EJO European Journal of Ophthalmology

Original research article

European Journal of Ophthalmology
1–9

DOI: 10.1177/11206721231210749
journals.sagepub.com/home/ejo
Sage

Immediate effect of anti-VEGF injections on optic nerve head: Correlation between intraocular pressure and anatomical peripapillary changes

Pasquale Viggiano[1], Rosa Buonamassa[1], Maria Oliva Grassi[1], Giacomo Boscia[1], Enrico Borrelli[2], Luca Landini[1], Federica Evangelista[3], Maria Giovanna Malerba[1], Giovanni Alessio[1] and Francesco Boscia[1]

Abstract

Purpose: This study was designed to investigate retinal nerve fiber layer (RNFL) and radial peripapillary capillaries (RPC) changes on optical coherence tomography (OCT) angiography and OCT thickness alterations associated with acutely increased intraocular pressure after intravitreal injections.

Methods: This observational clinical study was conducted on 35 eyes (35 patients) with treatment-naïve age-related macular degeneration (AMD) and type 1 or type 2 MNV were enrolled. All patients underwent anti-vascular endothelial grow factor (VEGF) intravitreal injections with 0.05-mL aflibercept (2 mg) between January 2022 and October 2022. Peripapillary OCT angiography perfusion density, retinal nerve fiber layer thickness, and intraocular pressure (IOP) were measured before and immediately after intravitreal injections. In particular, the analysis was performed at the following visits: (T0) 5 to 15 min before the injection of aflibercept; (T1) 2 to 5 min after the injection of aflibercept. Paired t-test was used to compare pre-injection and post-injection values.

Results: The mean baseline IOP (T0) value was 17.26 ± 2.4 mmHg and the immediate post-injection IOP (T1) mean value was 34.7 ± 11.50 mmHg ($P < 0.01$). The mean global RNFL thickness before and immediately after the injection was 100.9 ± 18.8 m and 98.6 ± 17.4 m ($P = 0.001$). Furthermore, the topographical RNFL analysis showed significant thickness reduction of the nasal and inferior sectors after the procedure when compared to T0 ($P = 0.046$ and $P = 0.001$). On the contrary, the mean RCP density changes at T1 did not reach statistically significant ($P = 0.636$). Furthermore, we found a significant negative correlation between the retinal nerve fiber layer global thickness and the IOP changes (Pearson's correlation = −0.126; $P = 0.031$). In particular, the nasal RNFL region showed a significant negative correlations with IOP values (Pearson's correlation = −0.198, P = 0,046).

Conclusions: We reported acute IOP changes that are associated with reduced RNFL thickness in a group of patients undergoing intravitreal injections of anti-VEGF drugs for neovascular age-related macular degeneration. Moreover, topographical sub-analysis revealed that the nasal RNFL region is most prone to IOP fluctuations. This finding may explain the sudden visual acuity change in patients immediately after injection and may sustain injuries to optic nerve head structures producing glaucomatous damage.

Keywords

Anti-VEGF injections, optic nerve head damage, RNFL damage, OCT, OCTA

Date received: 9 May 2023; accepted: 12 October 2023

[1]Department of Translational Biomedicine Neuroscience, University of Bari "Aldo Moro", Bari, Italy
[2]Ophthalmology Department, San Raffaele University Hospital, Milan, Italy
[3]Ente Ecclesiastico Ospedale Generale Regionale, "F.Miulli", Acquaviva delle Fonti, Italy

Corresponding author:
Pasquale Viggiano, Department of Translational Biomedicine Neuroscience, University of Bari "Aldo Moro", Piazza Giulio Cesare, 11, Bari, Italy.
Email: pasquale.viggiano90@gmail.com

Introduction

The intravitreal injections debut has drastically modified the prognosis of patients with several retinal disorders. In particular, intravitreal anti-vascular endothelial growth factor (VEGF) injections have become the ordinary treatment for neovascular age-related macular degeneration (nAMD), diabetic macular edema (DME), and retinal vein occlusion (RVO).[1]

Although the procedure is considered relatively safe, it can be rarely related to post injection and drug-class-associated adverse events.[2,3] Acute rise of intraocular pressure (IOP) (which is considered normal in a range between 12 and 21 mmHg) after intravitreal injection is a well-known condition, and appears to be related to the procedure, lasting from half to few hours according to different studies.[4] Numerous mechanisms have been suggested to describe the correlation between intravitreal injections and elevation of IOP including trabecular meshwork contracture, intraocular hydrostatic pressure eleva-tion secondary to volume excess, anterior chamber (AC) angle narrowing and trabecular clogging with large molecules and proteins.[5,6] Furthermore, it is well studied a relationship between elevated IOP and anatomic damage of the retinal nerve fiber layer (RNFL).[7] Repeated intravitreal injections can lead to IOP spikes with subsequent RNFL injury. In addition, the chronic suppression of VEGF through intraocular injections may have negative effects on the RNFL.[8] Although, previous papers did not find difference in the retinal nerve fiber layer in patients treated with Aflibercept at 12 months or with Ranibizumab/aflibercept at 1 month.[9]

Structural optical coherence tomography (OCT) has provided the ability to examine metrics reflecting the optic nerve head vitality (e.g. RNFL thickness). With the OCT angiography (OCTA) development, a non-invasive infrared imaging technique,[10] it has become possible to image vascular structures like the radial peripapillary capillary (RPC) network, whose function is most likely to nourish the inner portion of the retinal nerve fiber layer in its distribution around the optic nerve head (ONH). Because of their unique pattern and distribution, RPC might be more vulnerable to increase in the intraocular pressure (IOP) than other retinal capillaries.[11] Barash et al. showed acute macular and peripapillary angiographic variations after intravitreal injections using OCTA.[12,13] The authors suggested that the intravitreal injections may stress the same structures that get damaged in glaucomatous eyes. However, the current literature lacks evidence regarding the possible correlation between IOP and anatomical ONH damage immediately after intravitreal injections of anti-VEGF.

