Received: 28 February 2022 | Accepted: 25 October 2022

DOI: 10.1111/aos.15283

Acta Ophthalmologica

ORIGINAL ARTICLE

Impact of intravitreal ranibizumab, aflibercept and bevacizumab on retinal ganglion cell and nerve fibre layer thickness in Neovascular age-related macular degeneration

Yaser Abu Dail | **Berthold Seitz** | **Haris Sideroudi** | **Alaa D. Abdin**

Department of Ophthalmology, Saarland University Medical Center, Homburg/Saar, Germany

Correspondence
Yaser Abu Dail, Department of Ophthalmology, Saarland University Medical Center UKS, Kirrberger Street 100, Building 22, 66421 Homburg/Saar, Germany.
Email: yaser.abu-dail@uks.eu

Abstract

Purpose: To compare the effects of monotherapy with intravitreal ranibizumab, aflibercept and bevacizumab on retinal ganglion cell layer (RGCL) and retinal nerve fibre layer (RNFL) in patients with naïve neovascular age-related macular degeneration (nAMD).

Methods: This is a retrospective cohort study with three-groups comparison. 83 patients and 97 eyes on continuous monotherapy with an intravitreal anti-vascular endothelial growth factor (anti-VEGF) were followed for 24 months and divided into three groups according to anti-VEGF (aflibercept: 25 eyes, ranibizumab: 34 eyes, bevacizumab: 38 eyes). Main outcome measures included: RGCL and RNFL thickness, best corrected visual acuity (BCVA), central macular thickness (CMT), macular volume (MV) and the presence of intraretinal fluids (IRF), subretinal fluids (SRF) and retinal pigment epithelial atrophy (RPE-atrophy). All outcome measures were recorded at the time of the first injection, 1 and 2 years after treatment and compared longitudinally and between groups.

Results: The mean age was 79 ± 7 years. The RGCL thickness, MV, CMT and the presence of IRF and SRF decreased significantly within all three medication groups ($p < 0.05$ for all) with no significant difference between groups over the 2-year follow-up period ($p > 0.10$ for all). The decrease in RNFL thickness was not significant within or between the groups after a 2-year follow-up ($p > 0.055$ for all). RPE-atrophy increased significantly after 2 years in all three groups ($p < 0.028$ for all) with no significant difference between groups at all three time points ($p > 0.307$ for all). BCVA was comparable between the three groups over the 2-year follow-up period ($p > 0.22$ for all).

Conclusions: Monotherapy with intravitreal aflibercept, bevacizumab and ranibizumab was associated with comparable significant decreases in RGCL thickness, CMT, MV, IRF and SRF in naïve nAMD patients during the first 2 years of treatment. Furthermore, no significant differences either in BCVA or RNFL thickness were observed between the three intravitreal anti-VEFGs during the first 2 years of treatment.

KEYWORDS
intraretinal fluids, intravitreal anti-VEGF, retinal ganglion cell layer, retinal nerve fibre layer, subretinal fluids

1 | INTRODUCTION

Age-related macular degeneration (AMD) is estimated to be the fourth leading cause of blindness and the third leading cause of moderate to severe visual impairment in adults aged 50 years and older worldwide (Flaxman et al., 2017). Neovascular AMD (nAMD) is also estimated to be responsible for 90% of AMD-related legal blindness, although it occurs only in 10%–15% of AMD patients (Ferris III et al., 1984). Since their introduction in 2004, anti-vascular endothelial growth factor (anti-VEGF) medications have become the standard treatment of nAMD (Browning et al., 2012; Mitchell et al., 2018). Their effectiveness in reducing and sometimes reversing nAMD-related visual loss have been demonstrated in several randomized controlled trials (RCTs) (Nguyen et al., 2018; Solomon et al., 2019).

However, due to the need of long-term use of anti-VEGF medications, their long-term side effects are an increasing concern. In addition to inducing angiogenesis, VEGF also plays neuroprotective, neurotrophic and neuroregenerative roles in many neural tissues and cells including retinal ganglion cells (RGC), Müller cells, retinal pigment epithelium (RPE) and photoreceptors (Froger et al., 2020; Makri et al., 2017; Nishijima et al., 2007). Experimental studies have also shown that RGCs, RPEs and Müller cells secrete VEGF to promote their own survival (Ford et al., 2011; Froger et al., 2020; Saint-Geniez et al., 2008). Therefore, chronic suppression of VEGF could reduce the survival of RGCs and result in a deleterious downstream effect on retinal nerve fibres layer (RNFL) (Horsley et al., 2010). Indeed, several studies found a significant reduction in RGC Layer (RGCL) thickness after treatment with intravitreal anti-VEGFs (Abdolrahimzadeh et al., 2019; Aşikgarip et al., 2021; Beck et al., 2016; Inan et al., 2019; Lee, Sim, et al., 2020).

However, demonstrating causality between anti-VEGF treatment and RGCL and RNFL thinning has proven to be difficult. As eyes of patients with dry AMD or healthy eyes being the only ethically acceptable control groups, it remains a challenge to separate the effect of nAMD on RGCL and RNFL from the effect of anti-VEGF treatment. Additionally, in the absence of an alternative effective therapy for nAMD, anti-VEGFs will generally remain the standard therapy for nAMD regardless of their long-term side effects on the retina.

Nevertheless, a significant difference in long-term side effects between specific anti-VEGFs medications would have important implications for clinical practice and decision-making. There is increasing evidence that different intravitreal anti-VEGF medications may have different side effects. A study from CATT research group (Daniel et al., 2020) suggests a role for anti-VEGF treatment in development of geographic atrophy and shows that the use of ranibizumab carries a higher risk for the development of RPE-atrophy compared to bevacizumab. In monkeys, aflibercept has been shown to induce haemolysis, protein complex formation and subsequent individual RPE cell death compared to ranibizumab (Julien et al., 2014). Bevacizumab was also found to induce photoreceptor damage, immune complex formation and thrombotic micorangiopathy (Julien et al., 2014). However, the few clinical studies that compared the influence of different anti-VEGF medications on RGCL and RNFL had a relatively short follow-up period and showed inconsistent results (Ahn et al., 2021; Kim et al., 2019; Lee, Sim, et al., 2020; Sobacı et al., 2013). Therefore, the focus of this study was to compare the impact of specific anti-VEGF medications (ranibizumab, aflibercept and bevacizumab) on RGCL and RNFL during a 2-year study period.

2 | METHODS

This is a retrospective cohort study comparing three groups of naïve nAMD patients. It was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Medical Association of Saarland, Germany (Nr. 123/20). Due to the retrospective nature of the study, written informed consent was waived. All data of the study were collected as part of the normal treatment process.

The Medical records of the Department of Ophthalmology in the Saarland University Medical Center, Saarland, Germany were searched for nAMD patients (MNV types 1 and 2) who were continuously treated with either ranibizumab (Lucentis, Novartis Pharma GmbH, Nuernberg, Germany), bevacizumab (Avastin, Roche Holding AG, Basel, Switzerland), or aflibercept (Eylea, Bayer Pharma AG, Berlin, Germany) with a 2-year follow-up period using a spectral-domain optical coherence tomography (Spectralis SD-OCT; Heidelberg Engineering, Heidelberg, Germany) with auto-rescan mode in our intravitreal injection (IVI) centre (Abdin et al., 2020). Patients with an image quality-degrading cataract, glaucoma, any recorded intraocular pressure (IOP) of >24 mm Hg before or within the study period, uveitis, ocular hypertension, moderate and severe none-proliferative and proliferative diabetic retinopathy, diabetic macular oedema, retinal vein and/or artery occlusion, myopic macular neovascularization or a history of ocular trauma, rtPA lysis, pars-plana vitrectomy or photodynamic therapy were excluded from the study as these may confound the changes in RGCL and/or RNFL thickness.

