Optic Nerve Head Biomechanic and IOP Changes Before and After the Injection of Aflibercept for Neovascular Age-Related Macular Degeneration

Gema Rebolleda,1 Beatriz Puerto,1 Victoria de Juan,1 Marta Gómez-Mariscal,1 Francisco José Muñoz-Negrete,1 and Alfonso Casado2

1Department of Ophthalmology, Hospital Universitario Ramón y Cajal, Madrid, Spain
2Department of Ophthalmology, Hospital Sierrallana, Cantabria, Spain

Correspondence: Alfonso Casado, Ophthalmology Department, Hospital Sierrallana, Barrio de Ganzo, s/n, 39500 Torrelavega, Cantabria, Spain; casadorojo@hotmail.es.
Submitted: June 11, 2016
Accepted: September 25, 2016
Citation: Rebolleda G, Puerto B, de Juan V, Gómez-Mariscal M, Muñoz-Negrete FJ, Casado A. Optic nerve head biomechanic and IOP changes before and after the injection of aflibercept for neovascular age-related macular degeneration. Invest Ophthalmol Vis Sci. 2016;57:5688–5695. DOI:10.1167/iovs.16-20111

Purpose. We investigated the early effects of intravitreal aflibercept injection (IAI) on optic nerve head (ONH) morphology.

Methods. All of the participants underwent applanation tonometry and enhanced depth imaging by spectral-domain optical coherence tomography immediately before injection, and within 5 and 30 minutes after IAI. Changes in the anterior lamina cribrosa surface depth, prelaminar tissue thickness (PTT), optic cup width, optic cup depth, and Bruch’s membrane opening (BMO) were assessed.

Results. The study included 30 eyes of 30 subjects with a mean age of 77.4 ± 6.8 years (range, 65–89 years) following IAI (2 mg in 0.05 ml). Within 5 minutes after injection, the mean cup depth, mean cup width, and BMO were significantly increased (P = 0.013, P = 0.000, and P = 0.004, respectively), whereas the mean PTT was thinned (P = 0.009). These morphologic changes returned to near baseline values 30 minutes after injection. Cup deepening and BMO expansion (P = 0.000; r, 0.668), as well as cup deepening and prelaminar thinning (P = 0.000; r, −0.838), were significantly correlated. The magnitude of cup deepening and prelaminar tissue thinning correlated with the IOP change in the opposite direction than expected (P = 0.039; r, −0.379 and P = 0.377; r, 0.040).

Conclusions. A significant widening and deepening of the optic cup, BMO expansion, and prelaminar tissue thinning occurred following IAI for neovascular AMD. Eyes having greater optic disc cup deepening and prelaminar tissue condensation after IAI, associated with a lower IOP increase after injection, suggesting that ONH compliance might buffer the effect of additional intravitreal fluid injection on IOP values.

Keywords: Bruch’s membrane opening, intraocular pressure, lamina cribrosa, optic nerve head

The efficacy of anti-VEGF drugs in exudative age-related macular degeneration (AMD) has been reported in many studies.1–5 Currently available information suggests that the safety profile of aflibercept is comparable to that of ranibizumab, but the percentage of adverse events is small; therefore, it has the potential to reduce the risks associated with frequent injections.5 Numerous articles have been published showing ocular hypertension following the intravitreal injection of pegaptanib, bevacizumab, ranibizumab, and aflibercept.6–10 A transient, short-term IOP elevation following intravitreal anti-VEGF therapy has been described.11–15 This IOP increase can vary according to the injected volume,16 surgical technique,17–19 ocular outflow facility, and globe size.12,16 In addition, scleral rigidity may influence the postinjection pressure spike and must be considered.

