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Changes in inner retinal layer thickness in patients with exudative age-related macular degeneration during treatment with anti-vascular endothelial growth factor

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Abstract

The aim of this study was to identify any changes that occur in the retinal nerve fiber layer (RNFL) and ganglion cell-inner plexiform layer (GC-IPL) in patients with exudative age-related macular degeneration (AMD) during treatment with anti-vascular endothelial growth factor (VEGF) injections.

Patients were enrolled in this retrospective study if they had exudative AMD, had received at least 3 injections of ranibizumab or aflibercept, and had a minimum of 12 months of follow-up. We analyzed the changes in the RNFL and GC-IPL using spectral-domain optical coherence tomography in rescan mode.

Fifty-two eyes of 52 patients who had been treated with repeated anti-VEGF injections for exudative AMD were included. At the final visit, there was no significant between-group difference in best-corrected visual acuity or intraocular pressure. There was a significant decrease in central macular thickness in all groups ($P < .05$). There was a decrease in RNFL thickness that was only statistically significant in the ranibizumab group and when the ranibizumab or aflibercept groups were combined ($P = .036$ and .044, respectively). The thickness of the GC-IPL layer was significantly decreased in the aflibercept and total group ($P = .035$ and $P = .048$, respectively).

The thicknesses of the RNFL and GC-IPL decreased in patients with exudative AMD who underwent repeated anti-VEGF injections.

Abbreviations: AMD = age-related macular degeneration, BCVA = best-corrected visual acuity, CMT = central macular thickness, GC-IPL = ganglion cell-inner plexiform layer, IOP = intraocular pressure, RGC = retinal ganglion cell, RNFL = retinal nerve fiber layer, VEGF = vascular endothelial growth factor.

Keywords: age-related macular degeneration, ganglion cell-inner plexiform layer, inner retinal layer thickness, intravitreal anti-VEGF antibody injection, retinal nerve fiber layer

1. Introduction

Age-related macular degeneration (AMD) is 1 of the leading causes of irreversible visual impairment in patients aged 55 years or older in developed countries.[1] Given the rapid increase in the number of elderly people in western populations, it can be assumed that the prevalence of AMD is increasing as well.[2,3]

Vascular endothelial growth factor (VEGF) is a key regulator of angiogenesis and vascular permeability and plays a crucial role in the pathogenesis of exudative AMD by promoting choroidal neovascularization.[4–6]

Intravitreal anti-VEGF antibody injections are now widely used to treat exudative AMD. Anti-VEGF antibodies inhibit the growth of blood vessels and vascular leak by binding to VEGF, so these injections are effective for suppression of angiogenesis and macular edema. Recent reports have suggested that anti-VEGF therapy can significantly improve visual outcomes in patients with exudative AMD.[4,7] However, the duration of efficacy of the anti-VEGF agents is limited. Therefore, many patients with exudative AMD need repeat injections to maintain the anti-angiogenic effects and preserve visual function. Moreover, despite the beneficial effects of anti-VEGF therapy, several studies have reported that long-term inhibition of VEGF may have adverse effects, including retinal pigment epithelium atrophy[8] and scleral thinning.[9]

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VEGF has neurotrophic activity and stimulates axonal outgrowth, thereby enhancing cell survival and cell proliferation.[10] Therefore, long-term anti-VEGF therapy may accelerate apoptosis in the inner retinal layers, including the retinal nerve fiber layer (RNFL) and retinal ganglion cell (RGC) layer.

Although there have been some recent reports concerning the effect of anti-VEGF therapy on the RNFL,[6,11,12] few studies have focused on the effects of this treatment on the thickness of the macular ganglion cell-inner plexiform layer (GC-IPL).

The purpose of this study was to identify the changes in the intraretinal layer (ie, the RGC layer and the GC-IPL) during anti-VEGF injections in patients with exudative AMD.

