

# Retinal Ganglion Cell Layer Change in Patients Treated With Anti-Vascular Endothelial Growth Factor for Neovascular Age-related Macular Degeneration



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- **PURPOSE:** To evaluate macular retinal ganglion cell thickness in patients with neovascular age-related macular degeneration (AMD) and intravitreal anti-vascular endothelial growth factor (VEGF) therapy.
- **DESIGN:** Retrospective case series with fellow-eye comparison.
- **METHODS:** Patients with continuous unilateral anti-VEGF treatment for subfoveal and juxtafoveal neovascular AMD and a minimum follow-up of 24 months were included. The retinal nerve fiber (RNFL) and retinal ganglion cell layer (RGCL) in the macula were segmented using an ETDRS grid. RNFL and RGCL thickness of the outer ring of the ETDRS grid were quantified at baseline and after repeated anti-VEGF injections, and compared to the patients' untreated fellow eye. Furthermore, best-corrected visual acuity (BCVA), age, and retinal pigment epithelium (RPE) atrophy were recorded and correlated with RNFL and RGCL.
- **RESULTS:** Sixty eight eyes of 34 patients (23 female and 11 male; mean age 76.7 (SD  $\pm$  8.2) with a mean number of 31.5 (SD  $\pm$  9.8) anti-VEGF injections and a mean follow-up period of 45.3 months (SD  $\pm$  10.5) were included. Whereas the RGCL thickness decreased significantly compared to the noninjected fellow eye ( $P = .01$ ), the decrease of the RNFL was not significant. Visual acuity gain was significantly correlated with RGCL thickness ( $r = 0.52$ ,  $P < .05$ ) at follow-up and negatively correlated ( $r = -0.41$ ,  $P < .05$ ) with age. Presence of RPE atrophy correlated negatively with the RGCL thickness at follow-up ( $r = -0.37$ ,  $P = .03$ ).
- **CONCLUSION:** During the course of long-term anti-VEGF therapy there is a significant decrease of the RGCL in patients with neovascular AMD compared to the fellow (untreated) eye. (Am J Ophthalmol 2016;167:10–17. © 2016 The Authors. Published by

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**A**GE-RELATED MACULAR DEGENERATION (AMD) IS one of the leading causes of visual impairment in individuals over the age of 55 years in developed countries.<sup>1</sup> The neovascular form of AMD, with vascular endothelial growth factor (VEGF) as one of the key factors, causes severe and irreversible vision loss, frequently resulting in legal blindness.<sup>2,3</sup> In recent years, VEGF inhibition by anti-VEGF antibodies has significantly improved visual outcomes in patients with neovascular AMD. However, in many patients with neovascular AMD anti-VEGF needs to be continuously administered over many years to persistently suppress disease activity and maintain visual function.

The need for long-term treatment with anti-VEGF agents has also become evident in the extension studies, where long-term outcomes 7-8 years after initiation of intensive ranibizumab therapy suggest that many patients require long-term treatment with anti-VEGF agents.<sup>4</sup> However, despite the beneficial effect of anti-VEGF therapy, long-term side effects are not clarified yet and are a matter of ongoing controversy. There is evidence that repeated long-term anti-VEGF treatment may accelerate atrophy of different ocular tissues. Retinal pigment epithelium atrophy,<sup>5</sup> as well as scleral thinning, has been reported.<sup>6</sup> In the last years, several studies have investigated the effect of intravitreal anti-VEGF injections on the peripapillary retinal nerve fiber layer (RNFL). There exists some controversy regarding the effect of anti-VEGF agents on retinal ganglion cells (RGCs). In mice, some reports suggest severe damage to RGCs after local treatment with VEGF binding agents,<sup>7</sup> while another report did not find any changes within the retinal ganglion cell layer (RGCL) after VEGF receptor blockade in mice.<sup>8</sup> Because most studies have analyzed peripapillary optical coherence tomography (OCT) scans, these reports have focused on RNFL change after anti-VEGF treatment. However, several studies focusing on glaucoma patients have shown that RGCL thickness

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Accepted for publication Apr 5, 2016.