For years, lamina cribrosa (LC) has been considered the primary site of glaucomatous optic nerve damage. Lamina cribrosa displacement in response to artificial changes in IOP has been described in experimental glaucoma20–22 and enucleated human eyes.23–25 Some clinical studies also have found enlargement of cupping and compression of prelaminar tissue in living human eyes after a rapid increase of IOP by ophthalmodynamometry.26–27 Sclera deformation by indentation is a clear disadvantage of this model. More recently, Jiang et al.28 found widening and deepening of the optic disc cup without major changes in the LC depth in primary angle-closure suspects after a darkness-induced IOP increase of >15 mm Hg.

The evaluation of optic nerve head (ONH) changes in response to a transient and rapid IOP increase following anti-VEGF therapy may provide additional information to better understand the physiology of glaucomatous optic neuropathy. To the best of our knowledge, there are no previous reports investigating the morphologic changes of deep ONH structures after anti-VEGF intravitreal injections by optical coherence tomography (OCT) with enhanced depth imaging technology (EDI).

The main purpose of this study was to evaluate the changes in ONH structures in eyes with neovascular AMD, including the cup width, cup depth, LC depth, prelaminar tissue thickness, and Bruch’s membrane opening (BMO) immediately after injection (within 5 minutes) and 30 minutes after 0.05 ml of
intravitreal aflibercept injection (IAI), and to assess the relationship between the ONH morphologic changes and magnitude of the IOP change.

METHODS
This prospective study included patients with unilateral exudative AMD scheduled for IAI and age-matched controls selected from the relatives of patients scheduled for intravitreal injection. None of the patients was previously treated for AMD.

The protocol study was approved by the institutional Research Ethics Committee of Ramon y Cajal University Hospital, and it adhered to the tenets of the Declaration of Helsinki. All of the involved participants signed informed consent forms.

Exclusion criteria included a refractive error greater than 5.0 diopters (D) of spherical equivalent or 3.0 D of astigmatism, prior vitrectomy surgery or coexistence of ophthalmic surgery (other than uneventful cataract extraction), optic nerve disease, or any eye disease that might affect the quality of fundus images. Patients unable to cooperate with the imaging protocol, or those with a known history or suspicion of glaucoma, a baseline IOP > 22 mm Hg, and receiving triamcinolone acetonide also were excluded from the study.

All patients were evaluated by one of the authors (BP, GR), and underwent a complete ophthalmic examination, including best-corrected logMAR visual acuity (VA) evaluation, tonometry, anterior segment, and funduscopy examinations. The axial length (AL) was obtained using IOLMaster (Carl Zeiss Meditec, Jena, Germany).

Anti-VEGF Injection
Topical preparation before injection included tropicamide, povidone-iodine 5% solution to disinfect the anterior surface, and lidocaine 5% for local anesthesia. Intravitreal aflibercept injection was performed in a sterile operating room under stringent aseptic conditions, using sterile gloves, drapes, and an eyelid speculum.

Aflibercept was injected into the vitreous cavity by a retina specialist (BP) using a 30-gauge 0.5-inch needle attached to a syringe containing 0.05 ml (2 mg). The conjunctiva was gently displaced, and the injection needle was placed at a straight angle in the inferotemporal or superotemporal quadrant at 3.5 mm from the limbus, avoiding the horizontal meridian, and positioned toward the center of the globe. The needle was removed carefully, and a sterile cotton swab was placed immediately on the injection site to minimize reflux. No paracentesis was performed. Povidone-iodine 5% solution was applied at the end of the procedure.

OCT Imaging
All subjects underwent tonometry by Perkins and ONH scanning using the Spectralis OCT (Heidelberg Engineering, Inc., Heidelberg, Germany) and EDI technique immediately before and at 5 and 30 minutes after anti-VEGF injection. Tonometry always was performed immediately after ONH imaging in the upright position.

One vertical scan that was closest to the ONH center and where the visibility of the anterior LC surface was complete (excluding the main vessels) was selected from the baseline EDI images. The “follow-up” protocol was used to evaluate changes at the exact same location.