Demographic data, type of administered anti-VEGF medication and number of IVIs administered at 1- and 2-year follow-ups were collected. Best corrected visual acuity measured using Snellen charts (BCVA), intraocular pressure before the injection, the existence of retinal pigment epithelial atrophy (RPE-atrophy) in SD-OCT, regardless of its size, the existence of subretinal fluids (SRF) and of intraretinal fluids (IRF) were recorded at the start point and at 1- and 2-year follow-ups.

Since the decimal visual acuity chart is neither the standard nor easy to use for statistical analysis, a conversion to logMAR units was made to match the standard in the literature.

For the analysis, we divided the patients into three medication groups (ranibizumab: 34 eyes, bevacizumab: 38, aflibercept: 25) and investigated their effect on RGCL, RNFL, BCVA, CMT, MV and presence of RPE-atrophy, IRF and SFR.

Eventually, we examined the correlation between the presence of RPE-atrophy at 2-year follow-up on the one hand and RGCL and RNFL thickness on the other.

The OCT retinal images were acquired using a SD-OCT. The volumetric retinal scans of the fovea consisted of 19 parallel B-scans with a spacing of 240 µm and a pattern size of 20° x 15° with automatic real-time repetition function turned on. Baseline OCT was performed at the time the first IVI was administered, and treatment was indicated. Scans 1 year and 2 years after the first anti-VEGF treatment were obtained with an auto-rescan follow-up function turned on. B-Scans were averaged 8 times. The minimum image quality requirement for B-scans was 15 dB as recommended by the manufacturer (Huang et al., 2012). RNFL and RGCL thickness were initially obtained using the auto-segmentation function of Heidelberg eye explorer (Version 1.10.0.0). All B-scans were then manually checked by an experienced retinologist for segmentation errors in internal limiting membrane (ILM), RNFL, RGCL and in Bruch membrane (BM) and manually adjusted if necessary (de Azevedo et al., 2020) (Figure 2). As the names of the patients were visible in the OCT program and the patients were known to the graders, the graders could not be blinded as to which eye received which anti-VEGF medication. Study parameters were evaluated at baseline and at the 1- and 2-year visits. Mean RNFL and RGCL thickness of the inner (*r*: 0.5–1.5 mm) and outer rings (*r*: 1.5–3 mm) were calculated using the implemented early treatment diabetic retinopathy study grid (ETDRS grid) (Figure 1).

Statistical analysis was performed using SPSS Version 25. Continuous data were described as mean and standard error of the mean and categorical variables as percentages. Categorical variables were compared using the Chi-Square test. For continuous variables, as they were normally distributed, the Paired Samples T-Test, one-way and two-way ANOVA were used. For non-parametric variables the Wilcoxon as well as the Kruskal–Wallis test were used. For time series analysis, repeated measures were used for normally distributed variables and Friedman test for non-parametric variables. Spearman's rho was used to determine the relationship between the presence of RPE-atrophy and RGCL and RNFL thickness. A $p<0.05$ was considered a statistically significant result. For multiple comparisons, the Bonferroni adjusted *p*-value was used. As both eyes were included in 14 patients of 83 (17%), the intraclass correlation coefficient (ICC) (Armstrong, 2013; Rosner, 1982) between the left and right eye of the same patient was calculated for all parameters to exclude a significant effect due to correlated data.

3 | RESULTS

At baseline, there were no statistically significant differences between groups in age, gender, number of IVIs at 1 and 2 years (Table 1), RGCL and RNFL thickness at the inner and outer rings (Tables 2 and 3, respectively), BCVA, CMT (Table 4), the presence of IRF, SRF and RPE atrophy (Table 5) or the intraocular pressure (Table 6). However, MV was significantly higher in the aflibercept group than in the ranibizumab group at baseline (Table 4). The *p*-value of ICC for all main outcome

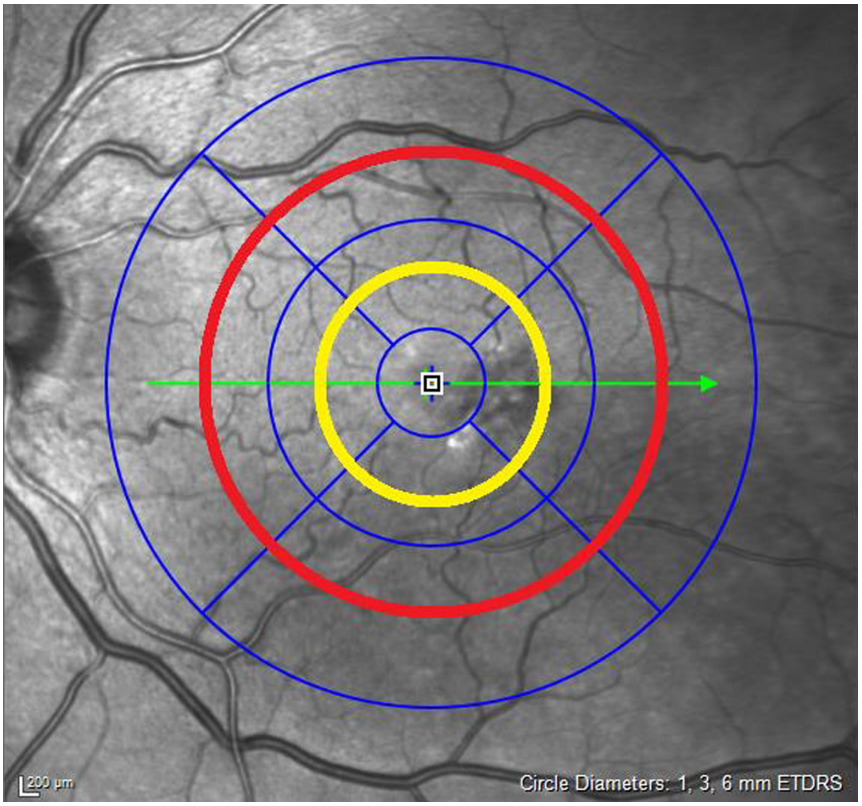

FIGURE 1 Early treatment diabetic retinopathy study (ETDRS) grid: (a) The area marked with the yellow circle is the parafoveal (-PF) area and the inner ring of ETDRS grid, extending between radius 0.5 and 1.5 mm. (b) The area marked with the red circle is the perifoveal (-O) area and the outer ring of the ETDRS grid, extending between radius 1.5 and 3 mm.

