of trabecular outflow facility with steroid use may influence sustained IOP rise after anti-VEGF injections probably needs further evaluation.

The extreme variations in reports on long-term IOP rise along with the risk factors responsible for it as reported in literature are testimony to the complexity of this disease process [1, 2, 18–22, 24–26]. Studies vary in their structure, number, indications, inclusion and exclusion of certain groups of patients (glaucomatous eyes, for instance), and their definitions of IOP rise [1, 2]. The current study is an attempt to compile, as comprehensively as possible, the overall data on potential risk factors (based on past literature) for sustained IOP rise following intravitreal injections and their outcomes on visual fields, optic nerve head changes, and RNFL thickness. RNFL thickness has not shown to vary significantly in literature published earlier [27]. Unlike most reports on dexamethasone implant induced transient ocular hypertension [28, 29], the rise in IOP with anti-VEGF agents seems to be chronic, sustained, thereby suggesting a higher chance of progression to glaucomatous changes, the lower incidence overall of ocular hypertension notwithstanding. We attempt to homogenize the data as much as possible in that we look exclusively at patients enrolled for the treat and extend protocol. On the other hand, the multicentric data ensures a composite ethnic assimilation and helps look at the influence of ethnicity on IOP rise. It also provides us an opportunity to look at lower ranibizumab injection volumes as protection against IOP rise. We provide data over a 3-year follow-up period, ensuring adequacy in terms of time and sufficient number of injections for analyses. We report on therapy switch to four of the most commonly used agents and their influence on IOP rise. We look at short-term IOP rise and measures to control IOP spikes in the immediate postinjection period, and we monitor patients for glaucomatous changes over the three-year follow-up period.

Our study is not without limitations: the retrospective nature and hence missed follow-ups, the lack of a control group for injections, the multicentric model (albeit adjusted statically) and perhaps the lack of a clear explanation for gender and ethnic susceptibilities, and the primacy of ranibizumab over aflibercept in IOP rise. Notwithstanding, we present several features of interest, a majority of which have already been elaborated above. Additionally, we compare head to head two FDA approved anti-VEGF agents and compile data on the treat and extend regime, the most recommended and currently the most commonly used posology, especially in insured markets in Europe, Asia, and probably the Americas, and we attempt to identify the populace most at risk for developing ocular hypertension. The compliance mandated by the insurance companies in terms of follow-up as well as our strict outreach program to avoid attrition and missed follow-ups help us draw meaningful conclusions from our data and eliminate to a large extent the fallacies of any retrospective analysis.

From our analysis, we hypothesize that the association of sustained IOP rise with age, narrow angles, greater number of injections, the volume of ranibizumab injected, and bevacizumab and ranibizumab suggests that a higher buildup of microdegradation products in the trabecular meshwork leads to sustained IOP rise. The association of AMD with sustained IOP rise is probably a pointer towards an overall degenerative process affecting the eye, a hypothesis that finds support in the fact that 14 control eyes developed ocular hypertension and all had dry AMD. Vein occlusions are closely associated with glaucoma, a pointer again to degenerative processes affecting the trabecular meshwork or dysfunctional trabecular meshwork. Whether circulating anti-VEGF molecules eventually reached the control eye is as of now unknown. The role of gender and ethnicity in trabecular meshwork function along with the proposed hypothesis needs further study. The differences in structure between aflibercept and ranibizumab may account for the difference in incidence of IOP rise too. The literature supports the role of trabecular alteration secondary to multiple injections, trabecular congestion due to antibodies, silicone microdroplets, or protein aggregation with bevacizumab and a chronic trabeculitis or a trabecular autoimmune reaction [30]. These factors seem to cause IOP rise in these patients.

To conclude, younger age, male sex, South Asian ethnicity, narrow angles, preexisting glaucoma, >6 injections, presence of AMD and RVO, use of ranibizumab, concentration of ranibizumab injected, and switch to ranibizumab or bevacizumab are independent risk factors for IOP spikes in patients who received either ranibizumab or aflibercept per the treat and extend regime for patients with AMD, DME, or RVO. Patients with the aforementioned characteristics will probably benefit with preemptive IOP lowering therapy, a close follow-up, and regular assessment for glaucomatous changes. The severity of the treat and extend regime might actually be beneficial in ensuring that these patients do not progress to develop glaucoma and end up with worse visual function.