2. Methods

This retrospective study was performed at Sanggye Paik Hospital. The study was conducted after receiving approval from the Institutional Review Board at Inje University and performed in adherence with the tenets of the Declaration of Helsinki. Informed consent was obtained from all study participants.

Patients were included in this study in patients with exudative AMD, had received at least 3 injections of ranibizumab (Lucentis; Genentech, South San Francisco, CA) or aflibercept (Eylea; Regeneron, Tarrytown, NY), and had a minimum of 12 months of follow-up using spectral-domain optical coherence tomography (Heidelberg Engineering, Heidelberg, Germany) in rescan mode between May 2014 and June 2018.

Patients with a history of surgery, such as pars plana vitrectomy, laser photocoagulation, or photodynamic therapy were excluded. Patients with any other ocular disease that could interfere with the results of retinal layer segmentation, such as diabetic retinopathy, history of ocular hypertension, were also excluded, as were those with media opacity that would significantly interfere with acquisition of OCT images.

Data on patient demographics, best-corrected visual acuity (BCVA), and intraocular pressure (IOP) at the time of the initial injection, 1 month after 3 monthly loading injections, and at the final follow-up were collected. The number of intravitreal injections, the types of anti-VEGF agents administered, and the duration of treatment were also recorded.

All OCT scans were acquired by the same operator using the enhanced depth imaging mode with an eye-tracking (automatic real time) system. The same sites were scanned at the time of diagnosis and at the follow-up visits during anti-VEGF treatment. Foveal volumetric retinal scans were obtained by collecting 49 parallel B-scans consisting of 512 A-scans, wherein each B-scan was averaged 9 times.

The inbuilt Heidelberg Eye Explorer version 1.9.10.0 software (Heidelberg Engineering) was used to measure the thickness of each retinal layer. The segmentation data were reviewed by 2 experienced ophthalmologists and adjusted manually if necessary. The respective parameters were evaluated at baseline, at 1 month after 3 loading injections, and at the final follow-up visit. The mean RNFL thickness, central macular thickness (CMT), and mean GC-IPL thickness were calculated automatically using the segmentation algorithm. The mean RNFL thickness and GC-IPL thickness of the outer ring (r = 3 mm) were evaluated using the implanted early treatment diabetic retinopathy study grid.

The study data are shown as the mean and standard deviation. The BCVA, IOP, and retinal thickness values at baseline and each evaluation point were compared between the groups using the paired *t*-test. Ocular characteristics, including retinal thickness, were compared between the ranibizumab and aflibercept groups using the Mann-Whitney *U* test. The relationship between the number of injections administered, duration of follow-up, and inner retinal layer thickness was analyzed by Pearson correlation coefficient analysis. The statistical analyzes were performed using PASW Statistics software version 18 (SPSS Inc., Chicago, IL). A P-value $< .05$ was considered statistically significant.

3. Results

3.1. Patient demographics

52 eyes of 52 patients who had been treated with repeated anti-VEGF injections for exudative AMD were included in the study. The mean duration of follow-up after the initial anti-VEGF injection was 19.9 ± 7.1 months. The baseline demographic and clinical characteristics of all patients are summarized and compared in Table 1. 23 of the 52 eyes were treated with ranibizumab injections and 29 with aflibercept injections. There were no significant between-group differences in baseline characteristics, number of injections, or duration of follow-up.

3.2. Ocular parameters at 1 month after the loading injection

The mean BCVA, IOP, CMT, RNFL thickness, and GC-IPL thickness values at 1 month after the loading injection are shown

Table 1

Demographics and clinical characteristics of all patients at baseline.