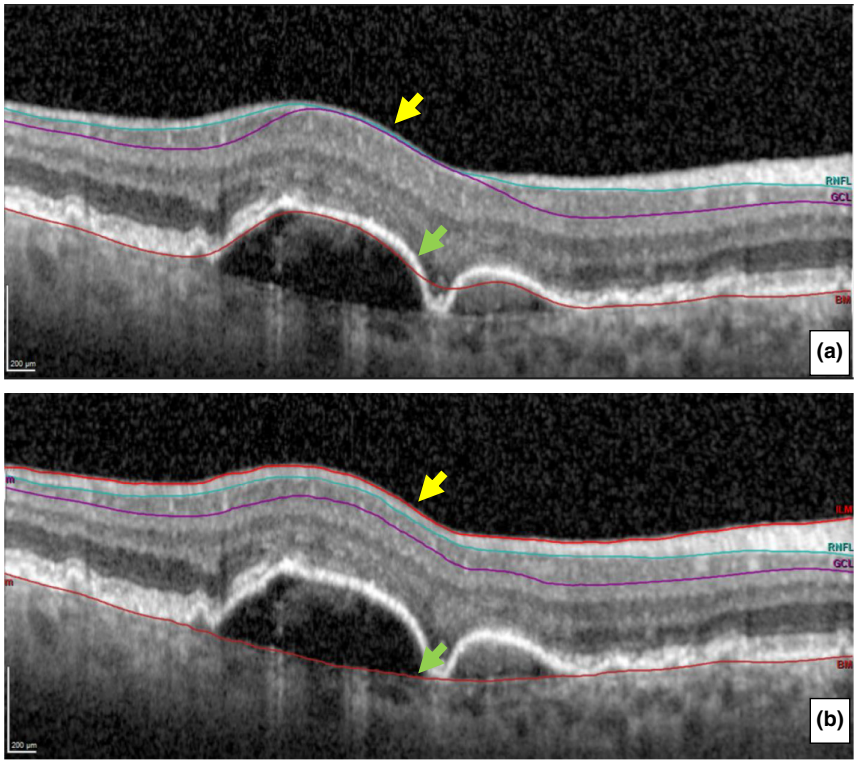

FIGURE 2 A macular OCT B-scan showing: (a) A mistake in auto-segmentation influencing retinal nerve fibres layer (RNFL) and retinal ganglion cells layer (RGCL) (yellow arrow) as well as the Bruch membrane (BM) (green arrow) due to prominent subretinal pigment epithelium (sub-RPE) fluids. (b) Same B-scan in (a) after manual correction.

TABLE 1 Demographic and ocular characteristics.

	Ranibizumab $N = 34$	Aflibercept $N = 25$	Bevacizumab $N = 38$	p-value
Age[a] (years) mean ± SD	79.4 ± 7.2	76.2 ± 7.5	79.5 ± 6.4	0.14[b]
Gender (%) Male:Female	56:44	52:48	45:55	0.6[c]
Lense status % Pseudophakic:Phakic	58:32	68:32	60:40	0.7[c]
Number of injections at 12 months Mean ± SD	7.4 ± 1.5	7.0 ± 1.4	8.1 ± 2.3	0.07[b]
Number of injections at 24 months Mean ± SD	12.7 ± 3.6	12.3 ± 3.1	14.2 ± 4.6	0.13[b]

Abbreviation: SD, standard deviation.
[a]Age calculated at date of first intravitreal injection.
[b]Analysis of variance test.
[c]Kruskal–Wallis test.

measures between left and right eyes was >0.05, which indicates a non-significant correlation between the two eyes in examined patients.

3.1 | RGCL thickness development

At baseline, the difference in RGCL thickness between the medication groups in the inner ring (parafoveal) (RGCL-PF) was not statistically significant (Table 2). Thickness decreased significantly in all three groups at 1- and 2-year follow-ups (Table 2) compared to baseline. The statistical differences between and longitudinally within the three groups at 1- and 2-year follow-ups were not significant (Table 2, Figure 3).

The RGCL thickness in the outer ring (RGCL-O) showed a similar pattern of progression over time. At baseline, the difference between the medication groups was not statistically significant (Table 2). Thickness decreased significantly in all three groups at 1- and 2-year follow-ups compared to baseline (Table 2). The statistical differences between and longitudinally within the three groups at 1- and 2-year follow-ups were not significant (Table 2).

3.2 | RNFL thickness development

At baseline, the difference in the RNFL thickness in the inner ring (parafoveal) (RNFL-PF) between the medication groups was not statistically significant (Table 3). Although thickness decreased in all three groups at 1- and 2-year follow-ups compared to baseline, the decrease was only significant in the ranibizumab and aflibercept groups at 1-year follow-up (Table 3). The statistical differences between and longitudinally within the three groups at 1- and 2-year follow-ups were not significant (Table 3, Figure 4).

TABLE 2 Comparison of retinal ganglion cell layer thickness between ranibizumab, bevacizumab and aflibercept at baseline, 1- and 2-year follow-ups.

	Aflibercept $N = 25$	Ranibizumab $N = 34$	Bevacizumab $N = 38$	p-value[a]		
RGCL-PF (μm) mean±SE				A-R	A-B	R-B
Baseline	45.6 ± 1.1	47.0 ± 1.0	45.9 ± 0.9	1	1	0.8
1-year follow-up	43.7 ± 1.1	45.6 ± 1.0	44.1 ± 0.9	0.6	1	0.8
2-year follow-up	42.9 ± 1.2	44.8 ± 1.0	43.8 ± 1.0	0.7	1	1
p-value[a]						
Baseline – 1-year	**0.002**[b] **[0.59–3.20]**	**0.012 [0.24–2.47]**	**0.007 [0.30–2.42]**			
Baseline – 2-year	**<0.001 [1.35–3.96]**	**<0.001 [1.01–3.25]**	**0.001 [0.60–2.72]**			
1–2-year	0.169	0.073	1.000			
RGCL-O (μm) mean±SE						
Baseline	32.7 ± 0.7	33.8 ± 0.6	33.3 ± 0.6	0.9	1	1
1-year follow-up	32.0 ± 0.7	32.8 ± 0.6	32.7 ± 0.6	1	1	1
2-year follow-up	32.0 ± 0.8	32.6 ± 0.6	32.4 ± 0.6	1	1	1
p-value[a]						
Baseline – 1-year	**0.018 [0.09–1.34]**	**<0.001 [0.40–1.47]**	**0.005 [0.17–1.18]**			
Baseline – 2-year	**0.034 [0.04–1.51]**	**<0.001 [0.53–1.79]**	**0.001 [0.34–1.53]**			
1–2-year	1	0.6	0.3			

Abbreviations:A, aflibercept; B, bevacizumab; CI, confidence interval; -O, outer ring of ETDRS ring (perifoveal); -PF, inner ring ETDRS grid (parafoveal); R, ranibizumab; RGCL, retinal ganglion cell layer; SE, standard error; .

[a]General linear model with estimated marginal means including the indicating variable, medications: ranibizumab, aflibercept and bevacizumab and three time points: baseline, 1- and 2-year follow-ups with Bonferroni adjustment for multiple comparisons.

[b]Bold p-value indicates statistical significance ($p < 0.05$). 95% confidence interval for difference is also given.

At baseline, the difference in RNFL thickness between medication groups in the outer ring (RNFL-O) was not statistically significant (Table 3). There was no statistical difference between or longitudinally within medication groups at baseline, 1-year or 2-year follow-ups (Table 3).

The RNFL thickness nasally in the outer ring (RNFL-nasal), which coincides with the papillomacular bundle, remained relatively stable at 1- and 2-year follow-ups in all three medication groups (Table 3). There was no statistically significant difference between the medication groups at baseline, 1- and 2-year follow-ups (Table 3).

3.3 | CMT

At baseline, the difference between the medication groups was not significant (Table 4). The thickness decreased significantly in all three groups at 1- and 2-year follow-ups compared to baseline. Statistical differences between the three groups at 1- and 2-year follow-ups were not significant. The comparison between the 1- and 2-year follow-ups showed a significant decrease in thickness only in the ranibizumab group ($p = 0.025$).

3.4 | MV

At baseline, the aflibercept group had a statistically significant higher MV compared to the ranibizumab group ($p = 0.013$) (Table 4). The difference between the bevacizumab group and the other two groups was otherwise not significant. Thickness decreased significantly in all three groups at 1- and 2-year follow-ups compared with baseline. The statistical differences between and longitudinally within the three groups at 1- and 2-year follow-ups were not significant.