Data Availability

Data pertaining to this manuscript will be made available on request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Research Article

Six-Year Real-World Outcomes of Antivascular Endothelial Growth Factor Monotherapy and Combination Therapy for Various Subtypes of Polypoidal Choroidal Vasculopathy

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The purpose of this study was to compare 6-year visual outcomes of antivascular endothelial growth factor (anti-VEGF) monotherapy and initial combination therapy of photodynamic therapy (PDT) and anti-VEGF therapy for polypoidal choroidal vasculopathy (PCV) in a Chinese population and to investigate imaging biomarkers associated with visual outcomes. Forty-eight treatment-naive PCV eyes of 46 patients were reviewed retrospectively, which underwent anti-VEGF monotherapy or initial combination therapy. PCV was classified into 2 subtypes. Mean best-corrected visual acuity (BCVA) using logarithm of minimal angle resolution and imaging morphological features was compared. No significant differences of mean BCVA changes were noticed between anti-VEGF monotherapy and combination therapy in either subtype 1 PCV or subtype 2 PCV during 6-year period (all P values >0.05). Compared with BCVA at baseline, the mean BCVA at 72 months deteriorated significantly in eyes with subtype 1 PCV ($P < 0.001$), while the mean BCVA at 72 months remained stable in eyes with subtype 2 PCV ($P = 0.941$). In subtype 2 PCV eyes with continuous retina pigment epithelium, the mean changes of BCVA in eyes treated with anti-VEGF monotherapy were better than those in eyes treated with combination therapy ($P = 0.020$). Anti-VEGF monotherapy and combination therapy for various subtypes of PCV had comparable long-term visual outcomes in most cases in real world. Imaging biomarkers which correlate with visual outcomes and treatment response should be included in the classification of PCV and validated in real world.

1. Introduction

Polypoidal choroidal vasculopathy (PCV) is characterized by polypoidal hyperfluorescence with or without a branching vascular network (BVN) in indocyanine green angiography (ICGA), which is the gold standard for diagnosing PCV [1, 2]. Currently, a wide spectrum of treatment options, including antivascular endothelial growth factor (anti-VEGF) therapy, photodynamic therapy (PDT), and various combinations of these therapies, have been performed in real world. Several clinical trials compared various treatment regimens [3–7]. The EVEREST-II study compared the intravitreal injection (IVT) of ranibizumab (IVT-R) and combination of PDT and IVT-R and concluded that combination therapy is preferred to IVR monotherapy [8]. Also, the PLANET study compared IVT aflibercept without and with rescue PDT after 3 months and suggested that no additional benefit was gained in combining with PDT as a rescue therapy [4]. These inconsistent conclusions reveal that more further studies are needed for management of PCV.

Anti-VEGF monotherapy and combination therapy of PDT and anti-VEGF therapy were recommended by recent guidelines and clinical trials [3–5, 9, 10]. Unlike clinical trials which enrolled subjects with restrict criteria prospectively, the efficacy of these treatment regimens needs to be confirmed in real world. Several studies have confirmed the efficacy of anti-VEGF therapies and PDT with additional

anti-VEGF therapy for PCV over a long-term period [11–16]. However, long-term outcomes of initial combination therapy of PDT and anti-VEGF therapy in real world have not been reported. And, it has been a consensus that more studies are needed to validate the long-term impact of various classifications of PCV on visual outcomes and treatment regimens [10].

The first aim of the present study was to report the 6-year outcomes of anti-VEGF monotherapy and combination therapy of PDT and anti-VEGF therapy for various subtypes of PCV. The second aim was to investigate imaging biomarkers that might correlate with long-term visual outcomes and treatment response, which should be considered when classifying PCV into various subtypes.

2. Materials and Methods

2.1. Enrollment of Study Subjects. We retrospectively reviewed 48 eyes of 46 consecutive patients with more than 6 years of follow-up who underwent anti-VEGF monotherapy and combination therapy for PCV at the Department of Ophthalmology, Peking Union Medical College Hospital between May 1, 2010, and May 1, 2013. All patients provided written informed consent after they received an explanation of the treatment. This retrospective study was performed with the approval of the Institutional Review Board of Peking Union Medical College Hospital (reference no. S-K631) and conducted in accordance with the tenets of the Declaration of Helsinki. No identifiable images were used in this retrospective study, and no patient consent was required.