Investigating this acute correlation may shed light on other cases of acute IOP elevation, such as those in acute angle closure or during intraocular surgery.

Therefore, our study aimed to investigate RNFL and radial peripapillary capillaries (RPC) acute changes after anti- VEGF injections and possible correlation with acutely increased IOP using OCT structural imaging and OCT angiography. An in-depth optic nerve analysis of the short-term impact of anti- VEGF injections could allow us to identify pa-tients who are at risk of developing long-term neurodegenerative damage.

Methods

Study design and participants

This observational study was conducted at the Department of Translational Bio-medicine Neuroscience, University of Bari “Aldo Moro”. This study respected the tenets of the Helsinki Declaration and was approved by our institutional review board of Department of Translational Biomedicine Neuroscience, University of Bari “Aldo Moro”. Patients gave their written consent to be included in the study.

Thirty-five eyes of 35 patients older than 18 years with treatment-naïve age-related macular degeneration (AMD) and type 1 or type 2 MNV were registered. All patients underwent anti-VEGF intravitreal injections with 0.05-mL aflibercept (2 mg) between January 2022 and October 2022.

The exclusion criteria included: (i) presence of type 3 MNV; (ii) glaucoma history ; (iii) significant cataract; (iv) myocardial infarction or cerebrovascular disease within the last 6 months; (iv) myopia greater than 3.00 diopters; (v) inflammation or infection of both eyes; (vi) previous anti-VEGF injection or retinal laser therapy; (vii) presence of other comorbid retinal and/or macular diseases (e.g. diabetic retinopathy and retinal venous occlusion); and (viii) any optic neuropathy.

Intravitreal injections were performed in the Arc Sterile of our hospital, the same described by previous papers.[14,15] The intravitreal procedures were performed by the same well- trained surgeon (F. B.) After informed consent was obtained, patient’s eyelids and ocular surfaces were sterilized with 5% topical povidone–iodine, a lid speculum was placed, and topical benoxinate anesthesia was given. The anti-VEGF drugs were prepared by the treating physician immediately before the injections, which were performed using a sterile 30-gauge (0.255 mm) needle through the infero-temporal pars plana, 3.5 to 4 mm posterior to the limbus, depending on the lens status of the patient. The needle was introduced into the vitreous cavity aiming posteriorly and slightly inferiorly, toward the optic disc. After the removal of the needle from the eye, a cotton-tip applicator simultaneously was rolled over the injection site. We did check for hand motion immediately to be sure that there was no IOP elevation high enough to occlude the central retinal artery; there were no such events. None of the eyes in our study required anterior chamber paracentesis.

Outcome measures

The main outcome measures were: (i) intraocular pressure (IOP); (ii) RNFL thickness, and (iii) RPC density.

All patients were imaged with RTVue XR Avanti spectral-domain (SD)-OCT (Optovue, Inc., Fremont, CA). Images with a strength index less than 40, with significant motion artifact or shadowing effect were excluded from the analysis. OCT and OCTA acquisitions were performed at the following visits: (T0) 5 to 15 min before the injection of aflibercept; (T1) 2 to 5 min after the injection of aflibercept. Furthermore, poor quality images (SSI: <6/10) or images with significant motion artifact and/or incorrect segmentation were excluded.[16,17]

Intraocular pressures were checked with Perkins MK3 tonometer (Haag-Streit) at T0 and T1.

Imaging analysis

Optic nerve head imaging was performed as a 4.5 × 4.5 mm OCT angiography scan (Figure 1). The peripapillary region was defined as a 750-μm wide annulus extending from the optic disc boundary. For radial peripapillary capillaries (RPC) analysis, the RTVue XR Avanti AngioVue built-in software automatically segments the inner limiting membrane (ILM) and the posterior boundary of retinal nerve fiber layer (RNFL) providing vessel density (VD) measurements, both in the peripapillary region and in the whole scan (Figure 1). We applied a manual correction when the segmentation was altered.

Peripapillary retinal nerve fiber layer thickness was obtained with a disc map software using RTvueXR Avanti (Optovue, Inc., Fremont, CA) (Figure 2). Using disc map data, peripapillary RNFL was compared in terms of total thickness and the thickness in each of the superior, inferior, nasal, and temporal quadrants.

Statistical analysis

All quantitative variables were reported as mean and standard deviation (SD). To detect departures from normality distribution, a Shapiro-Wilk test was performed for all variables. A paired t-test was used to compare the variables before and after the intravitreal injection. Pearson's correlation was computed to analyze the degree of correlation between retinal nerve fiber layer thickness, radial peripapillary capillaries density at different region of interest (ROI) and IOP changes at T0-T1. All statistical analyses were performed using Statistical Package for Social Sciences (version 20.0; SPSS Inc., Chicago, IL). The chosen level of statistical significance was $P < 0.05$. The sample size of the study was tested to be proper for a mean difference between groups of almost 10%, a power of 80% and type I error rate (α) of 5%.

Results

Characteristics of subjects included in the analysis

Thirty - five patients were included in this study. The mean age of the patients was 78.10 ± 10 years, and the median age was 81 years (range, 55–93). Fifteen patients (42.8%) were male, and twenty (57.2%) were female. Twenty – one patients were affected by type 1 MNV (60%), 14 patients were affected by type 2 MNV (40%). Ten patients (29%) had been smokers for more than 5 years. The characteristics of subjects analyzed are shown in Table 1.