3.5 | BCVA

Due to missing data, the numbers of eyes included in the general linear model were: aflibercept $N = 23$, ranibizumab $N = 27$, bevacizumab $N = 36$. The statistical difference between the groups was not significant at baseline, 1- or 2-year follow-ups (Table 4). Although BCVA-logMAR at 1-year follow-up showed a trend towards improvement in all three groups, the improvement was statistically significant only in the aflibercept group ($p = 0.001$). Compared to baseline, there was neither a statistically significant difference at 2-year follow-up nor between 1- and 2-year follow-ups in all three groups.

3.6 | Intraretinal and subretinal fluids

At baseline, 1- and 2-year follow-ups, there was no statistical difference between the medication groups in the presence of IRF and SRF (Table 5). The presence of IRF and SRF decreased significantly in all medication groups at 1- and 2-year follow-ups compared to baseline.

3.7 | Retinal pigment epithelial atrophy

At baseline, 1- and 2-year follow-ups, there was no statistical difference between the medication groups in

TABLE 3 Comparison of retinal nerve fibres layer thickness between ranibizumab, bevacizumab and aflibercept at baseline, 1- and 2-year follow-ups.

	Aflibercept $N = 25$	Ranibizumab $N = 34$	Bevacizumab $N = 38$	p-value[a]		
RNFL-PF (μm) mean±SE				A-R	A-B	R-B
Baseline	27.1 ± 0.8	26.7 ± 0.7	26.0 ± 0.7	1	1	1
1-year follow-up	25.8 ± 0.7	25.6 ± 0.6	25.1 ± 0.6	1	1	1
2-year follow-up	26.0 ± 0.8	25.7 ± 0.7	24.9 ± 0.6	1	0.9	1
p-value[a]						
Baseline – 1-year	**0.048**[b] **[0.008–2.59]**	**0.038 [0.04–2.26]**	0.12			
Baseline – 2-year	0.18	0.11	0.055			
1–2-year	1	1	1			
RNFL-O (μm) mean±SE						
Baseline	40.0 ± 1.3	39.6 ± 1.1	39.9 ± 1.1	1	1	1
1-year follow-up	39.1 ± 1.3	38.7 ± 1.1	39.3 ± 1.0	1	1	1
2-year follow-up	39.2 ± 1.3	39.1 ± 1.1	39.5 ± 1.1	1	1	1
p-value[a]						
Baseline – 1-year	0.18	0.09	0.5			
Baseline – 2-year	0.4	0.9	1			
1–2-year	1	0.6	1			
RNFL-Nasal (μm) mean±SE						
Baseline	55.4 ± 2.2	54.7 ± 1.9	55.7 ± 1.8	1	1	1
1-year follow-up	54.4 ± 2.1	54.1 ± 1.8	55.5 ± 1.7	1	1	1
2-year follow-up	54.5 ± 2.2	54.2 ± 1.9	55.3 ± 1.8	1	1	1
p-value[a]						
Baseline – 1-year	0.4	0.9	1			
Baseline – 2-year	0.7	1	1			
1–2-year	1	1	1			

Abbreviations: A, aflibercept; B, bevacizumab; CI, confidence interval; -O, outer ring of ETDRS ring (perifoveal); -PF, inner ring ETDRS grid (parafoveal); R, ranibizumab; RNFL, retinal nerve fibres layer; SE, standard error.

[a]General linear model with estimated marginal means including the indicating variable, medications: ranibizumab, aflibercept and bevacizumab and three time points: baseline, 1- and 2-year follow-ups with Bonferroni adjustment for multiple comparisons.

[b]Bold p-value indicates statistical significance ($p < 0.05$). 95% Confidence interval for difference is also given.

the presence of RPE-atrophy (Table 5). The presence of RPE-atrophy increased significantly in all medication groups at the 2-year follow-ups compared to baseline.

The presence of RPE-atrophy at 2-year follow-up correlated weakly, negatively and significantly with RGCL-PF thickness at 2-years follow-up ($R = -0.240$, $p = 0.018$) (Table 7). However, it showed no significant correlation to RGCL-O thickness, RNFL-PF, RNFL-O or RNFL-nasal.

3.8 | Number of IVIs

There was no statistically significant difference regarding the number of IVIs between the medication groups at 1- and 2-year follow-ups (Table 1).

3.9 | Intraocular pressure (IOP)

The IOP remained relatively stable at 1- and 2-year follow-ups in all three medication groups (Table 6). There was no statistically significant difference between the medication groups at baseline, 1- and 2-year follow-ups (Table 6).

4 | DISCUSSION

The difficulty in studying the effect of intravitreal anti-VEGF on RGCL and RNFL in nAMD patients is that there are many possible confounding factors. It is known that age leads to a decrease in RNFL and RGCL (Lee, Yoo, & Han, 2020; Zhang et al., 2016) thickness over time. nAMD manifestations such as retinal fluids and RPE-atrophy are also possible confounding factors. In a study of Beck et al (Beck et al., 2016), RPE-atrophy correlated negatively with RGCL thickness. Intraretinal and subretinal fluids could also cause a pathological thickness increase in RGCL and RNFL and consequently cause a greater reduction in thickness with intravitreal anti-VEGF therapy. Fortunately, in our study, all the aforementioned factors as well as the number of injections were balanced between the three groups, which significantly reduces the likelihood of bias in the comparison results.

TABLE 4 Comparison of functional and anatomical outcomes between ranibizumab, bevacizumab and aflibercept at baseline, 1- and 2-year follow-ups.

	Aflibercept $N = 25$	Ranibizumab $N = 34$	Bevacizumab $N = 38$	p-value[a]		
Macula-volume mean±SE				A-R	A-B	R-B
Baseline	9.36 ± 0.29	8.23 ± 0.25	8.87 ± 0.23	**0.013 [0.1–2.0]**	0.595	0.205
1-year follow-up	8.13 ± 0.28	7.67 ± 0.24	8.26 ± 0.22	0.6	1	0.2
2-year follow-up	8.00 ± 0.30	7.45 ± 0.25	8.21 ± 0.24	0.5	1	0.1
p-value[a]						
Baseline – 1-year	**<0.001**[b] **[0.70–1.75]**	**0.009 [0.11–1.03]**	**0.002 [0.18–1.03]**			
Baseline – 2-year	**<0.001 [0.74–1.96]**	**0.002 [0.24–1.29]**	**0.005 [0.16–1.16]**			
1–2-year	1	0.5	1			
CMT (μm) mean±SE						
Baseline	448 ± 24	402 ± 20	400 ± 19	0.4	0.3	1
1-year follow-up	319 ± 20	316 ± 17	324 ± 17	1	1	1
2-year follow-up	314 ± 18	291 ± 16	319 ± 15	1	1	0.6
p-value[a]						
Baseline – 1-year	**<0.001 [73182]**	**<0.001 [39132]**	**<0.001 [31120]**			
Baseline – 2-year	**<0.001 [78187]**	**<0.001 [64158]**	**<0.001 [37126]**			
1–2-year	1	**0.025 [2–47]**	1			
BCVA logMAR mean±SE						
Baseline	0.55 ± 0.05	0.47 ± 0.05	0.42 ± 0.04	0.814	0.225	1.000
1-year follow-up	0.36 ± 0.05	0.38 ± 0.05	0.37 ± 0.04	1.000	1.000	1.000
2-year follow-up	0.43 ± 0.05	0.36 ± 0.05	0.41 ± 0.04	1.000	1.000	1.000
p-value[a]						
Baseline – 1-year	**0.001 [0.06–0.31]**	0.1	0.6			
Baseline – 2-year	0.06	0.1	1			
1–2-year	0.3	1	0.4			

Abbreviations: A, aflibercept; B, bevacizumab; BCVA, best corrected visual acuity; CMT, central macula thickness; R, ranibizumab; SE, standard error.