The inclusion criteria were (1) symptomatic macular serosanguinous pigment epithelium detachment (PED) with subfoveal leakage on fluorescein angiography (FA) and (2) presence of polypoidal hyperfluorescence with or without a BVN on ICGA. The exclusion criteria were (1) any previous treatment for PCV, including anti-VEGF therapy, PDT, laser coagulation, or transpupillary thermotherapy; (2) any other concomitant ocular diseases, such as typical neovascular age-related macular degeneration (nvAMD), diabetic retinopathy, retinal artery or vein occlusion, and glaucoma; or (3) retinal pigment epithelium tears or ripping.

2.2. Examination. Main outcome measurement was best-corrected visual acuity (BCVA). All patients received a complete ocular examination, including BCVA using logarithm of minimum angle of resolution (logMAR) which was converted from decimal visual acuity measured with tumbling E chart, slit-lamp biomicroscopy, dilated fundus examination, FA and ICGA (Spectralis HRA, Heidelberg Engineering, Heidelberg, Germany), and optical coherence tomography (OCT; 3D-OCT 1000 and 2000, Topcon Corp., Tokyo, Japan, and Spectralis OCT, Heidelberg Engineering, Heidelberg, Germany).

The patients were observed at baseline, every 1 month in the first 3 months, at least every 3 months in the rest of the first year, and at least 6 months in the second to the sixth year. The FA and ICGA were performed at baseline. At every visit, the BCVA, dilated fundus examination, and OCT were performed. The examination data were collected from the baseline and the 1-, 2-, 3-, 6-, 9-, 12-, 18-, 24-, 30-, 36-, 42-, 48-, 54-, 60-, 66-, 72-month (±2 weeks in the last 5 years) follow-ups and were interpreted retrospectively.

PCV was diagnosed with confocal scanning laser ophthalmoscope-based ICGA while subretinal focal polypoidal hyperfluorescence with or without BVN was noticed. PCV was classified into 2 subtypes according to appearances on ICGA and OCT retrospectively: subtype 1 PCV and subtype 2 PCV, which have been found to be correlated with their pathogenesis and visual outcomes [17–19]. The subtype 1 PCV had feeder and draining vessels for polyps, also known as polypoidal CNV or nvAMD related polyps, which did not meet the definition of subtype 2 PCV as described below. Also, the subtype 2 PCV had no apparent feeder or draining vessels, also known as idiopathic PCV or PCV in the narrow sense in previous studies, which presents polypoidal alterations to neovascular or abnormal vascular tissue, usually accompanied by pachychoroid, in the absence of drusen, characteristic pigmentary abnormalities, and geographic atrophy. The greatest linear dimension (GLD) was determined by the ICGA, which included entire polyps and BVNs at the early phase of ICGA, assessed using HRA built-in software. The distance from foveola to the nearest polyp and BVN was also measured. Configuration of polyps was classified into 2 categories according to appearances on ICGA: isolated and interconnected (cluster or string) [20, 21]. The number of polypoidal lesions was also classified into 2 categories: single and multiple. OCT features at baseline included intraretinal fluid, subretinal fluid, and the continuity of external limiting membrane (ELM), ellipsoid zone (EZ), and retina pigment epithelium (RPE). The continuity of the lines or bands corresponding to ELM, EZ, and RPE was detected using dense OCT scans centered on lesions, at least using a 49-line raster scan pattern, 20×20 degrees, and multiple scans were performed on each eye. The discontinuity of ELM, EZ, or RPE was defined as a disruption of the corresponding line or band on OCT images. Because ICGA was an invasive examination and was not considered to be performed routinely in clinical practice during follow-up, the recurrence of fluid and exudation was defined as the recurrence of disease activity using OCT [13].

2.3. Intervention. Patients who underwent various interventions were enrolled and grouped into 2 groups: anti-VEGF monotherapy and combination therapy. Patients in the anti-VEGF monotherapy group underwent injection of only anti-VEGF agents, including ranibizumab, bevacizumab, and conbercept. After the initial treatment at baseline, repeat treatment of anti-VEGF therapy was applied as needed (pro re nata (PRN)), and conversion of anti-VEGF agents was recorded. Patients in the combination therapy group underwent a session of PDT guided by ICGA and an anti-VEGF injection within 10 days after PDT or on the same day. Retreatment was applied when retinal hemorrhage, intraretinal fluid, or subretinal fluid were observed without treatment. However, for those who presented persistent

intra- or subretinal fluid which were resistant to treatment, repeat treatment might be considered not to be performed if patients requested so. The decision was at the physicians' discretion and performed by the physicians in our department. Each treatment was explained detailedly to the patients until patients and we reached an agreement on the treatment plan.