Outcomes analysis

Intra-ocular pressure analysis. The mean baseline IOP (T0) value was 17.26 ± 2.4 mmHg and the immediate post-injection IOP (T1) mean value was 34.7 ± 11.50 mmHg (P

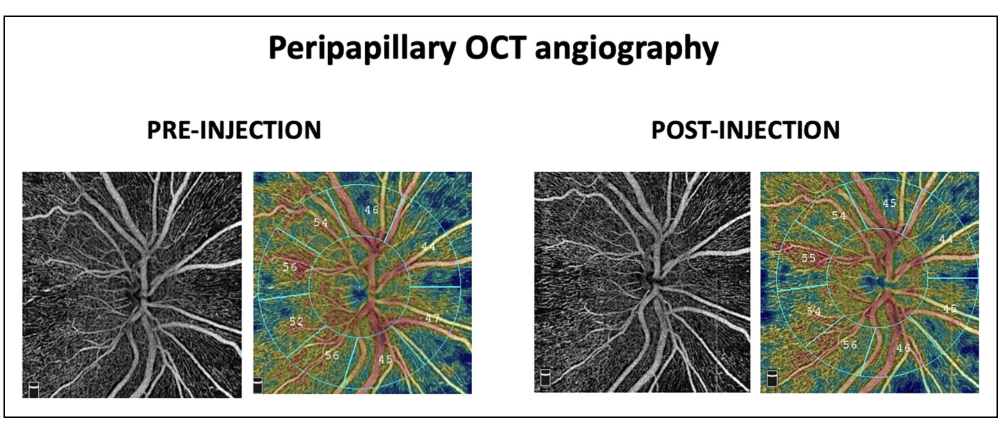

Figure 1. Representation of peripapillary OCT angiography before and after injection in nAMD eye. OCTA scan 4,5 × 4,5 mm centered on ONH before and after treatment. Color-coded density maps and automatized vessel density measurements of the RPC before and after Injection.

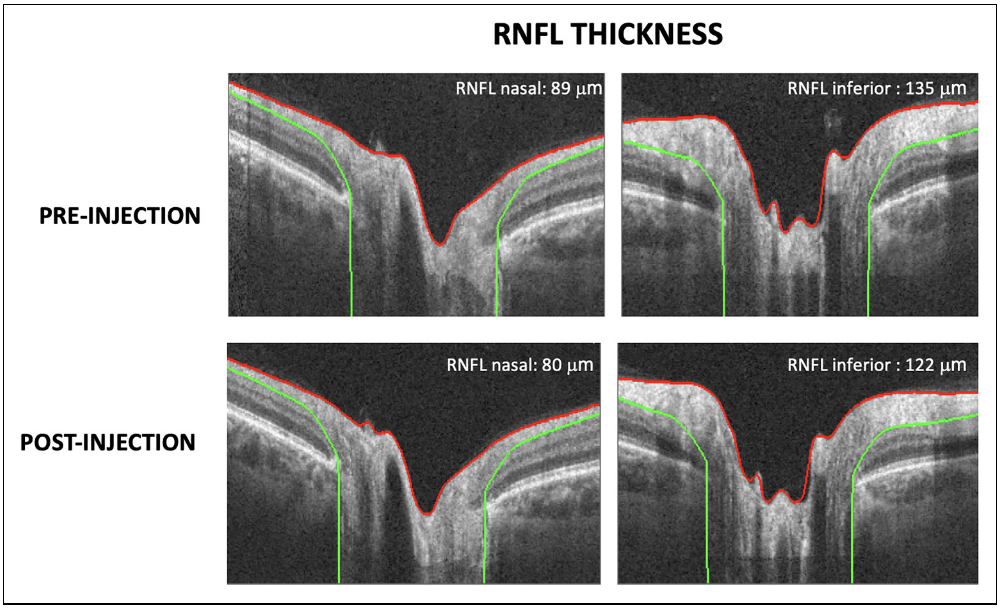

Figure 2. Representation of peripapillary RNFL thickness before and after injection in nAMD eye.

Table 1. The clinical and medical characteristics of subjects included in the analysis.

Variables	nAMD (n = 35)
Age (years)	78.10 ± 10
Gender (female,%)	20 (57.2%)
Type 1 MNV	21 (60%)
Type 2 MNV	14 (40%)
Hypertension (%)	6 (17%)
Smoking (%)	10 (29%)

Data are presented as Mean ± SD. *nAMD*, neovascular age-related macular degeneration; MNV, macular neovascularization.

< 0.01). Mean change of IOP from T0 at T1 was 17.43 ± 11.06 mmHg.

Retinal nerve fiber layer analysis. The mean global RNFL thickness before and immediately after the injection was 100.9 ± 18.8 μm and 98.6 ± 17.4 μm, respectively. This difference was statistically significant (P = 0.001). Furthermore, the topographical retinal nerve fiber layer analysis showed significant thickness reduction of the nasal and inferior sectors after the procedure when compared to T0 (P = 0.046 and P = 0.001). On the contrary, the superior and the temporal regions did not show significant modifications (P > 0.05) (Figure 3).

Radial peripapillary capillaries analysis. The mean RPC global density changes did not reach statistically significant after anti-VEGF injection (P = 0.636) (Table 2). Likewise, all quadrants examined did not show relevant variations at T1 (Figure 4).

Relationship between OCT and OCTA parameters with IOP changes. To concern the association between parameters analyzed, we found a significant negative correlation between the RNFL global thickness and the IOP changes (Pearson's correlation = −0.126; P = 0.031). In particular, the nasal retinal nerve fiber layer region showed a significant negative correlations with IOP values (Pearson's correlation = −0.198, P = 0. 046) (Figure 5). However, the other areas did not show significant correlation with IOP changes. Likewise, both the global optic nerve head perfusion and the topographic sub-analysis showed no relevant correlation with the IOP modifications (Table 3).