[a]General linear model with estimated marginal means including the indicating variable, medications: ranibizumab, aflibercept and bevacizumab and three time points: baseline, 1- and 2-year follow-ups with Bonferroni adjustment for multiple comparisons.

[b]Bold p-value indicates statistical significance ($p < 0.05$). 95% confidence interval for difference is also given.

4.1 | RGCL thickness

Few studies examined the effects of specific anti-VEGF on RGCL. However, their methods and results were inconsistent. Makri et al. (2017) ($N = 65$) and Inan et al. (2019) ($N = 33$) studied patients on intravitreal ranibizumab therapy over a 1 year period. While Inan et al and our study showed a significant reduction in RGCL thickness under intravitreal therapy with ranibizumab, the change in RGCL thickness in the Makri study was not significant, likely because they included only lesion-free areas and, therefore, did not detect the therapeutic reduction in fluids under intravitreal anti-VEGF. Aşikgarip et al. (2021) ($N = 36$) studied the effect of aflibercept over a 1-year period and also found a significant RGCL thickness reduction. Lee, Sim, et al. (2020) ($N = 52$), Kim et al. (2019) and Kim et al. (2019) ($N = 90$) studied two groups each of ranibizumab and aflibercept. In the Lee study, although both groups showed a reduction in RGCL thickness at 1-year, this reduction was only significant in the aflibercept group.

However, there was no direct comparison between the two groups, and the presence of IRF and RPE-atrophy was not recorded, so that a conclusion about the superiority of one medication over another was not possible. Kim et al compared ranibizumab and aflibercept with each other and with a control group ($N = 71$) and found a statistically significant reduction in ganglion cell-inner plexiform layer (GC-IPL) thickness at 6 months in both ranibizumab and aflibercept group. The comparison between the two medications at 6 months showed a significantly lower RGCL thickness in the aflibercept group. However, the relatively short follow-up time and the lack of data on IRF and RPE-atrophy at baseline do not allow the drawing of a conclusion about the superiority of ranibizumab.

In our study, the comparison of ranibizumab, aflibercept and bevacizumab showed no statistically significant difference concerning the change in RGCL thickness over 2 years, which suggests that all three medications have a similar therapeutic and/or side effect profile with respect to RGCL thickness.

The significant reduction in RGCL-PF and RGCL-O thickness that were observed in all three medications groups are not necessarily due to a pharmacological effect of the medications. Possible other explanations for the observed reductions are given below:

TABLE 5 Comparison of subretinal, intraretinal fluids and retinal pigment epithelium atrophy percentages between ranibizumab, bevacizumab and aflibercept at baseline, 1- and 2-year follow-ups.

	Aflibercept $N = 25$	Ranibizumab $N = 34$	Bevacizumab $N = 38$	p-value[a]
IRF (%)				
Baseline	60%	50%	50%	0.6
1-year follow-up	16%	24%	21%	0.7
2-year follow-up	8%	9%	16%	0.5
p-value[b]				
Baseline – 1-year	**0.001**[c]	**0.013**	**0.002**	
Baseline – 2-year	**<0.001**	**<0.001**	**<0.001**	
1–2-year	1	0.3	1	
SRF (%)				
Baseline	80%	76%	89%	0.3
1-year follow-up	28%	35%	29%	0.7
2-year follow-up	20%	29%	24%	0.6
p-value[b]				
Baseline – 1-year	**<0.001**	**<0.001**	**<0.001**	
Baseline – 2-year	**<0.001**	**<0.001**	**<0.001**	
1–2-year	1	1	1	
RPE-atrophy (%)				
Baseline	8%	9%	13%	0.7
1-year follow-up	28%	24%	24%	0.9
2-year follow-up	48%	35%	29%	0.3
p-value[b]				
Baseline – 1-year	0.1	0.1	0.2	
Baseline – 2-year	**<0.001**	**0.001**	**0.028**	
1–2-year	0.1	0.3	1	

Abbreviations: IRF, intraretinal fluids; RPE, retinal pigment epithelium; SRF, subretinal fluids.
[a]Kruskal–Wallis test.
[b]Pairwise comparisons between baseline, 1- and 2-year follow-up (2-sided tests) with Bonferroni adjustment for multiple comparisons.
[c]Bold p-value indicates statistical significance ($p < 0.05$).

TABLE 6 Comparison of intraocular pressure between ranibizumab, bevacizumab and aflibercept at baseline, 1- and 2-year follow-ups.

	Aflibercept $N = 23$	Ranibizumab $N = 27$	Bevacizumab $N = 36$	p-value[a]		
Intraocular pressure (IOP) mean±SE				A-R	A-B	R-B
Baseline	13.6 ± 0.54	14.1 ± 0.49	14.2 ± 0.43	1	1	1
1-year follow-up	12.7 ± 0.65	14.1 ± 0.60	14.0 ± 0.52	0.3	0.3	1
2-year follow-up	12.7 ± 0.73	13.7 ± 0.60	13.8 ± 0.52	0.7	0.5	1
p-value[a]						
Baseline – 1-year	0.2	1	1			
Baseline – 2-year	0.4	1	1			
1–2-year	1	1	1			

Abbreviations: A, aflibercept; B, bevacizumab; IOP, intraocular pressure; R, ranibizumab; SE, standard error.
[a]General linear model with estimated marginal means including the indicating variable, medications: ranibizumab, aflibercept and bevacizumab and three time points: baseline, 1- and 2-year follow-ups with Bonferroni adjustment for multiple comparisons.

4.2 | Age

It is known that age leads to a decrease in RNFL (Bendschneider et al., 2010; Celebi & Mirza, 2013; Hammel et al., 2017; Hougaard et al., 2006; Parikh et al., 2007; Valverde-Megías et al., 2019) and RGCL (Lee, Yoo, & Han, 2020; Zhang et al., 2016) thickness over time. With a follow-up of 2 years, it is, therefore, possible that the observed reduction in RGCL is at least partly due to age progression and not to the anti-VEGF medications themselves.

4.3 | IOP

While the occurrence of transient IOP spikes after intravitreal injections of anti-VEGF medications is well documented in literature, their impact on the health of

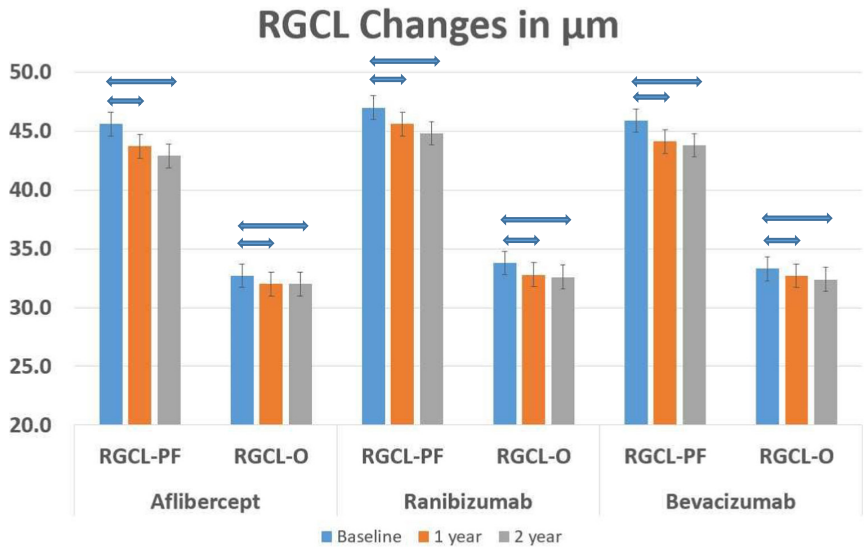

FIGURE 3 Development of retinal ganglion cell layer (RGCL) thickness parafoveally (-PF) and in the outer ring of ETDRS grid (-O). Statistically significant changes ($p<0.05$) are shown with a double headed arrow.