2.4. Statistical Analysis. SPSS 25.0 (IBM, Chicago, USA) was used for statistical analysis. Paired *t*-test and 2-sample *t*-test were used for analysis of continuous variables. The chi-squared test was used for categorical variables. Multiple linear regression analysis was performed on related imaging features (continuity of ELM, EZ, and RPE, intraretinal fluid, subretinal fluid, GLD, the distance from foveola to the nearest polyp and BVN, and the number and configuration of polyps), and the changes of BCVA were used as the dependent variable using the stepwise model with the threshold P value =0.05 for enter and 0.10 for remove, in which age, gender, and BCVA at baseline were adjusted. Considering that almost all participants had one or several missing data, the missing data were imputed using the last-observation-carried-forward method and compared for consistency with those obtained using observed data. Differences with $P < 0.05$ were considered statistically significant.

3. Results

In total, 48 eyes of 46 patients who completed 6-year follow-up visits after the initial treatments were analyzed. The patients' clinical details are listed in Table 1. Age, gender, baseline BCVA, and treatment regimens showed no significant differences between these two subtypes. GLD, distance from foveola to BVN, the distribution of continuous RPE, and configuration and number of polyps showed significant differences between these two subtypes (all P values <0.05). Age, gender, baseline BCVA, baseline distance from foveola to BVN and the nearest polyp, the baseline presence of continuous ELM, EZ, and RPE, and intraretinal fluid showed significant differences between various treatment regimens (all P values <0.05). The baseline GLD was greater in eyes treated with combination therapy than that in eyes treated with anti-VEGF monotherapy (3554.9 versus 2378.5, $P = 0.018$), while baseline subretinal fluid was more common in the eyes treated with anti-VEGF monotherapy than that in the eyes treated with combination therapy significantly (79.2% versus 43.5%, $P = 0.017$).

Among the enrolled eyes, 24 eyes received anti-VEGF monotherapy, while the other 23 eyes received combination therapy. The mean number of treatments is summarized in Table 2 according to various subtypes of PCV. The mean number of anti-VEGF therapy showed no significant differences between the treatment regimens of anti-VEGF monotherapy and combination therapy in both subtype 1 PCV and subtype 2 PCV during the follow-up period, except in year 5 in subtype 2 PCV, in which the mean number of anti-VEGF in the regimen of anti-VEGF monotherapy was less than that in the regimen of combination therapy significantly ($P = 0.019$). The mean number of anti-VEGF therapy showed no significant differences between subtype 1 PCV and subtype 2 PCV when using the treatment regimens of anti-VEGF monotherapy and combination therapy during the follow-up period, except in year 3 when using the combination therapy ($P = 0.033$) and in year 5 when using the anti-VEGF monotherapy ($P = 0.049$). Seventeen eyes (36.2%) received conversions between various anti-VEGF agents.

Figure 1 shows the mean vision changes over time for both subtype 1 PCV and subtype 2 PCV, and it was found that eyes with subtype 2 PCV had better visual outcomes than eyes with subtype 1 PCV since month 12. The mean BCVA at month 72 deteriorated significantly in eyes with subtype 1 PCV ($P < 0.001$), while the mean BCVA at month 72 remains stable in eyes with subtype 2 PCV ($P = 0.941$). However, no significant difference of mean vision change was noticed between various treatment regimens in eyes with either subtype 1 PCV or subtype 2 PCV (all P values >0.05) (Supplementary Figure 1).

Recurrence of disease activity was detected in 28 eyes (59.6%). For eyes with subtype 1 PCV, recurrence of disease activity was detected in 6 eyes treated with anti-VEGF monotherapy and 12 eyes treated with combination therapy, and no significant difference was found between various treatment regimens ($P = 0.061$). For eyes with subtype 2 PCV, recurrence of disease activity was detected in 4 eyes treated with anti-VEGF monotherapy and 6 eyes treated with combination therapy, and no significant difference was found between various treatment regimens either ($P = 0.222$). The number of eyes with intraretinal fluid, subretinal fluid, and macular atrophy at month 72 is shown in Table 3. For subtype 1 PCV, the percentage of macular atrophy in eyes treated with combination therapy was significantly higher than that in eyes treated with anti-VEGF monotherapy ($P = 0.041$). The percentage of subretinal fluid at month 72 in eyes treated with anti-VEGF monotherapy was significantly higher than that in eyes treated with combination therapy ($P = 0.046$).