A reference line connecting the two Bruch’s membrane termination points was drawn, and three equidistant points (inferior, middle, and superior), corresponding to one-half and one-third of this reference, were highlighted and connected to the anterior face of the prelaminar tissue and anterior surface of the LC (Fig. 1). Prelaminar tissue thickness (PIT) and anterior LC surface depth (LCD) were measured at the aforementioned three points. The arithmetic mean of the three measurements (inferior, middle, and superior) was considered the average. Prelaminar tissue thickness was defined as the distance between the position of the anterior face of the prelaminar tissue and anterior surface of the LC. Lamina cribrosa depth was determined by measuring the distance from the reference line to the level of the anterior LC surface. Cup width was defined as the distance between the cup borders along the BMO line and cup depth as the vertical distance between the BMO line and prelaminar tissue anterior surface. The BMO diameter was defined as the distance between the 2 opposite ends of Bruch’s membrane. Measurements were done using the manual caliper tool of the Spectralis software by the same observer (de JV) who was masked to the time point evaluation when the images were analyzed.

Inaccurate images due to errors in the segmentation algorithm or failure to detect the edges of the BMO were excluded from the analysis.

To evaluate intraobserver reproducibility, 15 randomly selected scans were remeasured on the same day at baseline, and the intraclass correlation coefficients (ICCs) were calculated.

Statistical Analysis
Statistical analysis was performed using IBM SPSS Statistics V21.0 (International Business Machine Corporation, Armonk, NY, USA).

A 1-sample Kolmogorov-Smirnov test was used to verify the normality of the data distribution. The BMO, cup width, cup depth, LCD, and PIT before and after anti-VEGF injection were compared using paired Student’s t-test. Pearson correlation analysis was performed to assess the relationship between patient age and AL, and the IOP increase after IAI, as well as between the ONH morphologic changes and IOP change after injection. The level of statistical significance was set at $P < 0.05$.

RESULTS
The study initially enrolled 45 nonvitrectomized eyes of 45 patients with neovascular AMD. Of these, 15 eyes (33.3%) were excluded due to the low quality of OCT images after IAI. The analyzed sample eventually included 12 men (40%) and 18 women (60%). The mean age was 77.4 ± 6.8 years (range, 65–89 years) and the mean AL was 23.2 ± 0.78 mm (range, 21.8–25.4 mm). There were 17 (56.7%) phakic and 13 (43.3%) pseudophakic eyes. The mean vertical cup/disc ratio was 0.39 ± 0.12. The clinical and demographic characteristics are shown in Table 1.

Within the first 5 minutes after injection, we found a significant increase in the mean disc cup width (from 793.4 ± 284.4 to 819.5 ± 287.2 μm; $P = 0.000$), average disc cup depth (from 158.5 ± 138.9 to 177.4 ± 144.1 μm; $P = 0.001$), and BMO (from 1507.4 ± 648.2 to 1531.9 ± 793.2 μm; $P = 0.004$), with a significant average prelaminar tissue thinning (from 241.6 ± 102.5 to 226.5 ± 100.6 μm; $P = 0.009$). The average LCD did not significantly differ 5 minutes after injection. At 30 minutes after injection, the average disc cup depth and width, mean BMO (Fig. 2A) and mean prelaminar tissue thickness returned to baseline values (Fig. 2B; Table 2).
Cup width enlargement correlated with BMO expansion ($P = 0.000$; $r, 0.668$) and cup deepening correlated with prelamina tissue thinning ($P = 0.000$; $r, -0.838$; Figs. 3A, 3B). The mean IOP increased from $15.1 \pm 2.4$ mm Hg immediately before injection to $25.7 \pm 6.4$ mm Hg 5 minutes after IAI ($P = 0.000$) and spontaneously decreased to $19.1 \pm 5.5$ mm Hg 30 minutes after injection ($P = 0.000$). Intraocular pressure increased by a mean of $10.6$ mm Hg (range, $-1.3$–$20.6$ mm Hg) 5 minutes after injection.

Eight eyes (26.6%) had an IOP increase equal to or greater than $15$ mm Hg within 5 minutes after injection.