Discussion

This observational study described acute changes in intraocular pressure, retinal nerve fiber layer and radial peripapillary capillaries using structural OCT imaging and OCT angiography, focusing on the association of IOP, structural and vascular optic nerve head changes in a group of patients undergoing intravitreal injections of anti-VEGF drugs for neovascular AMD. We found significant IOP and RNFL modifications immediately after aflibercept injection. In detail, this study showed significant acute IOP increase and significant total RNFL thinning after anti-VEGF drug injection. Furthermore, the topographical sub-analysis displayed that the nasal and in-ferior RNFL regions appear to be more affected by intraocular injections. On the contrary, no vascular optic nerve head changes were found. Importantly, we also reported a close negative correlation between increased IOP and RNFL thinning at T1 (P = 0.04). Topographical sub-analysis revealed that the nasal RNFL region is most prone to IOP fluctuations (P = 0.002).

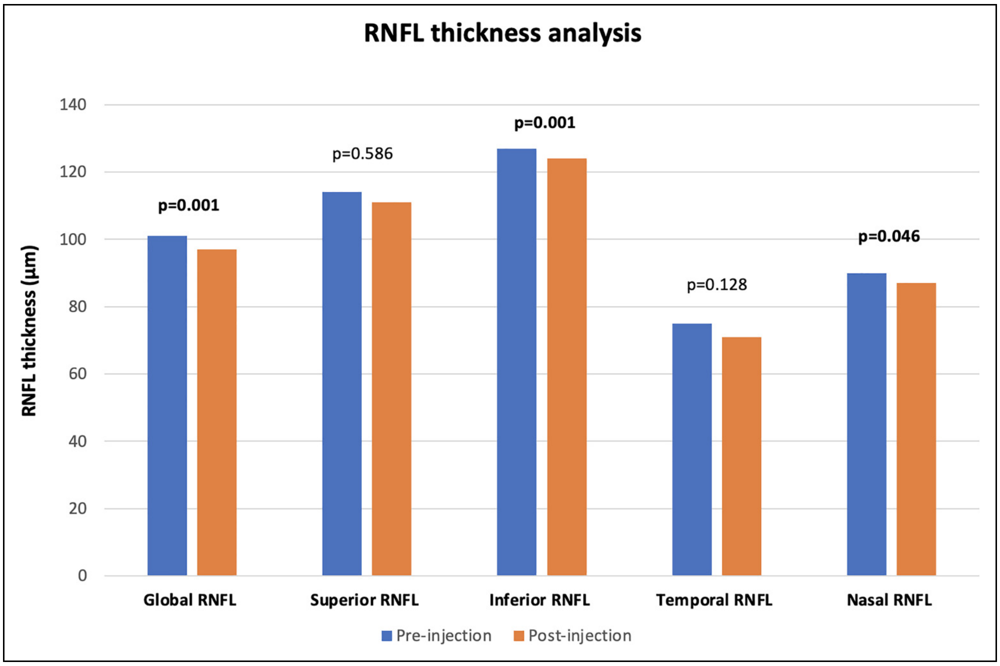

Figure 3. Comparison of pre- injection and post-injection RNFL thickness.

Table 2. Comparison between pre (T0) and post-injection (T1) parameters for IOP, RNFL thickness and RPC.

	Total n = 35		
	T0	T1	P value
IOP, mmHg	17,26 ± 2,4	34,7 ± 11,50	**0,001**
RNFL Thickness (µm)			
Global	100,9 ± 18,8	98,6 ± 17.4	**0,001**
Superior	113,9 ± 46,08	111,5 ± 43,6	0,586
Inferior	126,9 ± 22,1	124,7 ± 22,6	**0,001**
Temporal	75,5 ± 22,5	71,33 ± 15,7	0,128
Nasal	90,2 ± 18,7	88,7 ± 18,8	**0,046**
RPC Density (%)			
Global	46,6 ± 4,9	46,9 ± 4,8	0,636
Superior	46,2 ± 6,7	45,9 ± 7,9	0,709
Inferior	48,2 ± 8,9	49,4 ± 7,1	0,089
Temporal	49,5 ± 4,6	48,9 ± 5,6	0,405
Nasal	43,03 ± 5,2	43,8 ± 5,4	0,164

Data are presented as Mean ± SD. IOP, intraocular pressure; RNFL, retinal nerve fibre layer; RCP, radial peripapillary capillaries.
T0 before anti-VEGF therapy; T1 after anti-VEGF therapy, Values in bold are statistically significant (P < 0.05).

The anti-VEGF injections have become the ordinary treatment for the most common retinal diseases (neovascular age-related macular degeneration and diabetic macular edema). However, there are side effects to consider, including ocular hypertension, in-traocular hemorrhage, and endophthalmitis . Numerous studies have addressed these complications and a major concern in this regard is acute and sustained IOP increases after the intravitreal procedure.[18–20]

In this observational study, all post-injection IOP measurements displayed signifi-cantly higher values if compared to baseline with a mean change in IOP from T0 to T1 of 17.43 ± 11.06 mmHg. This is readily understandable since the injection of a volume of fluid in a relatively closed space contributes to the acute elevation in pressure. Previous studies[19,20] have reported transient intra-ocular pressure spikes immediately after the in-travitreal ranibizumab or bevacizumab due to an increase in the vitreous volume, altering aqueous outflow. Furthermore, this transient IOP increase seems to be related with altered visual acuity. Another cause of short-term IOP elevations is the injection technique itself. Indeed, we performed all the injections using 30-gauge sterile needles, whom small dimension does not allow a considerable vitreous reflux from the injection site, as already reported.[21–23] Importantly, the intravitreal injections of anti-vascular endothelial grow factor (VEGF) were carried out by a single surgeon (F.B.) to achieve a regular analysis.