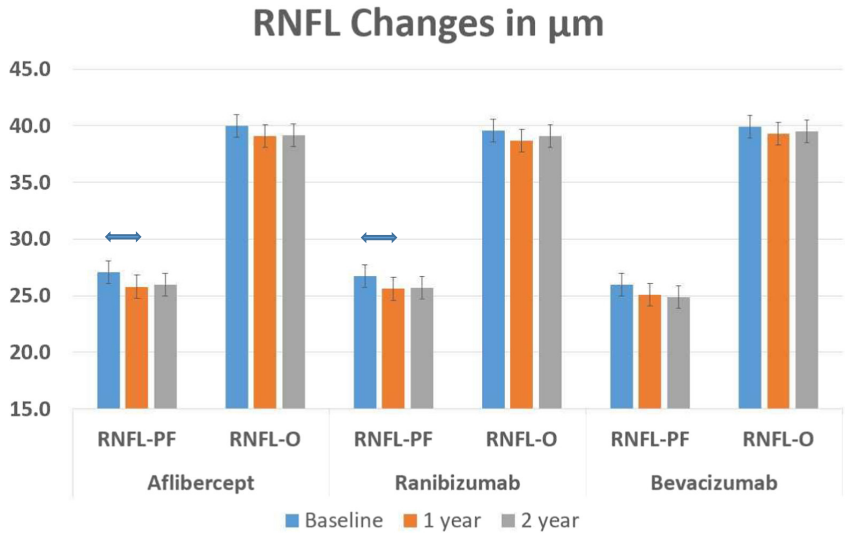

FIGURE 4 Development of retinal nerve fibre layer (RNFL) thickness parafoveally (-PF) and in the outer ring of ETDRS grid (-O). Statistically significant changes ($p<0.05$) are shown with a double headed arrow.

TABLE 7 Correlation between number of injections and existence of retinal pigment epithelium (RPE)-atrophy at 24 months and ganglion cell layer- and retinal nerve fibres layer thickness at 24 months.

	RGCL-PF	RGCL-O	RNFL-PF	RNFL-O	RNFL-nasal
RPE-atrophy-24-months *R* (*p*-value[a])	**−0.240 (0.018)**[b]	−0.052 (0.6)	0.198 (0.052)	0.084 (0.4)	−0.003 (0.9)

Abbreviations: -O, outer ring of ETDRS ring (perifoveal); -PF, inner ring ETDRS grid (parafoveal); *R*, correlation coefficient; RGCL, retinal ganglion cell layer; RNFL, retinal nerve fibres layer.

[a]Spearman's rho test.

[b]Bold *p*-value indicates statistical significance ($p<0.05$).

RGCs and on RNFL thickness is controversial (Levin et al., 2021). A large retrospective study by Cui et al. (Cui et al., 2019; Levin et al., 2021) also reported an increased likelihood of initiating IOP-lowering therapy or a new glaucoma diagnosis in eyes that received more injections (14 injections in 2 years and 20 injections in 3 years), making an acute and/or chronic increase in IOP also a plausible explanation for the observed decrease in RGCL thickness.

The absence of a statistical difference in IOP between medication groups or longitudinally within medication groups at baseline, 1- or 2-year follow-ups in this study

and the exclusion of glaucoma patients and patients with any recorded IOP of >24 mm Hg before or within the study period as well as the similarity in volume of all three anti-VEGF injections (0.05 ml) (Abdin et al., 2019; Abdin et al., 2020) make changes in IOP and IOP spikes unlikely to be confounders of the comparison results between the three medication groups.

4.4 | RPE-atrophy

The role of RPE in supporting and preserving photoreceptors is well documented in the literature (Bazan, 2006). Hence, a retrograde degeneration of RGCs because of RPE-atrophy and the accompanying loss of photoreceptors is plausible. This can explain the negative correlation between the presence of RPE-atrophy and RGCL-PF thinning in our study as well as in the study by Beck et al. (2016). Nevertheless, further studies taking the spatial and temporal relationships between RPE-atrophy and RGCL thinning are needed to establish causality and better understand the observed correlation.

It is also important to note that a difference in the risk of developing geographic atrophy (GA) among different anti-VEGF medications has been an area of significant interest in the literature. Grunwald et al. (2014) studied the risk factors for developing GA over 24 months in the CATT study population and reported a possible higher risk of developing GA in patients treated with ranibizumab compared to those treated with bevacizumab. On the other hand, Gillies et al. (2020) compared ranibizumab and aflibercept in terms of the rate of development or growth of macular atrophy (MA) over 24 months in the RIVAL study population and found no significant difference between them. Whether these differences also affect RGCL and RNFL thinning over time requires further investigation.

4.5 | RNFL thickness

Several studies investigated the impact of certain anti-VEGF medications on RNFL thickness. Their findings were also inconsistent. Makri et al. (2017), Inan et al. (2019), Demirel et al. (2015) (N = 29), Sengul et al. (2016) (N = 168), Martinez-de-la-Casa et al. (2012) (N = 49) and Valverde-Megías et al. (2019) (N = 20) studied ranibizumab. Only Martinez-de-la-Casa et al and Valverde-Megías et al found a significant reduction in RNFL after a follow-up period of 1 and 8 years, respectively. Aşikgarip et al. (2021) studied aflibercept and found a significant reduction in RNFL thickness over a 1-year follow-up period. Other studies have compared different medications directly and/or indirectly. Lee, Sim, et al. (2020), Kim et al. (2019) and Ahn et al. (2021) (N = 58) compared ranibizumab and aflibercept. Lee et al found a significant reduction in RNFL thickness in the ranibizumab but not in the aflibercept group. There was no direct comparison between the two groups, and the presence of IRF and RPE-atrophy was not recorded, so that a conclusion about the superiority of one medication over another is not possible.

Kim et al found no significant reduction in either group over a 6-month period. Ahn et al showed a significant reduction in RNFL thickness over a 1-year period in both medication groups. However, no direct comparison was made between the two groups. Sobacı et al. (2013) (N = 65) compared ranibizumab with bevacizumab and found no significant decrease in RNFL thickness in either group. In our study, there was no significant difference between the three medication groups in terms of changes in RNFL-PF, RNFL-O or in RNFL-nasal thickness over a 2-year follow-up period, indicating a similar therapeutic and/or side effect of the three medications on RNFL.

4.6 | BCVA

All three medications showed comparable BCVA results over the 2-year period. These results are consistent with those of the VIEW studies (Schmidt-Erfurth et al., 2014), CATT research group (Martin et al., 2020), Gillies et al. (2019) and Abdin et al. (2019).