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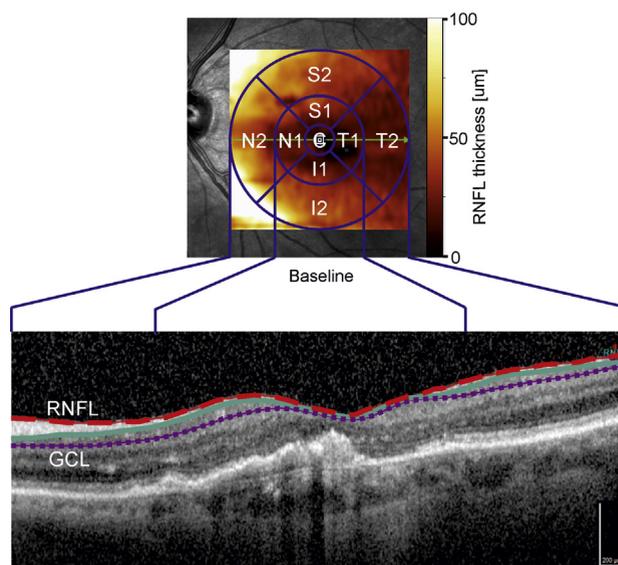
changes may be a more sensitive marker for global and regional visual field sensitivities.<sup>9,10</sup>

In the present study, we investigated RNFL and RGCL changes in the macular area in eyes receiving long-term intravitreal anti-VEGF treatment for neovascular AMD using spectral-domain optical coherence tomography (Spectralis SDOCT; Heidelberg Engineering, Heidelberg, Germany) and automated segmentation of macular scans.

## METHODS

THIS STUDY IS AN INSTITUTIONAL RETROSPECTIVE CASE SERIES with fellow-eye comparison and was conducted in accordance with the Declaration of Helsinki and approved by the local Ethics Committee (KEK-Nr. 093/13). Medical records of the Department of Ophthalmology at the University Hospital Bern, Bern, Switzerland, were screened for patients with exudative AMD under continuous anti-VEGF treatment. The need for written consent from each individual patient was waived because of the retrospective nature of the study. All data used in this study were collected as part of the normal treatment protocol. Study data were collected and managed using the REDCap electronic data management tool hosted at our institution. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies.<sup>11</sup> Patients were included in this retrospective study if they had unilateral exudative AMD and had received at least 15 injections of bevacizumab (Avastin; Genentech, South San Francisco, California, USA), ranibizumab (Lucentis; Genentech, South San Francisco, California, USA), and/or aflibercept (Eylea; Regeneron, Tarrytown, New York, USA) with a minimum of 24 months of follow-up with the Spectralis OCT using the rescan mode. Patients with bilateral exudative AMD and previous therapy such as photodynamic therapy and laser photocoagulation in the study or fellow eye were excluded. Patients with signs of diabetic retinopathy or glaucoma or a history of ocular hypertension were excluded because this may have confounded the results of retinal layer segmentation. Demographic data, best-corrected visual acuity (BCVA), number of intravitreal injections and administered anti-VEGF agents, duration of treatment, and intraocular pressure (IOP) were recorded.

• **IMAGE ACQUISITION AND EVALUATION:** For OCT imaging a spectral-domain (SD)-OCT (Heidelberg Engineering, Dossenheim, Germany) was used. Images were acquired using image alignment eye-tracking software (TruTrack; Heidelberg Engineering) to obtain foveal volumetric retinal scans with 49 parallel B-scans consisting of 512 A-scans separated by 120  $\mu\text{m}$  covering a volume of  $20 \times 20$  degrees, whereby each B-scan was averaged 9 times



**FIGURE 1.** Infrared images and retinal layer segmentation with optical coherence tomography (OCT); co-localized infrared image of a representative patient with average thickness of the retinal nerve fiber layer (RNFL) in each quadrant at baseline (Top), where C = central ring and T = temporal, I = inferior, N = nasal, and S = superior quadrants of the inner (1) and outer (2) ring of the ETDRS grid. (Bottom) Representative OCT image of inner retinal layers, where the red, dashed line represents the internal limiting membrane, the turquoise line represents the boundary between the RNFL and the retinal ganglion cell layer (RGCL), and the purple, dotted line represents the boundary between RGCL and inner plexiform layer.