Regarding the effects on RNFL thickness of intravitreal injections, contradictory results have been previously published. In contrast to our results, in literature most studies have shown that RNFL does not change significantly after the intravitreal injection of anti-VEGF drugs,[24,25] while other reports showed significant RNFL loss only after multiple intravitreal injections.[26–28] This discrepancy across studies may be due to different baseline characteristics of patients, follow-up times, or the number of injections, or different injection techniques.

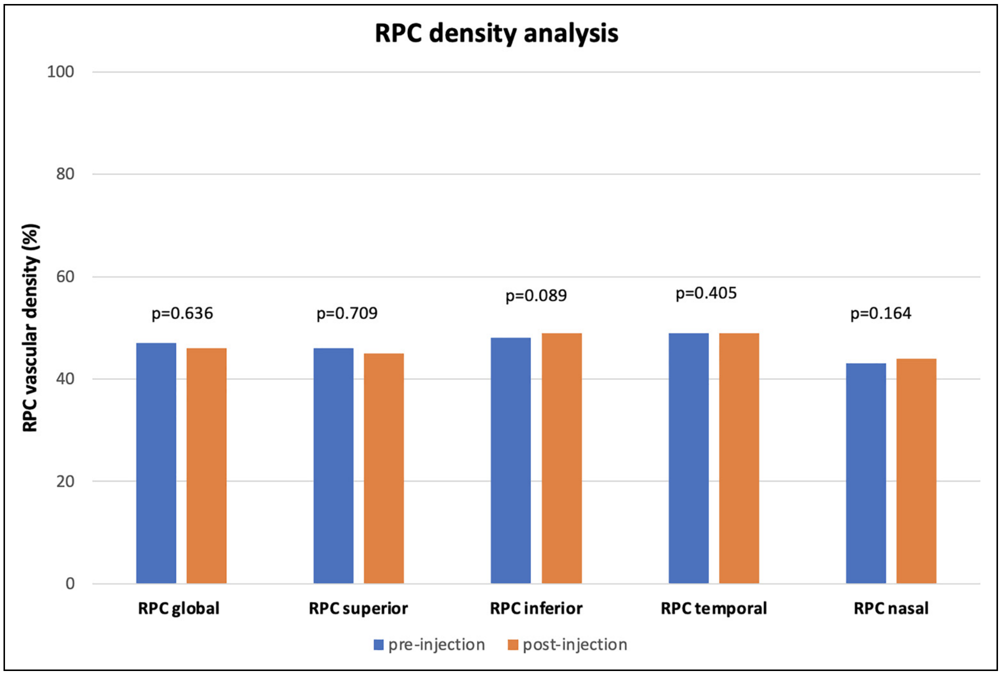

Figure 4. Comparison of pre-injection and post-injection optic nerve angiographic density.

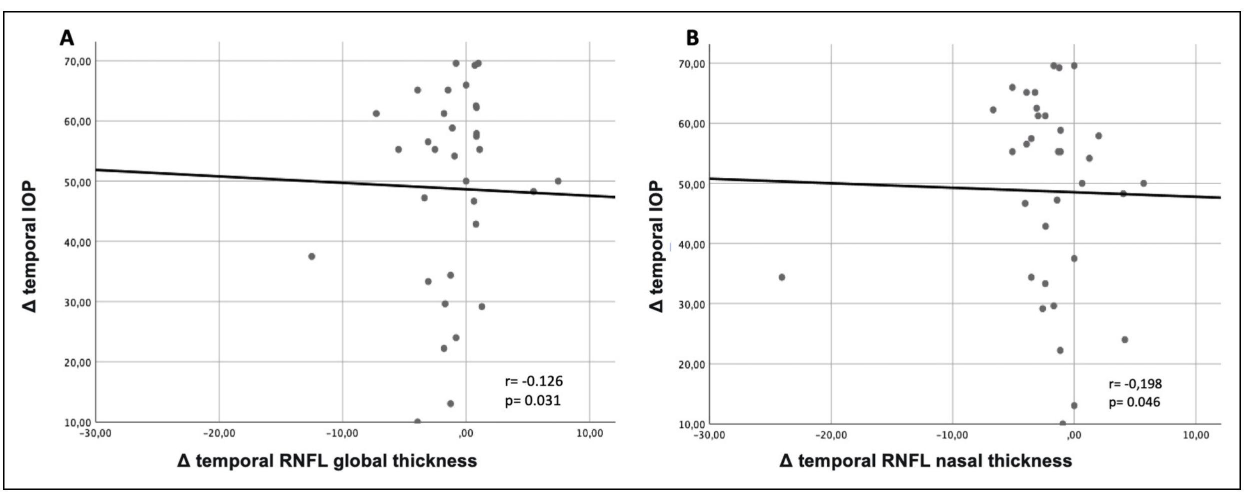

Figure 5. (A) Scatterplots illustrating the correlation between Δ IOP (T0-T1) and Δ RNFL global thickness (T0-T1). (B) Scatterplots illustrating the correlation between Δ IOP (T0-T1) and Δ RNFL nasal thickness (T0-T1). We have excluded the outlier observation. A value of $P < 0.05$ was considered statistically significant. Correlation coefficient from the Pearson rank correlation analysis.