	All participants (n = 52)	Ranibizumab group (n = 23)	Aflibercept group (n = 29)	*P*-value*
Age mean ± SD, yr	74.3 ± 8.1	75.0 ± 7.8	73.8 ± 8.6	.524
Sex, n (%)				
Male	28 (54)	11 (48)	17 (59)	
Female	24 (46)	12 (52)	12 (41)	
Follow-up period, mean ± SD (mo)	19.9 ± 7.1	21.4 ± 8.9	18.8 ± 5.3	.203
Number of injections mean ± SD	5.1 ± 2.0	5.4 ± 2.2	4.8 ± 1.9	.291
BCVA (logMAR) mean ± SD	1.0 ± 0.4	0.98 ± 0.5	1.1 ± 0.4	.471
IOP mean ± SD (mm Hg)	11.3 ± 3.2	11.1 ± 3.3	11.4 ± 3.3	.729
CMT mean ± SD (μm)	425.8 ± 136.5	421.3 ± 153.4	429.3 ± 126.9	.839
RNFL thickness mean ± SD (μm)	41.6 ± 14.4	42.9 ± 19.3	40.6 ± 9.5	.574
GC-IPL thickness mean ± SD (μm)	56.6 ± 10.7	55.7 ± 11.1	57.3 ± 10.7	.575

BCVA = best corrected visual acuity, CMT = central macular thickness, GC-IPL = ganglion cell-inner plexiform layer, IOP = intraocular pressure, RNFL = retinal nerve fiber layer, SD = standard deviation.
* Mann-Whitney *U* test.

Table 2

Comparison of the clinical characteristics and changes in CMT, RNFL thickness and GC-IPL thickness at the point of 1mo after 3 loading Injection.

	Ranibizumab group (n = 23)			Aflibercept group (n = 29)			Total group (n = 52)		
	Baseline	1 mo after 3 loading injection	*P*-value*	Baseline	1 mo after 3 loading injection	*P*-value*	Baseline	1 mo after 3 loading injection	*P*-value*
BCVA (logMAR) mean ± SD	0.98 ± 0.5	0.87 ± 0.4	0.393	1.1 ± 0.4	0.97 ± 0.4	0.871	1.04 ± 0.4	0.93 ± 0.4	.222
IOP mean ± SD (mm Hg)	11.1 ± 3.3	10.8 ± 3.1	0.714	11.4 ± 3.3	9.8 ± 2.1	0.032†	11.3 ± 3.2	10.3 ± 2.6	.075
CMT mean ± SD (μm)	421.3 ± 153.4	296.2 ± 98	0.002†	429.3 ± 126.9	286.3 ± 51.7	0.000†	425.8 ± 136.5	290.7 ± 74.4	.000†
RNFL thickness mean ± SD (μm)	42.9 ± 19.3	35.6 ± 17.3	0.180	40.6 ± 9.5	35.8 ± 11.9	0.096	41.6 ± 14.4	35.7 ± 14.3	.039†
GC-IPL thickness mean ± SD (μm)	55.7 ± 11.1	52.3 ± 11.5	0.321	57.3 ± 10.7	53.6 ± 11.1	0.190	56.6 ± 10.7	53.0 ± 11.1	.098

BCVA = best corrected visual acuity, CMT = central macular thickness, GC-IPL = ganglion cell-inner plexiform layer, HD = high dose, IOP = intraocular pressure, RD = regular dose, RNFL = retinal nerve fiber layer, SD = standard deviation, VEGF = vascular endothelial growth factor.

* Paired *t*-test.

† Statistically significant difference between the 2 groups.

in Table 2. There was no significant between-group difference in BCVA or IOP. There were significant decreases in CMT and RNFL thickness when both study groups were combined ($P = .000$ and $P = .039$, respectively). There was also a decrease in GC-IPL thickness in both groups, but the difference was not statistically significant.

3.3. Ocular parameters at the final visit

At the final visit, there was no significant difference in BCVA or IOP between the groups. The CMT was significantly decreased in both groups ($P < .05$), as was the RNFL thickness; however, only the results for the ranibizumab group and both groups combined were statistically significant ($P = .036$ and $P = .044$, respectively). There was a significant decrease in GC-IPL thickness in the aflibercept group and total group ($P = .035$ and $P = .048$, respectively). These findings are summarized in Table 3.