(automated real-time repetition rate = 9).<sup>6</sup> The baseline was chosen to be the time point, when SD-OCT was introduced in our clinic with the AutoRescan follow-up function available. For retinal layer segmentation the inbuilt Heidelberg Eye Explorer version 1.9.10.0 (Heidelberg Engineering) was used to measure the RNFL and RGCL thickness (Figure 1). Segmentation data were reviewed by 2 experienced graders and adjusted manually if necessary. The graders were not masked to which eye received anti-VEGF therapy, because the neovascular component was clearly evident in the OCT scans. Respective parameters were evaluated at baseline and at last follow-up visit. Heidelberg Eye Explorer segments 11 different retinal boundaries: the inner limiting membrane (ILM); the boundaries between the RNFL and the RGCL, between the RGCL and the inner plexiform layer (IPL), between the IPL and the inner nuclear layer (INL), between the INL and the outer plexiform layer (OPL), and between the OPL and the outer nuclear layer (ONL); the external limiting membrane (ELM); 2 photoreceptor layers (PR1/2); the retinal pigment epithelium (RPE); and the basal membrane (BM) with the underlying choroid. Based on this segmentation algorithm the area between the ILM

**TABLE 1.** Demographics and Clinical Characteristics of Patient Cohort

Demographic Features	Study Eyes (n = 34)	Fellow Eyes (n = 34)	P <sup>a</sup>
Mean age ± SD, y	76.7 ± 8.2	76.7 ± 8.2	
Sex, F/M	23/11	23/11	
Follow-up time, mean ± SD (mo)	45.3 ± 10.5	44.1 ± 11.3	.1012
Number of injections, mean ± SD	31.5 ± 9.8	0 ± 0.0	<.0001*
BCVA (ETDRS) at BL, mean ± SD	61.5 ± 18.4	75.5 ± 20.9	.0066*
BCVA (ETDRS) at FU, mean ± SD	57.9 ± 20.2	67.9 ± 21.9	.0517
IOP (mm Hg) at BL, mean ± SD	15.0 ± 3.1	15.0 ± 2.7	.9424
IOP (mm Hg) at FU, mean ± SD	14.8 ± 3.0 SD	15.3 ± 2.9 SD	.1215
AREDS category 4	34	2	
AREDS category 3	0	15	
AREDS category 2	0	15	
AREDS category 1	0	2	

AREDS = Age-Related Eye Disease Study; BCVA = best-corrected visual acuity; BL = baseline; FU = follow-up; IOP = intraocular pressure.

AREDS categories: 4 = presence of neovascular age-related macular degeneration or geographic atrophy involving the central subfield; 3 = presence of large drusen (>125 μm) and/or geographic atrophy outside the central foveal subfield; 2 = intermediate drusen (<125 μm) and/or retinal pigment epithelial abnormalities; 1 = none or small drusen (<63 μm).

<sup>a</sup>Significant difference ( $P < .05$ ) in Student *t* test between study eye and fellow eye. Asterisk indicates statistically significant differences.

and the RNFL segmentation line (= mean RNFL thickness) and the area between the RNFL and RGCL segmentation line (= mean RGCL thickness) were automatically calculated by the inbuilt software. Mean RNFL and RGCL thickness of the outer ring (OR;  $r = 3$  mm) was calculated using the implemented ETDRS grid. For further analyses SDOCTs were graded for the presence and/or development of RPE atrophy and the area of RPE atrophy measured in the infrared image.

• **STATISTICS:** Statistical analyses were performed using GraphPad Prism and R (GraphPad Prism 6; GraphPad Software, LaJolla, California, USA; [www.r-project.org](http://www.r-project.org)). In order to compare the segmentation data of the outer ring between study and fellow eyes a 1-way analysis of variance (ANOVA) with Holm-Sidak multiple comparisons test was employed. Differences between groups were analyzed using an unpaired 2-tailed Student *t* test (GraphPad Prism 6; GraphPad Software). Square root transformation was used to analyze RPE atrophy data.

**TABLE 2.** Injections and Eye Characteristics

	Study Eyes (n = 34)	Fellow Eyes (n = 34)	P <sup>a</sup>
Number of injections	31.6 ± 9.8 SD	0 ± 0.0	<.0001 <sup>b,*</sup>
Number of injections at study entry	13.4 ± 10.2	0 ± 0.0	<.0001 <sup>b,*</sup>
Total number of injections at FU	44.9 ± 12.3	0 ± 0.0	<.0001 <sup>b,*</sup>
Duration from BL to FU (mo)	45.3 ± 10.5	44.1 ± 11.3	.1012 <sup>b</sup>
Total duration of therapy (mo)	67.1 ± 14.6	66.0 ± 14.6	.1012 <sup>b</sup>
Outer ring	36.4 ± 8.1	36.2 ± 6.5	.9725 <sup>c</sup>
RNFL thickness at baseline (μm)			
RNFL thickness at follow-up (μm)	32.2 ± 6.4	36.8 ± 6.9	.0438 <sup>c,*</sup>
RGCL thickness at baseline (μm)	29.6 ± 6.6	32.9 ± 5.4	.0681 <sup>c</sup>
RGCL thickness at follow-up (μm)	25.3 ± 6.5	31.0 ± 5.2	.0006 <sup>c,*</sup>

BL = baseline; FU = follow-up; RGCL = retinal ganglion cell layer; RNFL = retinal nerve fiber layer.