Our analysis displayed a significant acute global RNFL loss after anti-VEGF injection. Moreover, investigating the different fields of the optic nerve head, the nasal and inferior regions appeared to be more affected by intraocular injection of anti-vascular endothelial grow factor. According to our results, in a prospective interventional case series, Entezari et al.[29] showed that RNFL thickness may decrease temporarily following two intravi-treal injections in patients with neovascular AMD. These observations suggested the acute effect of anti-VEGF therapy on the RNLF thickness. However, in the long-term analysis no significant changes were detectable from baseline values.

Concerning the intraocular pressure analysis, it's well-known that intravitreal injection, through increase of IOP may be harmful to the optic nerve.[30] Moreover, short-term IOP fluctuations has been considered a potential risk factor for the progression of glaucomatous damage to the optic nerve head.[31] Indeed, the cumulative effect of the initial injections could potentially damage the layers of nerve

Table 3. Results of Pearson correlation between intraocular pressure (IOP) and other variables.

	IOP
RNFL total thickness (μm)	−0.126 **(p = *0.031*)**
RNFL nasal thickness (μm)	−0.198 **(*p* = *0.046*)**
RNLF inferior thickness (μm)	−0.39[1]
RNFL superior thickness(μm)	−0.314
RNFL temporal thickness (μm)	−0.403
RPC total density (%)	−0.481
RPC nasal density (%)	−0.474
RPC inferior density (%)	−0.446
RPC superior density (%)	−0.396
RPC temporal density (%)	−0.297

Pearson correlation values and p-values are specified in the table as followed: (*p-value*), P-values are specified only if < 0.05. Parameter acronyms: RNFL, retinal nerve fiber layer; RPC, radial peripapillary capillaries. Significant values are placed in brackets.

fibers. However, these are long term analysis that cannot be achieved by the results of the present study since our cases received only one injection.

Besides, we found sectoral changes that may indicate more susceptibility to glaucomatous damage from repeated spikes in IOP due to injections. In particular, the nasal and inferior regions of the optic nerve head should be particularly monitored for evidence of early retinal nerve fiber layer thinning after anti-VEGF injections. This effect might be important in cases with advanced glaucoma, in which even the slightest change in IOP could have a detrimental effect on the optic nerve.

Here in this study, we found that IOP spikes recorded immediately after the injection and the global RNFL thickness were inversely related: as IOP increased, the global RNFL thickness decreased (Table 3). In addition, the topographical RNFL thickness sub analysis showed a close correlation between nasal sector reduction and IOP increased (Table 3). We might hypothesize two co-existing mechanisms behind the latter finding: 1) A hypothesis could be that as the RNFL is a part of the retina, the structural changes like intraretinal fluid due to nAMD may affect the measurements of RNFL thickness. Hwang et al.[21] reported that the peripapillary RNFL thickness was increased in patients with DME, and the increment correlated with the degree of macular edema. They hypothesized that an increase in the RNFL thickness in the temporal sector in patients with acute diabetic macular edema might be related to the change in macular tomography due to diabetic macular edema. Because the nasal sector RNFL is less affected by macular lesion change even in neovascular age-related macular degeneration, it can better reflect the damage caused by anti-VEGF injection and justify the statistically significant change of RNFL thickness in this sector. 2) The injection procedure itself may be a possible explanation for the changes only in the nasal and inferior RNFL. Indeed, all the injections were performed using a temporal approach, directing the flow towards these sectors. Definitely, these results indicates the nasal ONH region most susceptible to re-peated injections, thus we should contemplate to prepare the patients most susceptible to neurodegenerative damage with IOP lowering drug.

On the other hand, several studies pointed out that the adverse effects of the increased IOP are not limited to RNFL loss and glaucoma damages. OCT angiography was used to measure acute peripapillary changes in perfusion density resulting from intravitreal injections[28,32–34] Wen et al.[31] observed acute reductions in optic nerve head perfusion parameters after intravitreal injections due to IOP increase. The authors measured RPC perfusion approximately 2 min after the injection. According to our results, Arumuganathan et al.[35] reported no significant alterations in OCT angiography parameters in eyes measured at 5 min post-intravitreal therapy. Likewise, in our study we did not find any difference between the pre-injection and the post-injections RPC perfusion density. Probably, the analysis performed at 5 min after anti-VEGF drug injection did not show the transient ischemic vasculature damage.

We acknowledge that this study has several limitations. First, the limited number of patients included in this study. Second, short-term evaluation of IOP and RNFL thickness and the absence of follow-up. Additionally, the patient population may contain people with undiagnosed glaucoma which could alter the data analysis. Another limitation to acknowledge is that we did not conduct OCT and OCTA assessments after the normalization of intraocular pressure. This aspect could be significant in comprehending whether RNFL thinning is a transient phenomenon or not. A larger randomized controlled study with follow-up time is required to assess the effect of intravitreal injections on these parameters.

In conclusion, our study reports acute intra- ocular pressure and retinal nerve fiber layer changes in a group of patients undergoing intravitreal injections of anti-VEGF drugs for neovascular AMD. We demonstrated that the intravitreal injections induce increased IOP and RNFL thinning. This preliminary study of 35 eyes shows that the inferior and nasal RNFL regions are more affected by these changes after anti-VEGF injection. In addition, we found significant negative close correlation between increased IOP and RNFL thinning at T1. Topographical sub-analysis revealed that the nasal RNFL region is most prone to IOP fluctuations. Given these peripapillary changes, it may be prudent to follow nasal areas with RNFL measurements, and visual fields to assess the intravitreal injection effects. Further studies with prospective design including longer follow-up duration are needed to confirm the findings of our study.

Authors' contribution

PV, RB, MOG, GB: Data collection and analysis, GB, EB and LL: results Interpretation, PV and FB: Drafting manuscript, GA, FE and MGM: review.