3.4. Correlation between number of injections, duration of follow-up, and RNFL thickness

There was no significant correlation between RNFL thickness and number of injections or duration of follow-up (Tables 4 and 5).

3.5. Correlation between number of injections, duration of follow-up, and GC-IPL thickness

There was no significant correlation between GC-IPL thickness and number of injections or duration of follow-up (Tables 6 and 7).

4. Discussion

In this study, we detected significant changes in GC-IPL thickness after an average of 5.1 intravitreal anti-VEGF injections and a mean follow-up duration of 19.9 months. There was no significant difference in the mean duration of follow-up or number of injections administered between the ranibizumab group and the aflibercept group.

One month after the anti-VEGF loading injection, there was a significant decrease in CMT in both study groups ($P = .000$). There was also a decrease in RNFL thickness in both groups, which was statistically significant only when the study groups were combined ($P = .039$). There was a decrease in GC-IPL thickness in both groups, but the change was not statistically significant in either group.

At the final visit, there was a significant decrease in CMT in the 2 study groups (both $P = .000$) and RNFL thickness was significantly decreased in the ranibizumab group and when the 2 groups were combined ($P = .036$ and .044, respectively). Some authors have evaluated RNFL thickness after repeated anti-VEGF treatment for AMD, and the findings seem to be contradictory. Martinez-de-la-Casa et al[13] reported that the RNFL thickness in patients after chronic anti-VEGF therapy was significantly thinner than that in the control group with the same duration of follow-up. In contrast, Michael et al[11] reported in patients with exudative AMD, treatment with anti-VEGF did not result in a significant decrease in RNFL thickness. In the present study, significant changes in RNFL thickness were detected after anti-VEGF treatment in the ranibizumab group and when the 2

Table 3

Changes in CMT, RNFL thickness and GC-IPL thickness at the final visit.

	Ranibizumab group (n = 23)			Aflibercept group (n = 29)			Total group (n = 52)		
	Baseline	Final visit	*P*-value*	Baseline	Final visit	*P*-value*	Baseline	Final visit	*P*-value*
BCVA (logMAR) mean ± SD	0.98 ± 0.5	1.04 ± 0.8	.775	1.1 ± 0.4	1.07 ± 0.4	.970	1.04 ± 0.4	1.06 ± 0.6	.830
IOP mean ± SD (mm Hg)	11.1 ± 3.3	12.2 ± 3.5	.265	11.4 ± 3.3	10.3 ± 2.8	.162	11.3 ± 3.2	11.2 ± 3.2	.833
CMT mean ± SD (μm)	421.3 ± 153.4	329.2 ± 110.5	.02†	429.3 ± 126.9	329.4 ± 109.6	.02†	425.8 ± 136.5	329.3 ± 107.9	.000†
RNFL thickness mean ± SD (μm)	42.9 ± 19.3	33.2 ± 9.4	.036†	40.6 ± 9.5	37.4 ± 16.3	.372	41.6 ± 14.4	35.6 ± 13.6	.044†
GC-IPL thickness mean ± SD (μm)	55.7 ± 11.1	52.1 ± 11.2	.282	57.3 ± 10.7	51.8 ± 8.9	.035†	56.6 ± 10.7	52.4 ± 10.9	.048†

BCVA = best corrected visual acuity, CMT = central macular thickness, GC-IPL = ganglion cell-inner plexiform layer, HD = high dose, IOP = intraocular pressure, RD = regular dose, RNFL = retinal nerve fiber layer, SD = standard deviation, VEGF = vascular endothelial growth factor.

* Paired *t*-test.

† Statistically significant difference between the 2 groups.

Table 4

Correlation between number of injection and change of RNFL thickness.