The IOP increase within the first 5 minutes was inversely correlated with the magnitude of cup deepening following IAI ($P = 0.039$; $r, -0.379$), and was directly correlated with prelaminal tissue thinning ($P = 0.377$; $r, 0.040$).

No significant correlation was found between optic disc widening or BMO expansion and IOP change after injection ($r, -0.044$; $P = 0.818$, and $r, 0.103$; $P = 0.608$, respectively).

We found no significant correlation between the IOP change and age ($P = 0.738$) or AL ($P = 0.475$).

There were no significant differences between phakic and pseudophakic eyes regarding IOP change ($P = 0.738$) and ONH morphologic changes, cup depth change ($P = 0.533$), LC depth movement ($P = 0.902$), and PT change ($P = 0.636$).

The ICCs were 0.999, 0.998, 0.993, 0.989, and 0.968 for BMO, cup width, cup depth, LCD, and PTT, respectively.

To establish the causal relationship between these ONH morphologic changes and intravitreal injection and the variability of the imaging technique, we recruited a small cohort of 20 age-matched healthy eyes of 20 subjects (control group) who underwent a similar imaging technique at 0, 5, and 30 minutes. All of the involved participants in the control group signed informed consent forms and followed a complete ophthalmic evaluation applying the exclusion criteria detailed in the Methods section for the patient group. The clinical and demographic characteristics are shown in Table 1 with no significant differences with the patient group regarding the mean IOP, age, AL, cup/disc ratio, sex, or lens status (Table 1).

### Table 1. Clinical and Demographic Characteristics of the Patient and Control Groups

<table>
<thead>
<tr>
<th>Variables</th>
<th>Patient Group, $n = 30$</th>
<th>Control Group, $n = 20$</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean IOP</td>
<td>$15.1 \pm 2.4$</td>
<td>$14.8 \pm 3.3$</td>
<td>0.824*</td>
</tr>
<tr>
<td>Age, y</td>
<td>$77.4 \pm 6.8$</td>
<td>$74.5 \pm 7.7$</td>
<td>0.432*</td>
</tr>
<tr>
<td>AL</td>
<td>$23.2 \pm 0.78$</td>
<td>$23.1 \pm 1.1$</td>
<td>0.959*</td>
</tr>
<tr>
<td>Mean vertical cup/disc ratio</td>
<td>$0.39 \pm 0.12$</td>
<td>$0.38 \pm 0.11$</td>
<td>0.240*</td>
</tr>
<tr>
<td>Female (%)</td>
<td>18 (60)</td>
<td>13 (65)</td>
<td>0.090†</td>
</tr>
<tr>
<td>Pseudophakic (%)</td>
<td>15 (43.3)</td>
<td>9 (45)</td>
<td>0.396†</td>
</tr>
</tbody>
</table>

* $P$ was calculated by Student’s $t$test.
† $P$ was calculated by the $\chi^2$ test.
Furthermore, we found no significant change in any ONH parameter among the measurements obtained at 0, 5, and 30 minutes (Table 3).

**DISCUSSION**

Intravitreal anti-VEGF injection is used commonly in the treatment of various retinal diseases. Currently, the most expanding indication is exudative AMD.1–5

Several studies have demonstrated that IOP increases significantly in many patients after intravitreal injections of 0.05 ml ranibizumab and spontaneously declines to near baseline levels within 30 minutes after injection.13–15

Experimental, histologic and clinical studies have reported ONH morphologic changes resulting from artificially induced IOP elevations, including cupping increase, prelaminar tissue thinning, and LC posterior displacement, suggesting that the tissues of the ONH have viscoelastic properties.20–28 We hypothesized that the additional volume injected for neovascular AMD therapy, also might result in transient ONH morphologic changes.

Seth et al.29 did not find any significant change in the vertical cup/disc ratio in patients receiving multiple intravitreal injections of pegaptanib by fundus photography. However, to the best of our knowledge, deeper ONH structures have not been studied by EDI-OCT in patients following anti-VEGF injection.