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

ORCID iDs

Pasquale Viggiano https://orcid.org/0000-0002-0323-967X
Maria Oliva Grassi https://orcid.org/0000-0002-5952-7910
Giacomo Boscia https://orcid.org/0000-0002-8768-899X
Enrico Borrelli https://orcid.org/0000-0003-2815-5031
Luca Landini https://orcid.org/0000-0003-3016-3620
Federica Evangelista https://orcid.org/0000-0003-3781-8124

References

1. Hoguet A, Chen PP, Junk AK, et al. The effect of anti-vascular endothelial growth factor agents on intraocular pressure and glaucoma: a report by the American academy of ophthalmology. *Ophthalmology [Internet]* 2019 [cited 2023 May 9]; 126: 611–622. https://pubmed.ncbi.nlm.nih.gov/30472176/
2. Falavarjani KG and Nguyen QD. Adverse events and complications associated with intravitreal injection of anti-VEGF agents: a review of literature. *Eye (Lond) [Internet]* 2013 [cited 2023 May 9]; 27: 787–794. https://pubmed.ncbi.nlm.nih.gov/23722722/
3. Viggiano P, Grassi MO, Bisceglia G, et al. Short-term peripapillary structural and vascular changes following anti-VEGF vs. Dexamethasone intravitreal therapy in patients with DME. *Eur J Ophthalmol [Internet]* 2023 [cited 2023 May 9]: 112067212311636. https://pubmed.ncbi.nlm.nih.gov/36938676/
4. de Vries VA, Bassil FL and Ramdas WD. The effects of intravitreal injections on intraocular pressure and retinal nerve fiber layer: a systematic review and meta-analysis. *Sci Rep [Internet]* 2020 [cited 2023 May 9]; 10. https://pubmed.ncbi.nlm.nih.gov/32764619/
5. Wen JC, Cousins SW, Schuman SG, et al. Dynamic changes of the anterior chamber angle produced by intravitreal anti-vascular growth factor injections. *Retina [Internet]* 2016 [cited 2023 May 9]; 36: 1874–1881, https://pubmed.ncbi.nlm.nih.gov/26938953/
6. Morshedi RG, Ricca AM and Wirostko BM. Ocular hypertension following intravitreal antivascular endothelial growth factor therapy: review of the literature and possible role of nitric oxide. *J Glaucoma [Internet]* 2016 [cited 2023 May 9]; 25: 291–300. https://pubmed.ncbi.nlm.nih.gov/25318578/
7. Medeiros FA, Alencar LM, Zangwill LM, et al. The Relationship between intraocular pressure and progressive retinal nerve fiber layer loss in glaucoma. *Ophthalmology [Internet]* 2009 [cited 2023 May 9]; 116. https://pubmed.ncbi.nlm.nih.gov/19376584/
8. Jee D and Lee WK. Inhibitory effect of intravitreal injection of bevacizumab on nerve growth factor. *Curr Eye Res [Internet]* 2012 [cited 2023 May 9]; 37: 408–415. https://pubmed.ncbi.nlm.nih.gov/22040304/
9. Lee SW, Sim HE, Park JY, et al. Changes in inner retinal layer thickness in patients with exudative age-related macular degeneration during treatment with anti-vascular endothelial growth factor. *Medicine (Baltimore) [Internet]* 2020 [cited 2023 May 9]; 99: e19955. https://pubmed.ncbi.nlm.nih.gov/32332680/
10. Spaide RF, Fujimoto JG, Waheed NK, et al. Optical coherence tomography angiography. *Prog Retin Eye Res [Internet]* 2018 [cited 2023 May 9]; 64: 1–55. https://pubmed.ncbi.nlm.nih.gov/29229445/
11. Mansoori T, Sivaswamy J, Gamalapati JS, et al. Measurement of radial peripapillary capillary density in the normal human retina using optical coherence tomography angiography. *J Glaucoma [Internet]* 2017 [cited 2023 May 9]; 26: 241–246. https://pubmed.ncbi.nlm.nih.gov/27906811/
12. Mitsch C, Pemp B, Pollreisz A, et al. Short-time effect of intravitreal injections on retinal vascular oxygenation and vessel diameter in patients with diabetic macular oedema or neovascular age-related macular degeneration. *Acta Ophthalmol [Internet]* 2020 [cited 2023 May 9]; 98: e301. /pmc/articles/PMC7216886/.
13. Barash A, Chui TYP, Garcia P, et al. Acute macular and peripapillary angiographic changes with intravitreal injections. *Retina [Internet]* 2020 [cited 2023 May 9]; 40: 648–656, https://pubmed.ncbi.nlm.nih.gov/30762649/
14. Furino C, Grassi MO, Bini V, et al. Intravitreal injections in arc sterile setting: safety profile after more than 10,000 treatments. *J Ophthalmol [Internet]* 2020 [cited 2023 May 9]; 2020. https://pubmed.ncbi.nlm.nih.gov/32377417/
15. Viggiano P, Grassi MO, Boscia G, et al. Short-term morpho-functional changes in previously treated neovascular AMD eyes switched to brolucizumab. *J Clin Med* 2022; 11: 5517.
16. Borrelli E, Viggiano P, Evangelista F, et al. Eyelashes artifact in ultra-widefield optical coherence tomography angiography. *Ophthalmic Surg Lasers Imaging Retin* 2019; 50: 740–743.
17. Mastropasqua R, D'Aloisio R, Costantini E, et al. Serum microRNA levels in diabetes mellitus. *Diagnostics* 2021; 11: 284.
18. Bilgic A, Kodjikian L, Chhablani J, et al. Sustained intraocular pressure rise after the treat and extend regimen at 3 years: aflibercept versus ranibizumab. *J Ophthalmol [Internet]* 2020 [cited 2023 May 9]; 2020. https://pubmed.ncbi.nlm.nih.gov/32051764/
19. Falkenstein IA, Cheng L and Freeman WR. Changes of intraocular pressure after intravitreal injection of bevacizumab (avastin). *Retina [Internet]* 2007 [cited 2023 May 9]; 27: 1044–1047. https://pubmed.ncbi.nlm.nih.gov/18040242/
20. Kim JE, Mantravadi AV, Hur EY, et al. Short-term intraocular pressure changes immediately after intravitreal injections of anti-vascular endothelial growth factor agents. *Am J Ophthalmol [Internet]* 2008 [cited 2023 May 9]; 146. https://pubmed.ncbi.nlm.nih.gov/18775528/