Data are mean ± SD.

<sup>a</sup>Asterisk indicates statistically significant differences.

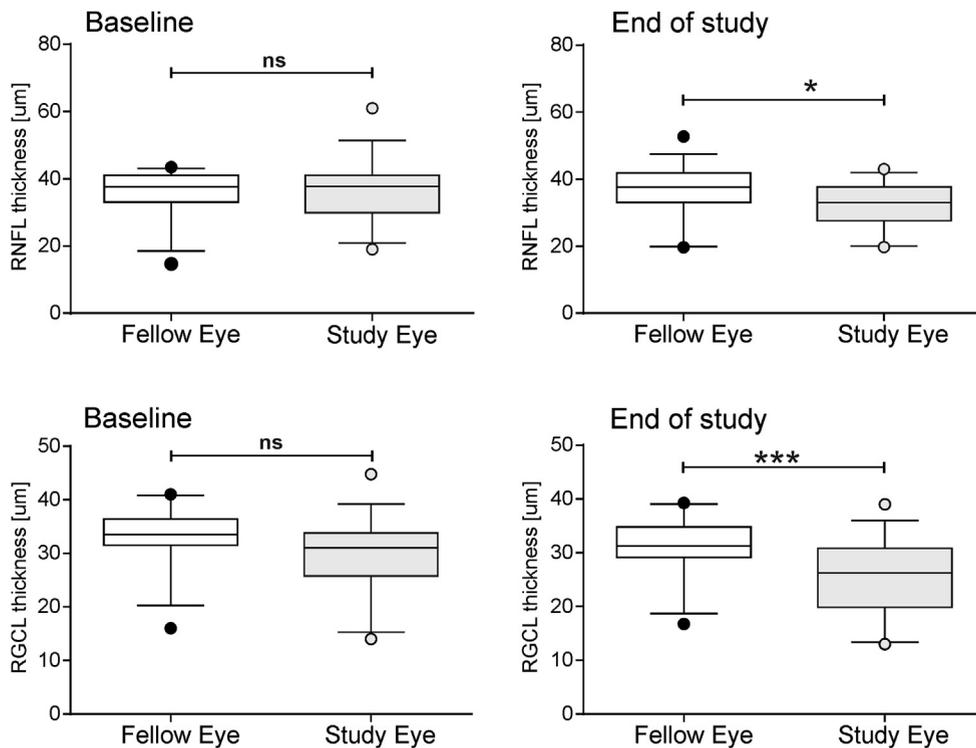
<sup>b</sup>Student *t* test between study eye and fellow eye.

<sup>c</sup>Ordinary 1-way analysis of variance with Holm-Sidak multiple comparisons.

Furthermore, the association between BCVA, age, RPE atrophy, and RNFL and RGCL decrease was investigated by calculating pairwise correlations. Pearson or Spearman correlation was used according to the D'Agostino & Pearson omnibus normality test. *P* values < .05 were considered statistically significant. Values are given in mean ± standard deviation.

## RESULTS

THIS WAS A RETROSPECTIVE STUDY OF 34 PATIENTS (23 women) with a mean age of 76.7 ± 8.2 years with fellow eye comparison. Mean ETDRS BCVA of the study eyes at baseline was 61.5 ± 18.4 letters. Mean ETDRS BCVA at the last follow-up visit was 57.9 ± 20.2 letters. The mean change in BCVA over the course of the study period was -3.7 ± 4.8 letters, which was not statistically significant ( $P = .45$ , *t* test). The mean number of anti-VEGF injections was 31.5 ± 9.8 (min.: 15; max.: 59 injections) and the mean treatment period between baseline and follow-up was 45.3 ± 10.5 months (min.: 25.6; max.: 73.3 months). IOP at baseline and at last follow-up visit as well as AREDS



**FIGURE 2.** Effect of continuous anti-vascular endothelial growth factor (VEGF) treatment on the retinal nerve fiber layer (RNFL) and the retinal ganglion cell layer (RGCL). Box-and-whisker plots of RNFL thickness of the study eye and fellow eye at baseline (Top left) and after treatment (end of study) with anti-VEGF for neovascular age-related macular degeneration (Top right). Box-and-whisker plots of RGCL thickness at baseline (Bottom left) and after treatment with anti-VEGF for neovascular age-related macular degeneration (Bottom right). ns = not significant; \* $P < .05$ , \*\*\* $P < .001$ ;  $P$  values are adjusted for multiple comparisons.

categories for the study and fellow eyes according to AREDS report number <sup>612</sup> are summarized in Table 1. The study eye received on average a mean number of  $13.4 \pm 10.2$  injections during a mean of  $20.7 \pm 4.1$  months prior to the study baseline visit; thus a mean of  $44.9 \pm 12.3$  injections during a mean of  $67.1 \pm 14.6$  months were administered overall (Table 2).