In the current study, we analyzed the ONH changes induced by IAI in the optic disc cup, optic disc width, LC position, and PTT, and their relationship with IOP. The optic disc cup became significantly deeper (change in the anterior-posterior direction) and wider (change in the lateral direction). Furthermore, we found a significant thinning of the prelaminar tissue and BMO enlargement 5 minutes after injection, with no

---

**FIGURE 2.** Graph representing the changes in the mean values of BMO, optic disc cup width, and depth (A); and in PTT (B) immediately before and 5 and 30 minutes after IAI. Cup widening, deepening, PT thinning, and BMO expansion were found 5 minutes after injection, which returned to near baseline values 30 minutes after IAI.
significant LC displacement. By contrast, no significant morphologic change was found in the control group imaged at the same time intervals, ruling out the variability of the imaging technique as the cause of the ONH changes. Our results showed that transient ONH morphologic changes represent mostly compression of the prelaminar tissue and canal, and demonstrated that the ONH space is not as rigid as we could think. In our study, BMO was enlarged by 1.6% 5 minutes after IAI and shrunk to baseline values 30 minutes later. The transient nature of this change probably is statistically but not clinically significant. However, additional longitudinal studies are necessary to determine whether these changes continue to be transient after repeated injections. Although BMO widening also has been reported in nonarteritic anterior ischemic optic neuropathy, the underlying mechanisms are completely different, and this is the first time that BMO expansion was reported after intravitreal injection.30

Average prelaminar tissue thinned by 6% 5 minutes after injection, returning to baseline thickness 30 minutes later. Cupping enlargement and prelaminar tissue compression also have been described during an artificial increment of IOP in nonglaucomatous eyes using an ophthalmodynamometer.26,27

In the current study, there was no evidence of the significant LC displacement, contrary to that observed in glaucomatous optic neuropathy, suggesting that, in most cases, one anti-VEGF injection is well tolerated. In addition, BMO expansion will pull the lamina taut, increasing LC resistance to deformation.

Jiang et al. 28 found that the prelaminar tissue became condensed in acute primary angle closure suspects during a dark room prone provocative test, whereas the position of the anterior LC surface and BMO did not change. Furthermore, the IOP increase was significantly associated with widening and deepening of the optic cup. By contrast, in our study, we found

Average prelaminar tissue thinned by 6% 5 minutes after injection, returning to baseline thickness 30 minutes later. Cupping enlargement and prelaminar tissue compression also have been described during an artificial increment of IOP in nonglaucomatous eyes using an ophthalmodynamometer.26,27

In the current study, there was no evidence of the significant LC displacement, contrary to that observed in glaucomatous optic neuropathy, suggesting that, in most cases, one anti-VEGF injection is well tolerated. In addition, BMO expansion will pull the lamina taut, increasing LC resistance to deformation.

Jiang et al. 28 found that the prelaminar tissue became condensed in acute primary angle closure suspects during a dark room prone provocative test, whereas the position of the anterior LC surface and BMO did not change. Furthermore, the IOP increase was significantly associated with widening and deepening of the optic cup. By contrast, in our study, we found

TABLE 2. Optic Nerve Head Biomechanic and IOP Changes Before Injection As Well As 5 and 30 Minutes After Injection

