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Branch Retinal Vein Occlusion Causes Topographic Optic Neuropathy and Retrograde Maculopathy

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Abstract

Background To evaluate retinal ganglion cell (RGC) loss and axonal affection in branch retinal vein occlusion (BRVO).

Methods 13 eyes of 12 non-glaucomatous BRVO patients were included. Thickness of peripapillary and macular retinal nerve fiber layer (pRNFL, mRNFL), ganglion cell-inner plexiform layer (GCIPL), inner nuclear layer, outer and total retina were measured at baseline and after a mean follow-up of 14 months. We compared the thickness between the affected and their internal reference regions. Additionally, pRNFL thickness was compared between the occluded and the healthy fellow eyes in the 11 unilateral cases.

Results Significant degeneration of the pRNFL was observed in the affected sector of the BRVO eyes (P < 0.01 versus reference sector and versus fellow eye). In contrast, mRNFL and GCIPL thickness showed no difference between affected and reference regions and no correlation with pRNFL thickness. Degenerative microcystic macular edema (MME) was present in 25% of the eyes with macular edema following BRVO.

Conclusion Axonal degeneration occurs in pRNFL, which suggests that anterograde degeneration is the mechanism of RGC affection in BRVO. Our results emphasized the importance of pRNFL monitoring in BRVO treatment, and considering degenerative MME in persistent edema following BRVO.

Background

Branch retinal vein occlusion (BRVO) is a common type of retinal vein occlusion (RVO) with an incidence of 0.5% to 1.2%.(1, 2) The primary etiology of BRVO is
compression of a branch vein at an arteriovenous crossing with a retinal artery. (3) Although the natural course of BRVO is often favorable, some patients suffer permanent visual impairment, primarily when the macula is affected. About 15% of patients have persistent macular edema with non-improving or even worsening best-corrected visual acuity (BCVA) after 12 months of intravitreal anti-vascular endothelial growth factor (anti-VEGF) treatment. (4) Functional decline results as one consequence of impaired retinal perfusion. (5)

Retinal ganglion cells (RGC) are located in the inner layers of the retina. The cell bodies of the RGCs form part of the ganglion cell layer (GCL), while the axons converge to form the retinal nerve fiber layer (RNFL). The macular axons are conveyed to the super-temporal and infero-temporal sectors of the neuronal rim, whereas foveal axons occupy the papillo-macular bundle. Structurally, the inner plexiform layer (IPL) consists of the synaptic connections between the axons of the bipolar cells and the dendrites of the RGCs. (6) RNFL, GCL and IPL together are referred to as ganglion cell complex (GCC). (7)

There is good clinical evidence that the peripapillary RNFL (pRNFL) as well as the macular GCC are affected after BRVO. Meanwhile, we wonder whether a close spatial relationship exists between the occlusion region and axonal involvement. There are some suggestive findings in existing studies: Kim et al. presented a significant decrease in the pRNFL thickness after BRVO compared to the unaffected fellow eyes. (8) Alshareef et al. also found macular RNFL (mRNFL) and ganglion cell-inner plexiform layer (GC-IPL) significantly thinner in the BRVO eyes than in the healthy fellow or control eyes. (9)

In addition, regional ischemia caused by BRVO, along with potential compression and inflammation may harm axonal function, and eventually induces retrograde
maculopathy. This may be associated with microcystic macular edema (MME), featuring with small vacuoles in the inner nuclear layer (INL) of the macula. (10) MME is believed to be a nonspecific finding possibly caused by impaired fluid absorption due to transcellular Müller cell degeneration, and therefore not sensitive to anti-VEGF treatment. The frequency of MME in BRVO patients has not been investigated. We wonder whether MME could explain some cases of persistent edema after anti-VEGF treatment.

In this study, we comprehensively evaluated the thickness changes of both the pRNFL and individual macular layers after BRVO. The aim was to explore the spatial relationship between the occlusion area and the related axonal degeneration affecting the optic nerve, as well as to investigate retrograde maculopathy in BRVO patients.

Methods
Study design and patients
This retrospective, observational study was approved by the ethics committee (KEK 93/13) of the University of Bern, Switzerland, and was conducted in compliance with the tenets of the Declaration of Helsinki. Given the retrospective design, the need for individual informed consent was waived.

We reviewed the medical records of 347 consecutive RVO patients for inclusion in the institutional database at the Department of Ophthalmology, Bern University Hospital, Switzerland between January 2011 and January 2018. 32 BRVO patients met the eligibility criteria which consisted of (1) ophthalmic examination including slit lamp examination and dilated fundus exam, (2) measurement of BCVA assessment, (3) measurement of intraocular pressure (IOP) measurement by
Goldman applanation tonometry, (4) color fundus photograph and spectral-domain optical coherence tomography (SD-OCT) imaging for both peripapillary and macular scans of both eyes. Of these patients, 19 cases had to be excluded due to either glaucoma history (8) or loss to follow-up (11).