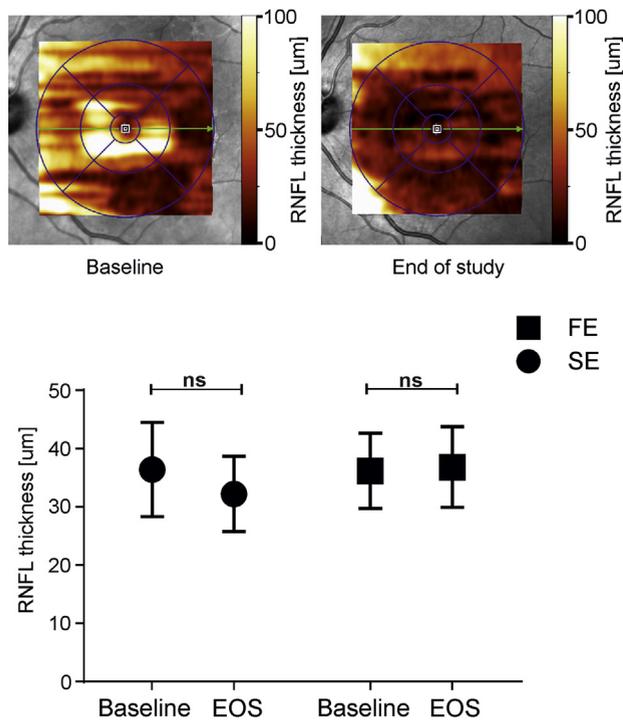
• **RETINAL GANGLION CELL LAYER AND RETINAL NERVE FIBER LAYER THICKNESS AT BASELINE:** At baseline, the RGCL thickness in the outer ring of the ETDRS grid was slightly thinner in the study eye ( $29.6 \pm 6.6 \mu\text{m}$ ) compared with the fellow eyes ( $32.9 \pm 5.4 \mu\text{m}$ ); however, this was not statistically significant (Figure 2, Bottom left). The RNFL thickness did not show significant differences between study and untreated fellow eyes at baseline ( $36.4 \pm 8.1 \mu\text{m}$  vs  $36.2 \pm 6.5 \mu\text{m}$ ) (Figure 2, Top left).

• **RETINAL GANGLION CELL LAYER AND RETINAL NERVE FIBER LAYER THICKNESS AT THE END OF THE STUDY:** At end of the study the RGCL was significantly thinner in the study eye ( $25 \pm 6.5 \mu\text{m}$ ) compared to untreated fellow eyes ( $31.0 \pm 5.2 \mu\text{m}$ ) ( $\Delta -5.8 \mu\text{m}$ ,  $P < .001$ , Holm-Sidak) (Figure 2, Bottom right). The RNFL thickness in the treated study eyes, at  $32.2 \pm 6.4 \mu\text{m}$ , was significantly

thinner compared to the untreated fellow eyes, at  $36.8 \pm 6.9 \mu\text{m}$  ( $\Delta -4.6 \mu\text{m}$ ,  $P = .04$ , Holm-Sidak) (Figure 2, Top right).

• **CHANGE OF RETINAL GANGLION CELL LAYER AND RETINAL NERVE FIBER LAYER DURING THERAPY WITH ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR:** In the fellow eyes (controls) there were no significant longitudinal changes in either the RNFL thickness or RGCL thickness, which decreased by  $-0.7 \mu\text{m}$  ( $P = .97$ , Holm-Sidak) (Figure 3) and  $-1.4 \mu\text{m}$  ( $P = .34$ , Holm-Sidak), respectively (Figure 4). In the study eyes, RGCL thickness showed a significant decrease between baseline and last follow-up in the outer ETDRS ring (RGCL:  $\Delta -4.4 \pm 0.9 \mu\text{m}$  [SE of diff.],  $P = .01$ ) (Figure 4), whereas the change in RNFL did not reach statistical significance (RNFL:  $\Delta -4.2 \pm 1.5 \mu\text{m}$  [standard error of difference],  $P = .07$ ) (Figure 3).