<table>
<thead>
<tr>
<th>Variables</th>
<th>Baseline, Mean ± SD</th>
<th>5 Min, Mean ± SD</th>
<th>P*</th>
<th>30 Min, Mean ± SD</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td>IOP, mm Hg</td>
<td>15.1 ± 3.4</td>
<td>25.4 ± 5.8</td>
<td>0.000‡</td>
<td>19.1 ± 5.4</td>
<td>0.000‡</td>
</tr>
<tr>
<td>BMO</td>
<td>1507.4 ± 160.6</td>
<td>1531.9 ± 178.4</td>
<td>0.004‡</td>
<td>1509.4 ± 167.1</td>
<td>0.002‡</td>
</tr>
<tr>
<td>Cup width</td>
<td>793.4 ± 284.4</td>
<td>819.5 ± 287.2</td>
<td>0.000‡</td>
<td>795.6 ± 284.5</td>
<td>0.000‡</td>
</tr>
<tr>
<td>Cup depth</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inferior</td>
<td>105.3 ± 170</td>
<td>134 ± 165.4</td>
<td>0.013‡</td>
<td>116.5 ± 163.9</td>
<td>0.292</td>
</tr>
<tr>
<td>Middle</td>
<td>204.7 ± 121.5</td>
<td>226.9 ± 125.1</td>
<td>0.000‡</td>
<td>214.5 ± 125.3</td>
<td>0.003‡</td>
</tr>
<tr>
<td>Superior</td>
<td>165.6 ± 152.8</td>
<td>180.6 ± 159.6</td>
<td>0.107</td>
<td>171.6 ± 155.3</td>
<td>0.266</td>
</tr>
<tr>
<td>Mean</td>
<td>158.5 ± 138.9</td>
<td>177.4 ± 144.1</td>
<td>0.001‡</td>
<td>167.5 ± 139.8</td>
<td>0.034‡</td>
</tr>
<tr>
<td>LCD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inferior</td>
<td>390.8 ± 103.9</td>
<td>388.9 ± 108.9</td>
<td>0.829</td>
<td>394.1 ± 95.7</td>
<td>0.839</td>
</tr>
<tr>
<td>Middle</td>
<td>386.3 ± 97.3</td>
<td>390.7 ± 95.9</td>
<td>0.434</td>
<td>390.5 ± 96.9</td>
<td>0.622</td>
</tr>
<tr>
<td>Superior</td>
<td>423 ± 15.2</td>
<td>426 ± 115.1</td>
<td>0.480</td>
<td>425.3 ± 110.3</td>
<td>0.226</td>
</tr>
<tr>
<td>Mean</td>
<td>400.1 ± 102.7</td>
<td>401.9 ± 108.1</td>
<td>0.600</td>
<td>403.3 ± 98.5</td>
<td>0.409</td>
</tr>
<tr>
<td>PTT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inferior</td>
<td>285.5 ± 127.5</td>
<td>254.8 ± 120.5</td>
<td>0.019‡</td>
<td>277.6 ± 128.5</td>
<td>0.200</td>
</tr>
<tr>
<td>Middle</td>
<td>181.7 ± 81.4</td>
<td>171.1 ± 82.3</td>
<td>0.063</td>
<td>176 ± 87.6</td>
<td>0.089</td>
</tr>
<tr>
<td>Superior</td>
<td>257.5 ± 139.7</td>
<td>253.6 ± 143.8</td>
<td>0.427</td>
<td>253.7 ± 154.1</td>
<td>0.731</td>
</tr>
<tr>
<td>Mean</td>
<td>241.6 ± 102.5</td>
<td>226.5 ± 100.6</td>
<td>0.009‡</td>
<td>235.8 ± 111.8</td>
<td>0.099</td>
</tr>
</tbody>
</table>

Units for ONH morphologic changes are µm.
* Comparison between baseline and 5 minutes.
† Comparison between baseline and 30 minutes to help guide the reader using paired t-test.
‡ P value is < 0.05.

FIGURE 3. Dot plot representing the correlation between BMO changes and cup width (A) and between cup depth and PTT changes after intravitreal injection (B).
PTT 

zumab and/or bevacizumab.9,10 However, in the current study, switched to aflibercept after previous treatments with ranibizumab and/or bevacizumab.9,10 We have found that IOP was significantly lower in patients transient IOP elevation after aflibercept injection. Some papers of additional intravitreal fluid injection on IOP values. Condensation might counteract or buffer the expected effect suggesting that cup deepening and/or prelaminal tissue increase after intravitreal anti-VEGF injections reported in the literature. However, this effect might be lacking in the literature.