Multiple linear regression analysis showed that the mean changes of BCVA during the follow-up period were significantly related to the configuration of polyps ($\beta = 0.723$; $P < 0.001$) and the continuity of RPE at baseline ($\beta = -1.185$; $P < 0.001$). In subtype 2 PCV eyes with continuous RPE (examples can be seen in Supplementary Figure 2), the mean changes of BCVA in eyes treated with anti-VEGF monotherapy were better than those in eyes treated with combination therapy (−0.464 versus 0.131; $P = 0.020$). However, no significant difference of mean changes of BCVA was found between various treatment regimens in both subtype 1 PCV and subtype 2 PCV in eyes with either isolated or interconnected polyps (all P values >0.05).

4. Discussion

The current study compared 6-year outcomes of anti-VEGF monotherapy and combination therapy of PDT and anti-VEGF therapy for various subtypes of PCV. The present

Table 1: Baseline characteristics of the participants with various subtypes of polypoidal choroidal vasculopathy.

	Subtype 1	Subtype 2	P
Patients (n)	24	23	
Gender (n), female/male	8/16	10/13	0.556
Age (year), mean ± SD	64.3 ± 7.6	61.3 ± 8.0	0.184
Best-corrected visual acuity (logMAR), mean ± SD	0.54 ± 0.36	0.55 ± 0.37	0.965
Optical coherence tomography features			
Continuous external limiting membrane (n)	2	3	0.666
Continuous ellipsoid zone (n)	0	2	0.234
Continuous retinal pigment epithelium (n)	6	17	0.001
Intraretinal fluid (n)	15	11	0.375
Subretinal fluid (n)	11	18	0.036
Indocyanine green angiography features			
Greatest linear dimension (μm), mean ± SD	3859.7 ± 1625.6	1862.0 ± 1011.0	<0.001
The distance from foveola to the nearest polyp (μm), mean ± SD	1897.2 ± 1126.4	655.5 ± 540.7	<0.001
The distance from foveola to branching vascular network (μm), mean ± SD	255.1 ± 497.4	340.7 ± 433.2	0.551
Configuration of polyps (n), isolated/interconnected	7/17	18/5	0.001
Number of polyps (n), single/multiple	1/23	11/12	0.001
Treatment regimen (n), anti-VEGF monotherapy/combination therapy	11/13	13/10	0.564

logMAR, logarithm of minimum angle of resolution; SD, standard deviation; VEGF, vascular endothelial growth factor.

Table 2: Mean (standard deviation) number of anti-VEGF therapy and PDT in the regimen of anti-VEGF monotherapy and the regimen of combination therapy for various subtypes of polypoidal choroidal vasculopathy during the 6-year period.

	Subtype 1			Subtype 2		
	Anti-VEGF monotherapy	Combination therapy		Anti-VEGF monotherapy	Combination therapy	
		Anti-VEGF therapy	PDT		Anti-VEGF therapy	PDT
Year 1	2.73 (1.10)	4.62 (3.10)	1.00 (0)	2.62 (2.57)	2.40 (1.84)	1.00 (0)
Year 2	1.09 (1.14)	1.77 (1.88)	0 (0)	0.62 (1.19)	1.10 (1.10)	0.20 (0.42)
Year 3	1.82 (1.94)	1.54 (1.76)	0.15 (0.38)	0.69 (1.55)	0.40 (0.70)	0.10 (0.32)
Year 4	1.27 (2.00)	1.46 (1.56)	0 (0)	0.23 (0.60)	1.60 (2.91)	0.20 (0.42)
Year 5	0.91 (1.22)	1.00 (1.08)	0 (0)	0 (0)	0.90 (0.99)	0 (0)
Year 6	0.91 (1.38)	0.62 (0.51)	0 (0)	0.15 (0.38)	0.70 (1.06)	0 (0)
Total	8.73 (6.17)	11.00 (4.24)	1.15 (0.38)	4.31 (3.71)	7.10 (5.97)	1.50 (0.71)

PDT, photodynamic therapy; VEGF, vascular endothelial growth factor.

study showed that eyes with subtype 2 PCV had favorable long-term visual outcomes, and no significant differences of long-term visual outcomes and treatment numbers were found between anti-VEGF monotherapy and initial combination therapy of PDT and anti-VEGF therapy in eyes with either subtype 1 PCV or subtype 2 PCV. Anti-VEGF monotherapy had better visual outcomes than combination therapy for subtype 2 PCV eyes with continuous RPE.