• **CORRELATION OF AGE, VISUAL ACUITY MEASUREMENTS, INJECTIONS, AND RETINAL PIGMENT EPITHELIUM ATROPHY:** Visual acuity gain and RGCL thickness at the last follow-up were positively correlated ( $P = .01$ ,  $r = 0.44$ ) (Figure 5). There were weak but not significant correlations between visual gain and decrease of RNFL

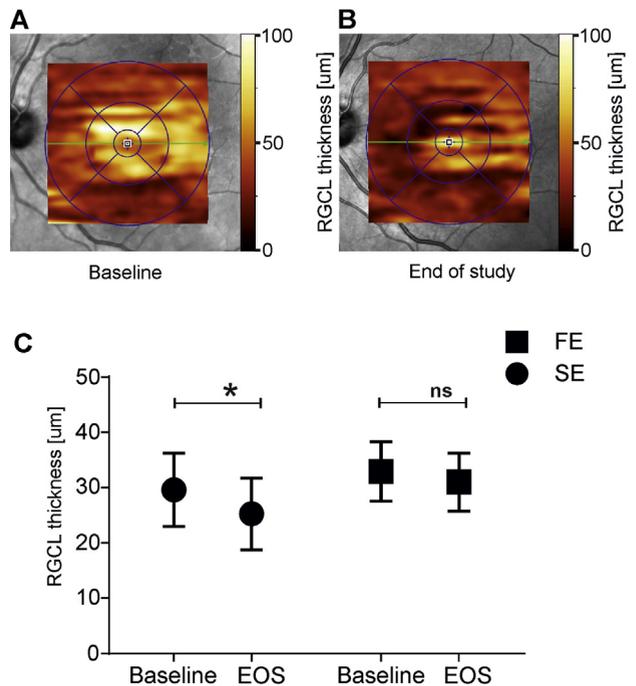


**FIGURE 3.** Representative map of retinal nerve fiber layer (RNFL) thickness within the ETDRS grid at baseline (Top left) and after treatment with anti-vascular endothelial growth factor (VEGF) for neovascular age-related macular degeneration (Top right). Graph showing mean RNFL thickness within the outer ring of the ETDRS grid at baseline and after treatment with anti-VEGF for neovascular age-related macular degeneration for the study eye (SE) and the fellow eye (FE). ns = not significant; *P* values are adjusted for multiple comparisons.

( $P = .33$ ,  $r = -0.17$ ) and RGCL thickness decrease ( $P = .11$ ,  $r = -0.28$ ), and between the number of injections and the decrease of both the RNFL thickness ( $P = .22$ ,  $r = 0.22$ ) and the RGLC thickness ( $P = .34$ ,  $r = -0.17$ ). The age of the patients correlated negatively with the visual gain and the RGCL thickness at follow-up ( $P = .03$ ,  $r = -0.4$ ). As expected, the correlation between the RNFL thickness and the RGCL thickness at follow-up ( $P < .0001$ ,  $r = 0.72$ ) was high. The number of injections showed no significant correlation with the RNFL thickness at follow-up ( $P = .53$ ,  $r = -0.1$ ) or with the RGCL thickness ( $P = .34$ ,  $r = -0.17$ ). Area of macular atrophy correlated negatively with the RGCL thickness at follow-up ( $r = -0.37$ ,  $P = .03$ ).

## DISCUSSION

THIS STUDY REPORTS CHANGES IN THE RGCL AND RNFL OF patients under a continuous and frequent anti-VEGF



**FIGURE 4.** Representative map of retinal ganglion cell layer (RGCL) thickness within the ETDRS grid at baseline (Top left) and after treatment with anti-vascular endothelial growth factor for neovascular age-related macular degeneration (Top right). Graph showing mean RGCL thickness within the outer ring of the ETDRS grid at baseline and after treatment with anti-VEGF for neovascular age-related macular degeneration for the study eye (SE) and the fellow eye (FE). ns = not significant; \* $P < .05$ ; *P* values are adjusted for multiple comparisons.

treatment regimen for exudative AMD. We report significant changes in the RGCL with a decrease of around 15% after an average of 31.5 injections and a follow-up period of 45 months compared to 6% in the untreated fellow eye. This is, to our knowledge, the first report investigating changes in the RGCL layer after repeated injections with anti-VEGF.

Although this change may not be clinically significant for patients at this stage, there may be functional changes resulting from RGCL thinning over longer follow-up periods. In addition, it may be of clinical relevance for patients suffering from other diseases that impair the RGCL, such as glaucoma, a common disease in this age group.