In agreement with previous reports, our study shows a change in intraocular volume may have two effects, one in the sagittal direction (cup widening and BMO or canal expansion), and the other in the coronal plane (cup deepening and prelaminal tissue thinning). Unexpectedly, the cup deepening observed in our study was inversely correlated with prelaminal tissue thinning. An IOP increase in the sagittal direction (cup widening and BMO or canal). Therefore, the magnitude and direction of the LC displacement will depend on the geometric ONH anatomy and interplay between the LC and sclera stiffnesses.

A change in intraocular volume may have two effects, one in the sagittal direction (cup widening and BMO or canal expansion), and the other in the coronal plane (cup deepening and prelaminal tissue thinning). Unexpectedly, the cup deepening observed in our study was inversely correlated with the magnitude of the IOP change and was directly correlated with prelaminal tissue thinning. An IOP increase < 10 mm Hg 5 minutes after IAI was associated with a larger cup deepening and PT thinning compared to an IOP increase ≥ 10 mm Hg (19.8 vs. 13.9 and 17.6 vs. 12.5 µm, respectively), suggesting that cup deepening and/or prelaminal tissue condensation might counteract or buffer the expected effect of additional intravitreal fluid injection on IOP values.

In agreement with previous reports, our study shows a transient IOP elevation after aflibercept injection. Some papers have found that IOP was significantly lower in patients switched to aflibercept after previous treatments with ranibizumab and/or bevacizumab.9,10 However, in the current study, no patient was treated previously with anti-VEGF drugs, and data about immediate effects on IOP with aflibercept are lacking in the literature.

Despite using the same injected volume, the range of IOP increase after intravitreal anti-VEGF injections reported in the literature is highly variable. In the current study, 0.05 ml was injected in all eyes, and the IOP change ranged from −1.3 to 20.6 mm Hg from baseline to 5 minutes after IAI; thus, other potential variables, such as the ONH compliance mentioned above, age, and AL, surgical technique, ocular outflow facility, and dynamic changes of the anterior chamber, must be considered. For instance, depending on how much and the duration of pressure placed over the injection site with the cotton-tipped applicator, the reflux of vitreous is prevented, but it may cause an additional IOP increase besides the injection. This might cause variable rates of flow through the trabecular meshwork. Recently, a significant narrowing of the temporal anterior chamber angle was reported after anti-VEGF injection, suggesting that it represents another potential mechanism for the eye to accommodate the intravitreous injected volume.32

The IOP increase is dependent on the intravitreal injection technique. It has been reported that eyes without subconjunctival reflux had a higher increase in IOP than eyes with any reflux.17–19 In the current study, a cotton-tipped sterile applicator was used immediately after the injection to minimize postinjection reflux. However, subclinical reflux may have occurred given that one of the injected eyes (3.33%) had a decrease in IOP following IAI.

Glaucoma patients who had a compromised aqueous outflow facility might have a higher immediate postinjection IOP, a longer IOP spike, or a sustained IOP elevated more commonly than healthy subjects.35 Another point to consider is the presumed age-related increase in scleral rigidity and stiffening on the lamina cribrosa.34–36 Therefore, age could be a modifying factor in the response of the ONH and in the magnitude of IOP observed after IAI. Although we did not find a significant correlation between age, ONH morphologic changes, and IOP magnitude of change, all of the patients included in this study were older than 65 years. The lower LC elasticity in older patients also might explain the nonsignificant LC displacement that we found.

Previous investigators have found that eyes with a shorter AL had a higher IOP elevation immediately after intravitreal injections.13,16 This result is not surprising considering that the additional volume injected in shorter eyes represents a slightly
greater percentage of the original volume, than that in longer myopic eyes. In addition, ONH and peripapillary structures could have different elasticity properties in myopic eyes and, therefore, respond differently to volume changes. In the current study, we did not find any significant correlation among AL, ONH, and IOP changes, but the ability to assess this relationship is low due to the limited range of the AL included (21.8–25.4 mm).