In the current study, anti-VEGF monotherapy and combination therapy had comparable long-term visual outcomes, which was in accordance with the results of the PLANET study [4]. However, combination therapy in real world was considered for eyes with greater severity and activity according to current guidelines [2, 10]. Still, caution should be taken when considering PDT for eyes with PCV because of rare incidences of complications, including subretinal hemorrhage, choroidal infarction, and RPE tear [22–26].

Imaging morphological features that might predict response to therapy and visual outcomes could be regarded as imaging biomarkers in the management of PCV. In this long-term real-world study, we found that anti-VEGF monotherapy for eyes with continuous RPE had better visual outcomes than combination therapy in subtype 2 PCV. Therefore, the continuity or RPE could be taken into consideration when investigating future classification and management of PCV. Neurosensory retina might be affected by abnormal vessels or BVN directly when RPE was discontinuous, and the higher percentage of discontinuous RPE, which refers to alterations of the outer blood-retinal barrier of tight junctions between RPE cells, might contribute to the deteriorated BCVA outcomes [27, 28]. Besides, it has been reported that PDT might lead to choriocapillary occlusion, RPE, and neuroretina injury, which still needs to be validated furtherly using ICGA or OCT angiography [22, 29]. Therefore, we speculated that the dysfunction of

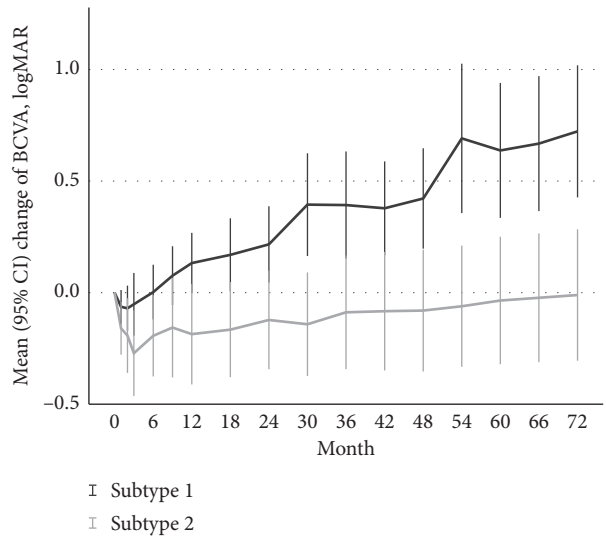

Figure 1: Mean (95% confidence interval) changes of best-corrected visual acuity (BCVA) from baseline using logMAR over 72 months after antivascular endothelial growth factor (VEGF) monotherapy or combination therapy of photodynamic therapy and anti-VEGF therapy for polypoidal choroidal vasculopathy (PCV). The subtype 2 PCV had better mean changes of BCVA than the subtype 1 PCV since month 12 ($P < 0.05$).

Table 3: Anatomical outcomes for 72 months in eyes with PCV by optical coherence tomography.

	Subtype 1		Subtype 2	
	Anti-VEGF monotherapy	Combination therapy	Anti-VEGF monotherapy	Combination therapy
Intraretinal fluid	5	6	3	1
Subretinal fluid	1	4	6	0
Macular atrophy	0	5	3	4

PCV, polypoidal choroidal vasculopathy; VEGF, vascular endothelial growth factor.

RPE and outer layers of neuroretina after PDT might lead to unfavorable visual outcomes. Similarly, PDT might cause choroidal hypoperfusion [30]; therefore, macular atrophy was more common in subtype 1 eyes treated with combination therapy. Additionally, the method of classification for PCV in the current study has aroused attention increasingly in clinical practice [10]. In the present study, the subtype 2 PCV had significantly more favorable long-term visual outcomes when compared with the subtype 1 PCV. Similarly, Jang et al. also reported a better BCVA at baseline and at month 12 after the initial treatment in eyes with subtype 2 PCV than that in eyes with subtype 1 PCV, [17] which accords with our results. Therefore, the current study not only validated the previous classification but also came up with another imaging feature, the continuity of RPE that might correlate with visual outcome and treatment response and could be considered in future classification for PCV. However, it needs to be noted that the classification for PCV is still under investigation because of its complexity. Previous clinicopathological studies have confirmed that both VEGF-positive lesions and VEGF-negative lesions existed in various PCV specimens, [31, 32] which suggested that the pathogenesis of PCV was complicated and eyes with PCV of various imaging morphological features might have different pathogenesis. Therefore, imaging-based classification for PCV needs further investigation and validation, and correlation with visual outcomes and treatment response should be evaluated in detail.