There are ambiguous data about the effect of anti-VEGF therapy on RNFL, with only 1 study reporting significant decrease of RNFL after 1 year of anti-VEGF treatment.<sup>13</sup> The longest follow-up in most of the published studies on the association between RNFL changes and anti-VEGF treatment is around 2 years (Table 3). Most of these studies did not find a correlation of RNFL change with anti-VEGF therapy, and this is in keeping with our data.<sup>14-18</sup> However,

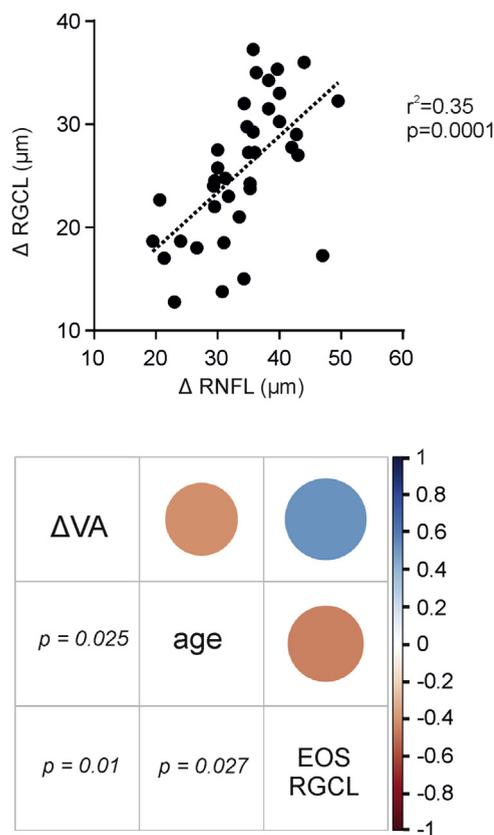


FIGURE 5. (Top) Graph showing the correlation between retinal nerve fiber layer thickness change ( $\Delta RNFL$ ) and retinal nerve fiber layer change ( $\Delta RGCL$ ) (Spearman correlation). (Bottom) Correlation matrix with visual acuity gain ( $\Delta VA$ ), age, and thickness of retinal ganglion cell layer (RGCL) after treatment with anti-vascular endothelial growth factor. EOS = end of study.

because these studies analyzed the peripapillary RNFL, there are so far no data on changes of RGCL under continuous anti-VEGF therapy. The RGCL accounts for up to 35% of the retinal thickness of the posterior pole, and therefore changes may be less prone to segmentation errors and more pronounced than changes in RNFL.<sup>19</sup> Using automated retinal layer segmentation of the outer ring of the ETDRS grid, we were able to show that, although there is no significant change in RNFL in patients receiving long-term anti-VEGF treatment, there is significant decrease of the RGCL under long-term anti-VEGF treatment.

There are several possible mechanisms that may explain our findings that merit further discussion. In the first instance, it has been shown that the RGCL thickness is affected by AMD. In a cross-sectional study the RGCL thickness was significantly reduced in eyes with recent-onset neovascular AMD compared to healthy control eyes.<sup>20</sup> This reduction could be due to chronically reduced input from damaged photoreceptors

to the ganglion cells, causing apoptosis of the RGCL. This may be reflected in our findings that the presence of macular atrophy correlated positively with RGCL thickness after intravitreal injections with anti-VEGF agents. In our study we did not find a significant decrease of either RNFL or RGCL thickness in eyes with neovascular AMD compared to their fellow eyes with non-neovascular AMD, which is in keeping with recent reports.<sup>20</sup> However, there was a significant decline of RGCL compared to baseline in eyes being intensively treated with anti-VEGF agents.

Secondly, it is well known that intravitreal injections cause short-term pressure elevation in the eye, similar to acute glaucoma.<sup>13,21,22</sup> With IOP reported to rise over 40 mm Hg after intravitreal injection of 0.05 mL,<sup>23</sup> RGCLs may be damaged by the pressure spikes, and this may explain the significant change in RGCL thickness after repeated injection. The effect of repeated IOP fluctuations has been confirmed in a rabbit model, where 9 anti-VEGF injections at 14-day intervals induced RNFL damage.<sup>24</sup>

Lastly, it has been shown that VEGF-A signaling via VEGFR-2 inhibits caspase-3 activation and that VEGF-A acts as a survival factor for RGCs.<sup>7,25</sup> A recent report has shown increased apoptosis of RGCs after anti-VEGF treatment by TUNEL staining in diabetic rats.<sup>26</sup> Furthermore, VEGF inhibitors such as bevacizumab have been shown to block the protective effect of VEGF on RGCs in an in vitro model of oxidative stress.<sup>27</sup> As such, repeated exposure to anti-VEGF agents may affect the neurophysiologic role of VEGF and therefore may impair RGC homeostasis.