	Delta GC-IPL(um)			Delta GC-IPL(um)(%)		
	Total (n = 52) Co	Ranibizumab (n = 23) Co	Aflibercept (n = 29) Co	Total (n = 52) Co	Ranibizumab (n = 23) Co	Aflibercept (n = 29) Co
Number of injection	0.04 (*P* = .76)	-0.15 (p = .46)	0.21 (*P* = .26)	0.10 (*P* = .43)	-0.14 (*P* = .52)	0.21 (*P* = .26)

Co = coefficient, GC-IPL = ganglion cell-inner plexiform layer, RNFL = retinal nerve fiber layer. *Statistically significant.

Table 5

Correlation between follow-up period and change of RNFL thickness.

	Delta GC-IPL(um)			Delta GC-IPL(um)(%)		
	Total (n = 52) Co	Ranibizumab (n = 23) Co	Aflibercept (n = 29) Co	Total (n = 52) Co	Ranibizumab (n = 23) Co	Aflibercept (n = 29) Co
Follow-up Period	0.11 (*P* = .42)	0.01 (*P* = .93)	0.18 (*P* = .32)	0.15 (*P* = .26)	0.14 (*P* = .52)	0.16 (*P* = .39)

Co = coefficient, GC-IPL = ganglion cell-inner plexiform layer, RNFL = retinal nerve fiber layer. *Statistically significant.

study groups were combined, and these results were consistent with those of Martinez-de-la-Casa et al.[13]

In this study, the GC-IPL thickness at the final visit was significantly decreased in the aflibercept group and when the 2 study groups were combined ($P = .035$ and .048, respectively). VEGF, which induces angiogenesis, is a type of growth factor specific for endothelial cells. In addition to its angiogenic role, VEGF also has a neuroprotective function. Zachary et al[14] described VEGF as having both neurotrophic and neuroprotective effects on glial cells. Nishijima et al[15] reported the VEGF is a key factor in the survival of RGCs and VEGF deficiency may result in neurodegenerative disorders.[16] Several reports have described the effects of anti-VEGF therapy on the inner retinal layers. Beck et al[17] and Kim et al[18] reported a significant reduction in RGC layer thickness in patients with exudative AMD in comparison with the fellow eyes during long-term anti-VEGF treatment. Recently, Lee et al[19] reported data for GC-IPL thickness during anti-VEGF treatment in patients with open-angle glaucoma. They reported that the rate of GC-IPL thinning was significantly more rapid in the eyes of subjects with bilateral open-angle glaucoma treated with anti-VEGF injections for exudative AMD than in untreated fellow eyes with dry AMD. Moreover, anti-VEGF agents target not only new vessels but also other ocular tissues. Thinning of the sclera and retinal pigment epithelium during anti-VEGF treatment have been reported.[8,9] Some reports have related intravitreal injections of anti-VEGF agents to both transient and sustained elevations of IOP.[20,21] However, in this study, sustained elevation of IOP was not found. If transient elevation of IOP affected the thickness of the inner retinal layers, there would have been changes in both GC-IPL thickness and RNFL thickness. Therefore, the hypothesis that the GC-IPL is thinner because of the increase in IOP is not convincing. Nevertheless, in the RNFL, there is a limited possibility that the fibers from the adjacent ganglion cells as well as those from the distant ganglion cells are joined together; given that RNFL parameters are more redundant and supernumerary in comparison with GC-IPL parameters, the changes in the RNFL will not only be smaller but would also be likely to be detected later.[19,22]

Another possibility is that the decrease in GC-IPL thickness may be caused by the AMD itself rather than an anti-VEGF agent. Several reports have described the thickness of the inner retinal

Table 6

Correlation between number of injection and change of GC-IPL thickness.

	Delta GC-IPL(um)			Delta GC-IPL(um)(%)		
	Total (n = 52) Co	Ranibizumab (n = 23) Co	Aflibercept (n = 29) Co	Total (n = 52) Co	Ranibizumab (n = 23) Co	Aflibercept (n = 29) Co
Number of injection	0.19 (*P* = .16)	0.24 (*P* = .26)	0.35 (*P* = .06)	0.17 (*P* = .22)	0.19 (*P* = .36)	0.32 (*P* = .09)

Co = coefficient, GC-IPL = ganglion cell-inner plexiform layer. *Statistically significant.