Intraocular pressure measurement is influenced by central corneal thickness (CCT); however, it has been reported (21.8–25.4 mm).

Because the effects of anti-VEGF agents are of limited duration, repeated intravitreal injections are required in many cases. As a result, brief or sustained ocular hypertension and increased IOP fluctuations with changes in ocular blood flow, and adverse effects on the optic nerve can ensue. It is well known that a greater number of intravitreal injections is associated with an increased risk of sustained IOP elevation. Monitoring the ONH changes following anti-VEGF injections would be useful to evaluate their relationship with IOP increase and may improve our understanding of glaucoma pathophysiology.

We used Pubmed and the following search terms: lamina cribrosa, intravitreal injection, anti-vascular endothelium growth factors (VEGF), IOP, ONH, aflibercept, OCT, and EDI-OCT, to review prior information about ONH changes following anti-VEGF injection. To the best of our knowledge, this is the first report evaluating structural changes in the deep ONH tissues in eyes following the intravitreal injection of anti-VEGF.

We have been able to demonstrate a transient increased optic disc cup enlargement (widening and deepening) with prelaminar tissue condensation and BMO expansion in normal living human eyes after IAI, without major changes in the position of the anterior LC surface. Optic nerve head compliance influences the magnitude of IOP occurring after IAI, so that eyes with larger cup deepening are associated with a lesser IOP rise.

Our study has some limitations. First, our sample size was smaller than expected, in fact 15 eyes (1/3) had to be excluded due to the low quality of the OCT images after IAI. In most cases an abnormal tear film linked to intraoperative povidone was the most plausible explanation. However, given the statistical significance observed, the overall results obtained in this study may be relevant.

Second, ideally, the control group would have been the fellow uninjected eye, but the short interval between scans (5 and 30 minutes after injection) and poor vision of the injected eye hindered the study of both eyes. Furthermore, a systemic response to the IAI affecting the fellow eye cannot be excluded, so an age-matched cohort control group seemed to be a reasonable surrogate. No significant differences in ONH morphologic features were found in the control group evaluated at the same intervals as the injected eyes, supporting a causal relationship between the ONH changes observed and injection. Control eyes did not have AMD, so the influence of AMD on the ONH response cannot be ruled out.

Third, one single vertical ONH scan was chosen for the morphometric analysis, while the remaining peripheral scans were not evaluated. However, only the highest quality image and most centered vertical scan without retinal vasculature and where borders were more clearly visible was evaluated. Although complete information was not collected, we believe that selected scan can be representative of the structural changes and may be convenient for clinical practice due to its simplicity.

Fourth, the LC thickness was not evaluated because the contour delineation of the posterior surface of the LC was broadly less accurate than the other structures.

Fifth, after injection follow-up included only two evaluations at 5 and 30 minutes. However, most studies reported that IOP changes tend to normalize in most patients after 30 minutes.

Finally, eyes with glaucoma, suspicious glaucoma, or an IOP larger than 22 mm Hg were not included in the study. Therefore, our data cannot be extrapolated to eyes with ocular hypertension or glaucomatous optic neuropathy.

A potential strength of the study is that the research protocol was undertaken in a real clinical setting, so observations from the current study very likely represent what occurs during day-to-day clinical practice.

Further studies with a larger sample size and repeated injections will be needed to evaluate whether these ONH changes are modified over time and contribute to the risk of developing glaucomatous optic neuropathy.

Acknowledgments

The authors alone are responsible for the content and writing of this paper.

Disclosure: G. Rebolleda, None; B. Puerto, None; V. de Juan, None; M. Gómez-Mariscal, None; FJ. Muñoz-Negrete, None; A. Casado, None

References

11. Kim JE, Mantravadi AV, Hur EY, Covert DJ. Short-term intraocular pressure changes immediately after intravitreal
Optic Nerve Head Changes After Intravitreal Injection