Although we cannot exclude the possibility that the RGCL decrease is attributable to the natural course of the disease, the decrease of RGCL during intensive anti-VEGF treatment with relative stability of the disease would suggest that our observed changes may be at least partly explained by the anti-VEGF treatment. This study has limitations owing to its retrospective nature. Furthermore, the effect size of our observations is relatively small and therefore is unlikely to be clinically significant, and there was no dose-response effect. However, there was a weak correlation between the number of injections and the decrease of RNFL and RGCL, and as such this study may have been underpowered to detect a significant correlation between intravitreal injections and RGCL change. Furthermore, there may be putative differences in susceptibility of RGCs to intravitreal injections.

To our knowledge, this report constitutes the first study in the literature evaluating longitudinal changes of RNFL and RGCL during repeated treatment with anti-VEGF agents. Further studies should identify patients at risk for RGC damage, such as patients with a history of glaucoma.

**TABLE 3. Study Review**

Author	Number of Patients	RNFL BL ( $\mu\text{m}$ ) (Mean $\pm$ SD)	RNFL FU ( $\mu\text{m}$ ) (Mean $\pm$ SD)	<i>P</i> <sup>a</sup>	Number of Injections (Mean $\pm$ SD)	Duration (mo) (Mean $\pm$ SD)
Parlak et al (2014) <sup>14</sup>	22	101.4 $\pm$ 14.2	99.9 $\pm$ 14.5	.814	4.86 $\pm$ 2.18	12 $\pm$ 0.0
Demirel et al (2014) <sup>15</sup>	29	92.3 $\pm$ 7.7	92.46 $\pm$ 8.1	.379	13.88 $\pm$ 3.81	38.9 $\pm$ 15.5
Shin et al (2014) <sup>16</sup>	82	98.0 $\pm$ 11.7	97.5 $\pm$ 12.1	.577	5.69 $\pm$ 2.7	21.3 $\pm$ 4.1
Sobaci et al (2013) <sup>17</sup> (Ranibizumab)	35	105.3 $\pm$ 6.9	104.6 $\pm$ 8.4	.57	6.3 $\pm$ 1.9	13.6 $\pm$ 2.1
Sobaci et al (2013) <sup>17</sup> (Bevacizumab)	30	105.8 $\pm$ 8.1	104.6 $\pm$ 8.1	.42	5.1 $\pm$ 1.3	14.05 $\pm$ 2.6
Martinez et al (2012) <sup>13</sup>	49	105.7 $\pm$ 12.2	100.2 $\pm$ 11.0	<.001*	4.8 $\pm$ 1.6	12 $\pm$ 0.0
Horsley et al (2010) <sup>18</sup>	37	92.4 $\pm$ 15.2	93.8 $\pm$ 15.2	.68	16.0 $\pm$ 5.5	27.0 $\pm$ 9.7

BL = baseline; FU = follow-up; RNFL = retinal nerve fiber layer.

<sup>a</sup>Difference in Student *t* test between study eye and fellow eye. Asterisk indicates statistically significant difference.

FUNDING/SUPPORT: NO FUNDING OR GRANT SUPPORT. FINANCIAL DISCLOSURES: MARION R. MUNK: CONSULTANT FEES FROM Novartis, Travel Grant from Bayer; Consultant for Lumithera; Andreas Ebnetter: Honoraria from Bayer for lectures, Travel Grant from Allergan; Sebastian Wolf: grants from Swiss National Science Foundation (SNSF); nonfinancial support from Heidelberg Engineering; Consultant or Advisory Board: Alcon, Allergan, Bayer Healthcare, Novartis Pharma, and Roche; Martin S. Zinkernagel: grants from Swiss National Science Foundation (SNSF); nonfinancial support from Heidelberg Engineering; Consultant or Advisory Board: Bayer Healthcare, Novartis Pharma; Stock or equity interests in Novartis Pharma. The following author has no financial disclosures: Marco Beck. All authors attest that they meet the current ICMJE criteria for authorship.

The authors acknowledge the facilities and the scientific and technical assistance of the Department for Clinical Research (DCR) of the University of Bern, Bern, Switzerland.

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