Table 7

Correlation between follow-up period and change of GC-IPL thickness.

	Delta GC-IPL(um)			Delta GC-IPL(um)(%)		
	Total (n = 52) Co	Ranibizumab (n = 23) Co	Aflibercept (n = 29) Co	Total (n = 52) Co	Ranibizumab (n = 23) Co	Aflibercept (n = 29) Co
Follow-up Period	0.07 (*P* = .61)	0.06 (*P* = .76)	0.03 (*P* = .85)	0.08 (*P* = .55)	0.06 (*P* = .77)	0.04 (*P* = .80)

Co = coefficient, GC-IPL = ganglion cell-inner plexiform layer. *Statistically significant.

layers in eyes with inhibition of VEGF. Lee and Yu[23] reported that the GC-IPL and RNFL thicknesses were smaller in eyes with dry AMD than in controls. Zucchiatti et al[24] reported that eyes with exudative AMD had reduced RNFL thickness and GCL thickness. Recently, Muftuoglu et al[25] reported preservation of the RNFL and GCL in patients with dry AMD. However, patients with dry AMD showed involvement of the inner plexiform layer with disease progression. Muftuoglu et al[25] considered that the cause is trans-synaptic degeneration with loss of dendrites and that the parafoveal inner plexiform and ganglion cell layers are vulnerable to the changes that occur in dry AMD. Saha et al[26] have raised the possibility that the retinal photoreceptors and cells in the inner retinal layers are chronically hypoperfused and ischemic as a result of the microvascular choroidal damage in AMD. Lee at al[19] reported that the number of anti-VEGF injections, type of anti-VEGF agent administered, and duration of anti-VEGF injections were not associated with the rate of GC-IPL thinning. In the present study, we investigated the correlation between the number of anti-VEGF injections and change in the thickness of the GC-IPL to evaluate the effect of anti-VEGF injection on the inner retinal layer. We found no statistically significant correlation, but did find a positive correlation that was almost significant in the aflibercept group (coefficient = 0.35, $P = .06$). We also investigated the correlation between duration of follow-up and the change in GC-IPL thickness to identify the effect of AMD itself on the inner retinal layer. There was no significant correlation and the coefficient was in the range of 0.03–0.07. Therefore, it is likely that thinning of the GC-IPL in patients treated with anti-VEGF agents is the result of the effect of these agents rather than AMD itself. Moreover, we cannot exclude the possibility that the effects of anti-VEGF on normal microvascular structures are responsible for the decrease in the microvasculature of the GC-IPL. In the future, microvascular studies using OCT angiography may be helpful to address this issue.

The present study had some limitations, mainly because of its retrospective design and small sample size. Furthermore, the automated segmentation software used in the OCT unit may have shown scan artifacts and errors in the retinal layers. Segmentation errors are more common than operator-related errors, which would likely introduce bias, including overestimation or underestimation of the thickness of the inner retinal layers. Lee et al[27] suggested that these errors are likely to be more frequent in the presence of retinal disease. In the present study, to minimize these errors, we carefully checked all the scans to ensure accurate delineation of each retinal layer. Further studies should identify changes in the microvasculature of the inner retinal layers by using OCT angiography during repeated treatment with anti-VEGF agents.

In conclusion, patients with exudative AMD who underwent repeated anti-VEGF treatment showed a decrease in the thicknesses of the RNFL and GC-IPL. This was more likely to be the effect of the anti-VEGF injection than trans-synaptic degeneration of ganglion cell dendrites with loss of photoreceptors or chronic hypoperfusion and ischemia of the retinal photoreceptors because of microvascular choroidal damage. Further studies should aim to identify changes in the microvasculature of the inner retinal layers using OCT angiography during repeated treatment with anti-VEGF agents.

Author contributions

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