In summary, the current study showed that ranibizumab, aflibercept and bevacizumab have a similar impact on RGCL and RNFL thickness over a 2-year period when baseline conditions (age, IRF, SRF, RPE-atrophy, number of injections) are balanced and, therefore, appear to have a similar therapeutic and/or side effect profile regarding RGCL and RNFL. These results may help to simplify the design of further studies investigating the influence of anti-VEGFs on RGCL and RNFL thickness, as the three could then be used interchangeably, allowing the inclusion of patients with therapy switching and longer follow-up periods.

The strength of this study lies in the fact that only patients on anti-VEGF monotherapy over a 2-year period were included as well as in the strict inclusion criteria. However, the study was limited due to the retrospective design, the inclusion of both eyes of 17% of patients, the relatively small population, and the fact that it was a monocentre study. The fact that only patients with at least 2-year follow-up and a response to monotherapy were included also has a negative aspect, as these patients tend to be more responsive to therapy than the general population of nAMD and thus do not represent the more severe and refractory cases.

5 | CONCLUSION

Monotherapy with intravitreal aflibercept, bevacizumab, and ranibizumab was associated with comparable significant decreases in RGCL thickness, CMT, MV, IRF and SRF in naïve nAMD patients during the first 2 years of treatment. Furthermore, no significant differences either in BCVA or in RNFL thickness were observed between the three medication groups during the first 2 years of treatment.

AUTHOR CONTRIBUTIONS

All authors attest that they meet the current ICMJE criteria for Authorship.

ACKNOWLEDGEMENT

Open Access funding enabled and organized by Projekt DEAL.

ORCID

Yaser Abu Dail https://orcid.org/0000-0001-8642-0222

REFERENCES

Abdin, A.D., Suffo, S., Asi, F., Langenbucher, A. & Seitz, B. (2019) Intravitreal ranibizumab versus aflibercept following treat and extend protocol for neovascular age-related macular degeneration. *Graefe's Archive for Clinical and Experimental Ophthalmology*, 257, 1671–1677.

Abdin, A.D., Suffo, S., Bischoff-Jung, M., Daas, L., Pattmöller, M. & Seitz, B. (2020) Advantages of a designated IVI center for a German University Eye Hospital. *Der Ophthalmologe*, 117, 50–57.

Abdolrahimzadeh, S., Gharbiya, M., Formisano, M., Bertini, F., Cerini, A. & Pacella, E. (2019) Anti-vascular endothelial growth factor intravitreal therapy and macular ganglion cell layer thickness in patients with neovascular age-related macular degeneration. *Current Eye Research*, 44, 1000–1005.

Ahn, J., Jang, K., Sohn, J., Park, J.I. & Hwang, D.D.-J. (2021) Effect of intravitreal ranibizumab and aflibercept injections on retinal nerve fiber layer thickness. *Scientific Reports*, 11, 5010.

Armstrong, R.A. (2013) Statistical guidelines for the analysis of data obtained from one or both eyes. *Ophthalmic & Physiological Optics: The Journal of the British College of Ophthalmic Opticians (Optometrists)*, 33, 7–14.

Aşikgarip, N., Temel, E. & Örnek, K. (2021) Macular ganglion cell complex changes in eyes treated with aflibercept for neovascular age-related macular degeneration. *Photodiagnosis and Photodynamic Therapy*, 35, 102383.

Bazan, N.G. (2006) Survival signaling in retinal pigment epithelial cells in response to oxidative stress: Significance in retinal degenerations. *Advances in Experimental Medicine and Biology*, 572, 531–540.

Beck, M., Munk, M.R., Ebneter, A., Wolf, S. & Zinkernagel, M.S. (2016) Retinal ganglion cell layer change in patients treated with anti-vascular endothelial growth factor for neovascular age-related macular degeneration. *American Journal of Ophthalmology*, 167, 10–17.

Bendschneider, D., Tornow, R.P., Horn, F.K., Laemmer, R., Roessler, C.W., Juenemann, A.G. et al. (2010) Retinal nerve fiber layer thickness in normals measured by spectral domain OCT. *Journal of Glaucoma*, 19, 475–482.

Browning, D.J., Kaiser, P.K., Rosenfeld, P.J. & Stewart, M.W. (2012) Aflibercept for age-related macular degeneration: A game-changer or quiet addition? *American Journal of Ophthalmology*, 154, 222–226.

Celebi, A.R.C. & Mirza, G.E. (2013) Age-related change in retinal nerve fiber layer thickness measured with spectral domain optical coherence tomography. *Investigative Ophthalmology & Visual Science*, 54, 8095–8103.

Cui, Q.N., Gray, I.N., Yu, Y. & VanderBeek, B.L. (2019) Repeated intravitreal injections of antivascular endothelial growth factors and risk of intraocular pressure medication use. *Graefe's Archive for Clinical and Experimental Ophthalmology*, 257, 1931–1939.

Daniel, E., Maguire, M.G., Grunwald, J.E., Toth, C.A., Jaffe, G.J., Martin, D.F. et al. (2020) Incidence and progression of non-geographic atrophy in the comparison of age-related macular degeneration treatments trials (CATT) clinical trial. *JAMA Ophthalmology*, 138, 510–518.

de Azevedo, A.G.B., da Silva Takitani, G.E., Godoy, B.R., Marianelli, B.F., Saraiva, V., Tavares, I.M. et al. (2020) Impact of manual correction over automated segmentation of spectral domain optical coherence tomography. *International Journal of Retina and Vitreous*, 6, 4.

Demirel, S., Batioğlu, F., Özmert, E. & Erenler, F. (2015) The effect of multiple injections of ranibizumab on retinal nerve fiber layer thickness in patients with age-related macular degeneration. *Current Eye Research*, 40, 87–92.

Ferris, F.L., III, Fine, S.L. & Hyman, L. (1984) Age-related macular degeneration and blindness due to neovascular maculopathy. *Archives of Ophthalmology*, 102, 1640–1642.

Flaxman, S.R., Bourne, R.R.A., Resnikoff, S., Ackland, P., Braithwaite, T., Cicinelli, M.V. et al. (2017) Global causes of blindness and distance vision impairment 1990–2020: A systematic review and meta-analysis. *The Lancet Global Health*, 5, e1221–e1234.

Ford, K.M., Saint-Geniez, M., Walshe, T., Zahr, A. & D'Amore, P.A. (2011) Expression and role of VEGF in the adult retinal pigment epithelium. *Investigative Ophthalmology & Visual Science*, 52, 9478–9487.

Froger, N., Matonti, F., Roubeix, C., Forster, V., Ivkovic, I., Brunel, N. et al. (2020) VEGF is an autocrine/paracrine neuroprotective factor for injured retinal ganglion neurons. *Scientific Reports*, 10, 12409.

Gillies, M.C., Hunyor, A.P., Arnold, J.J., Guymer, R.H., Wolf, S., Ng, P. et al. (2019) Effect of ranibizumab and aflibercept on best-corrected visual acuity in treat-and-extend for neovascular age-related macular degeneration: A randomized clinical trial. *JAMA Ophthalmology*, 137, 372–379.

Gillies, M.C., Hunyor, A.P., Arnold, J.J., Guymer, R.H., Wolf, S., Pecheur, F.L. et al. (2020) Macular atrophy in neovascular age-related macular degeneration: A randomized clinical trial comparing ranibizumab and aflibercept (RIVAL study). *Ophthalmology*, 127, 198–210.

Grunwald, J.E., Daniel, E., Huang, J., Ying, G.S., Maguire, M.G., Toth, C.A. et al. (2014) Risk of geographic atrophy in the comparison of age-related macular degeneration treatments trials. *Ophthalmology*, 121, 150–161.