The mean number of anti-VEGF therapies in the present real-world study was less than that in previous studies, which did not classify PCV into various subtypes. An extensive study of the LAPTOP study reported a mean injection number of 14.8 for ranibizumab in the anti-VEGF monotherapy group over 5 years, in which the number of ranibizumab injection was 8.0 in 3 years after the LAPTOP study, while the number of aflibercept was 3.7 [14]. Another Japanese study reported a mean injection number of 18.2 for ranibizumab over 6 years [16]. Although conversive therapy of anti-VEGF agents might help reduce the injection number, other influential factors in real world should be taken into consideration. Firstly, the retreatment criteria in real world were not entirely the same as those of previous studies, and the retreatment decisions were made on the eyes with only explicit signs of recurrence rather than the eyes with potential signs or only decreased BCVA. In the current study, retreatment might not be performed on eyes with persistent intraretinal fluid or subretinal fluid which were resistant to treatment if patients requested so in real world. And, in the present retrospective study without a strict prospective protocol, eyes of less activity and severity were

allowed to visit us every 6 months in real world. Secondly, the enrolled Chinese patients might bear the financial burden, and the anti-VEGF agents used in this study have not been paid by the national medical insurance during majority of the follow-up period, which indeed reduced the patients' therapeutic compliance. Therefore, the mean number of anti-VEGF injections in real world was less than previous studies, especially in developing countries.

Our study has several limitations, including the relatively small patient number. Since long-term follow-up is difficult in ordinary clinical practice, the number of patients in each treatment group among various subtypes of PCV is relatively small, so that our results might need to be confirmed by further studies which include more subjects. Although we have examined the distribution of various treatment regimens among different subtypes of PCV, bias due to the small number of subjects seems to be unavoidable in such a study, which is similar to previous studies of long-term treatment for PCV [11–16]. Moreover, because of the retrospective nature of this study, long-term randomized clinical trials and prospective real-world studies are needed to investigate more effective treatment regimens for PCV according to imaging features. Besides, because the correlation between polypoidal choroidal vasculopathy and pachychoroid spectrum diseases was noticed after the time point that the enrolled eyes received treatment, data about choroidal morphology were not collected using OCT. Fortunately, a great number of studies about choroidal morphology in eyes with PCV have been published. Additionally, early treatment diabetic retinopathy study charts were not used for visual examination in this study because in clinical practice tumbling E charts were commonly used in China. However, logMAR was used to measure the changes of BCVA for statistical analysis in this study, which has been well accepted universally. Moreover, the OCT scan pattern we used might miss some subtle ELM, EZ, or RPE disruptions, so that the differences of visual outcomes between PCV eyes with and without continuous RPE might be slightly less significant. Because the imaging technique has developed during these years, more imaging biomarkers associated with visual outcomes need further investigation using current devices. Furthermore, only Chinese patients were enrolled, and worldwide multicenter investigations might be needed to study PCV in real world.

5. Conclusion

In conclusion, the 6-year outcomes of anti-VEGF monotherapy and initial combination therapy for PCV were reviewed. Our study demonstrated that both treatment regimens showed comparable visual outcomes over 72-month follow-up, except that anti-VEGF monotherapy had more favorable visual outcomes for subtype 2 PCV eyes with continuous RPE. Because this study was a retrospective review with limited size, large, long-term, and prospective randomized studies are needed to investigate the optimal management for PCV. Also, imaging-based classification for PCV which correlates with visual outcomes and treatment response needs further investigation and validation.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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Supplementary Materials

Supplementary Figure 1: mean changes of best-corrected visual acuity over 72 months for two subtypes of PCV after treatment. Supplementary Figure 2: examples of continuity of retinal pigment epithelium. (*Supplementary Materials*)

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