21. Hwang DJ, Lee EJ, Lee SY, et al. Effect of diabetic macular edema on peripapillary retinal nerve fiber layer thickness profiles. *Invest Ophthalmol Vis Sci [Internet]* 2014 [cited 2023 May 9]; 55: 4213–4219. https://pubmed.ncbi.nlm.nih.gov/24833740/
22. Benz MS, Albini TA, Holz ER, et al. Short-term course of intraocular pressure after intravitreal injection of triamcinolone acetonide. *Ophthalmology [Internet]* 2006 [cited 2023 May 9]; 113: 1174–1178. https://pubmed.ncbi.nlm.nih.gov/16647122/
23. Höhn F and Mirshahi A. Impact of injection techniques on intraocular pressure (IOP) increase after intravitreal ranibizumab application. *Graefes Arch Clin Exp Ophthalmol [Internet]* 2010 [cited 2023 May 9]; 248: 1371–1375. https://pubmed.ncbi.nlm.nih.gov/20407785/
24. El-Ashry MF, Lascaratos G and Dhillon B. Evaluation of the effect of intravitreal ranibizumab injections in patients with neovascular age related macular degeneration on retinal nerve fiber layer thickness using optical coherence tomography. *Clin Ophthalmol [Internet]* 2015 [cited 2023 May 9]; 9: 1269–1274. https://pubmed.ncbi.nlm.nih.gov/26203216/
25. Jo YJ, Kim WJ, Shin IH, et al. Longitudinal changes in retinal nerve fiber layer thickness after intravitreal anti-vascular endothelial growth factor therapy. *Korean J Ophthalmol [Internet]* 2016 [cited 2023 May 9]; 30: 114–120. https://pubmed.ncbi.nlm.nih.gov/27051259/
26. Soheilian M, Karimi S, Montahae T, et al. Effects of intravitreal injection of bevacizumab with or without anterior chamber paracentesis on intraocular pressure and peripapillary retinal nerve fiber layer thickness: a prospective study. *Graefes Arch Clin Exp Ophthalmol [Internet]* 2017 [cited 2023 May 9]; 255: 1705–1712. https://pubmed.ncbi.nlm.nih.gov/28616715/
27. Martinez-de-la-Casa JM, Ruiz-Calvo A, Saenz-Frances F, et al. Retinal nerve fiber layer thickness changes in patients with age-related macular degeneration treated with intravitreal ranibizumab. *Invest Ophthalmol Vis Sci [Internet]* 2012 [cited 2023 May 9]; 53: 6214–6218. https://pubmed.ncbi.nlm.nih.gov/22915037/
28. Toto L, Evangelista F, Viggiano P, et al. Changes in ocular blood flow after ranibizumab intravitreal injection for diabetic macular edema measured using laser speckle flowgraphy. *Biomed Res Int* 2020; 2020.
29. Entezari M, Ramezani A and Yaseri M. Changes in retinal nerve fiber layer thickness after two intravitreal bevacizumab injections for wet type age-related macular degeneration. *J Ophthalmic Vis Res [Internet]* 2014 [cited 2023 May 9]; 9: 449–452. https://pubmed.ncbi.nlm.nih.gov/25709770/
30. Bracha P, Moore NA, Ciulla TA, et al. The acute and chronic effects of intravitreal anti-vascular endothelial growth factor injections on intraocular pressure: a review. *Surv Ophthalmol [Internet]* 2018 [cited 2023 May 9]; 63: 281–295, https://pubmed.ncbi.nlm.nih.gov/28882597/
31. Nouri-Mahdavi K, Hoffman D, Coleman AL, et al. Predictive factors for glaucomatous visual field progression in the Advanced Glaucoma Intervention Study. *Ophthalmology [Internet]* 2004 [cited 2023 May 9]; 111: 1627–1635. https://pubmed.ncbi.nlm.nih.gov/15350314/
32. D'aloisio R, Viggiano P, Borrelli E, et al. Changes in iris perfusion following scleral buckle surgery for rhegmatogenous retinal detachment: an anterior segment optical coherence tomography angiography (as-octa) study. *J Clin Med* 2020; 9: 1231.
33. Wen JC, Chen CL, Rezaei KA, et al. Optic nerve head perfusion before and after intravitreal antivascular growth factor injections using optical coherence tomography-based microangiography. *J Glaucoma [Internet]* 2019 [cited 2023 May 9]; 28: 188–193. https://pubmed.ncbi.nlm.nih.gov/30817497/
34. Parravano M, De Geronimo D, Sacconi R, et al. Impact of intravitreal anti-VEGF therapy on microperimetry of the retinal nonperfusion areas of patients with proliferative diabetic retinopathy. *Ophthalmol Ther* 2022; 11: 2117–2128.
35. Arumuganathan N, Wiest MRJ, Toro MD, et al. Acute and subacute macular and peripapillary angiographic changes in choroidal and retinal blood flow post-intravitreal injections. *Sci Rep [Internet]* 2021 [cited 2023 May 9]; 11. https://pubmed.ncbi.nlm.nih.gov/34588594/