Hammel, N., Belghith, A., Weinreb, R.N., Medeiros, F.A., Mendoza, N. & Zangwill, L.M. (2017) Comparing the rates of retinal nerve fiber layer and ganglion cell-inner plexiform layer loss in healthy eyes and in glaucoma eyes. *American Journal of Ophthalmology*, 178, 38–50.

Horsley, M.B., Mandava, N., Maycotte, M.A. & Kahook, M.Y. (2010) Retinal nerve fiber layer thickness in patients receiving chronic anti-vascular endothelial growth factor therapy. *American Journal of Ophthalmology*, 150, 558–561.e1.

Hougaard, J.L., Ostenfeld, C., Heijl, A. & Bengtsson, B. (2006) Modelling the normal retinal nerve fibre layer thickness as measured by stratus optical coherence tomography. *Graefe's Archive for Clinical and Experimental Ophthalmology*, 244, 1607–1614.

Huang, Y., Gangaputra, S., Lee, K.E., Narkar, A.R., Klein, R., Klein, B.E.K. et al. (2012) Signal quality assessment of retinal optical coherence tomography images. *Investigative Ophthalmology & Visual Science*, 53, 2133–2141.

Inan, Ü.Ü., Baysal, Z. & Inan, S. (2019) Long-term changes in retinal layers in patients undergoing intravitreal ranibizumab for neovascular age-related macular degeneration: Retinal layers after anti-VEGF therapy. *International Ophthalmology*, 39, 2721–2730.

Julien, S., Biesemeier, A., Taubitz, T. & Schraermeyer, U. (2014) Different effects of intravitreally injected ranibizumab and aflibercept on retinal and choroidal tissues of monkey eyes. *The British Journal of Ophthalmology*, 98, 813–825.

Kim, S.W., Woo, J.E., Yoon, Y.S., Lee, S., Woo, J.M. & Min, J.K. (2019) Retinal and choroidal changes after anti vascular endothelial growth factor therapy for neovascular age-related macular degeneration. *Current Pharmaceutical Design*, 25, 184–189.

Lee, S.W., Sim, H.E., Park, J.Y., Kim, J.S., Chang, I.B., Park, Y.S. et al. (2020) Changes in inner retinal layer thickness in patients with exudative age-related macular degeneration during treatment with anti-vascular endothelial growth factor. *Medicine (Baltimore)*, 99, e19955.

Lee, Y.J., Yoo, Y.J. & Han, S.B. (2020) Age-related changes of macular ganglion cell-inner plexiform layer thickness in korean elderly subjects. *Korean Journal of Ophthalmology*, 34, 404–412.

Levin, A.M., Chaya, C.J., Kahook, M.Y. & Wirostko, B.M. (2021) Intraocular pressure elevation following intravitreal anti-VEGF injections: Short- and long-term considerations. *Journal of Glaucoma*, 30, 1019–1026.

Makri, O.E., Vavvas, D., Plotas, P., Pallikari, A. & Georgakopoulos, C.D. (2017) The effect of ranibizumab on normal neurosensory

retina in the eyes of patients with exudative age related macular degeneration. *The Open Ophthalmology Journal*, 11, 368–376.
Martin, D.F., Maguire, M.G., Fine, S.L., Ying, G.S., Jaffe, G.J., Grunwald, J.E. et al. (2020) Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: Two-year results. *Ophthalmology*, 127, S135–S145.
Martinez-de-la-Casa, J.M., Ruiz-Calvo, A., Saenz-Frances, F., Reche-Frutos, J., Calvo-Gonzalez, C., Donate-Lopez, J. et al. (2012) Retinal nerve fiber layer thickness changes in patients with age-related macular degeneration treated with intravitreal ranibizumab. *Investigative Ophthalmology & Visual Science*, 53, 6214–6218.
Mitchell, P., Liew, G., Gopinath, B. & Wong, T.Y. (2018) Age-related macular degeneration. *Lancet*, 392, 1147–1159.
Nguyen, C.L., Oh, L.J., Wong, E., Wei, J. & Chilov, M. (2018) Anti-vascular endothelial growth factor for neovascular age-related macular degeneration: A meta-analysis of randomized controlled trials. *BMC Ophthalmology*, 18, 130.
Nishijima, K., Ng, Y.-S., Zhong, L., Bradley, J., Schubert, W., Jo, N. et al. (2007) Vascular endothelial growth factor-A is a survival factor for retinal neurons and a critical neuroprotectant during the adaptive response to ischemic injury. *The American Journal of Pathology*, 171, 53–67.
Parikh, R.S., Parikh, S.R., Sekhar, G.C., Prabakaran, S., Babu, J.G. & Thomas, R. (2007) Normal age-related decay of retinal nerve fiber layer thickness. *Ophthalmology*, 114, 921–926.
Rosner, B. (1982) Statistical methods in ophthalmology: An adjustment for the intraclass correlation between eyes. *Biometrics*, 38, 105–114.
Saint-Geniez, M., Maharaj, A.S.R., Walshe, T.E., Tucker, B.A., Sekiyama, E., Kurihara, T. et al. (2008) Endogenous VEGF is required for visual function: Evidence for a survival role on Müller cells and photoreceptors. *PLoS One*, 3, e3554.
Schmidt-Erfurth, U., Kaiser, P.K., Korobelnik, J.-F., Brown, D.M., Chong, V., Nguyen, Q.D. et al. (2014) Intravitreal aflibercept injection for neovascular age-related macular degeneration: Ninety-six–week results of the VIEW studies. *Ophthalmology*, 121, 193–201.
Sengul, E.A., Artunay, O., Kumral, E.T., Yenerel, M., Rasier, R., Kockar, A. et al. (2016) Retinal nerve fiber layer thickness changes in age-related macular degeneration treated with multiple intravitreal ranibizumab. *Journal of Ocular Pharmacology and Therapeutics*, 32, 665–670.
Sobacı, G., Güngör, R. & Ozge, G. (2013) Effects of multiple intravitreal anti-VEGF injections on retinal nerve fiber layer and intraocular pressure: A comparative clinical study. *International Journal of Ophthalmology*, 6, 211–215.
Solomon, S.D., Lindsley, K., Vedula, S.S., Krzystolik, M.G. & Hawkins, B.S. (2019) Anti-vascular endothelial growth factor for neovascular age-related macular degeneration. *The Cochrane Database of Systematic Reviews*, 3(3), CD005139.
Valverde-Megías, A., Ruiz-Calvo, A., Murciano-Cespedosa, A., Hernández-Ruiz, S., Martínez-de-la-Casa, J.M. & García-Feijoo, J. (2019) Long-term effect of intravitreal ranibizumab therapy on retinal nerve fiber layer in eyes with exudative age-related macular degeneration. *Graefe's Archive for Clinical and Experimental Ophthalmology*, 257, 1459–1466.
Zhang, X., Francis, B.A., Dastiridou, A., Chopra, V., Tan, O., Varma, R. et al. (2016) Longitudinal and cross-sectional analyses of age effects on retinal nerve fiber layer and ganglion cell complex thickness by fourier-domain OCT. *Translational Vision Science & Technology*, 5, 1.

How to cite this article: Abu Dail, Y., Seitz, B., Sideroudi, H. & Abdin, A.D. (2023) Impact of intravitreal ranibizumab, aflibercept and bevacizumab on retinal ganglion cell and nerve fibre layer thickness in Neovascular age-related macular degeneration. *Acta Ophthalmologica*, 101, 330–341. Available from: https://doi.org/10.1111/aos.15283