**SD-OCT imaging and analysis**

One peripapillary and one macular cube scan per session had been acquired using high-speed resolution mode with SD-OCT (Spectralis HRA + OCT; Heidelberg Engineering, Heidelberg, Germany). Peripapillary scans were obtained with the following settings: center on the optic nerve head, 12° circle diameter, size $X = 768$ pixels, size $Z = 496$ pixels. Macular scans were obtained with the following settings: centered on the fovea, 20° scan angle, size $X = 512$ pixels, size $Z = 496$ pixels, number of horizontal B-scans = 49, pattern size $= 20° \times 20°$ and regular distance between B-scans of 120 $\mu m$.

We analyzed pRNFL thickness in both eyes of all included patients. Considering that occlusion of nasal veins has little or no effect on macular function, we only analyzed individual macular thickness changes in the cases with involvement of temporal and macular venous branches.

pRNFL thickness data were acquired from the inbuilt software (Heyex; Heidelberg Engineering GmbH, Heidelberg, Germany). Thickness was measured in 6 peripapillary sectors: temporal ($315°-45°$), supero-temporal ($45°-90°$), supero-nasal ($90°-135°$), nasal ($135°-225°$), infero-nasal ($225°-270°$) and infero-temporal ($270°-315°$). Global pRNFL thickness was calculated by averaging the results over the entire $360°$ measurement circle. Based on the known anatomical distributions of nerve fibres in the retina, one sector of pRNFL was matched to the area affected by BRVO. Since the pRNFL thickness profile for anatomical reasons is characterized by
horizontal symmetry, (11, 12) the horizontally opposite sector was chosen as the reference sector (e.g., infero-temporal reference sector for supero-temporal sector with damage). (Fig. 1)

The Orion software (Voxeleron LLC, San Francisco, USA) was used to analyze retinal thickness of the macular area. The software automatically recognized different retinal tissue interfaces, followed by manually correction by two independent, experienced retina specialists (SY, XL) if necessary. These interfaces allowed the software to calculate the thickness of the following retinal structures: total retina, mRNFL, GCIPL, INL and outer retinal layers (ORL). Thickness was measured in the fovea and four macular quadrants: supero-nasal, infero-nasal, supero-temporal and infero-temporal. The specific quadrants or hemifields with signs of venous occlusion (such as retinal edema, hemorrhages, cotton wool spots, hard exudates, etc.) were defined as the affected regions. The horizontally opposite quadrants or hemifields were used as reference regions. Average thickness was computed by averaging the results over the entire macular cube.

We subsequently calculated internal reference ratios of the pRNFL and individual macular layers to reflect the relative thickness differences between the affected area and the reference area. The ratios were computed as the thickness of the affected area divided by the thickness of the reference area.

Statistical analyses

SPSS (IBM, SPSS statistics, Version 25; SPSS Inc, Chicago, IL) was used for statistical analysis. Numeric data were presented as mean ± standard deviation and analyzed by Student’s t-test. Correlations between affected pRNFL and macular layers thickness were analyzed by Spearman’s correlation. P values of <.05 were considered statistically significant.
Results

Final analysis was performed in a sample of 13 eyes of 12 patients with a mean follow-up interval of 13.9 ± 5.8 months. Baseline characteristics are summarized in Table 1.

Macular edema outcome

All occluded veins were located in the superior hemifield, affecting 1 macular branch, 1 nasal branch and 11 temporal branches. The patient with macular branch occlusion had mild macular edema at baseline and did not require treatment.

Macular edema did not occur in the nasal branch case.

The 11 eyes with temporal branch occlusion all presented with macular edema at baseline and received 8.5 ± 4.6 anti-VEGF injections during the follow-up. After anti-VEGF treatment, macular edema resolved in 7 eyes (64%). Mean BCVA significantly increased with treatment by two lines to 0.22 ± 0.28 logMAR (P = .010).

However, macular edema presented in four eyes at the end of observation. In three eyes, persistent macular edema was restricted to the INL and deeper retinal layers. These eyes showed bigger cysts in the ORL, accompanied with small vacuoles in the INL, which indicated MME (Fig. 2). BCVA greatly improved in two cases (.20 to 0 logMAR and .50 to 10 logMAR, respectively) and remained stable in the other one (.40 logMAR). One eye had recurrent diffuse edema in the entire retina, and suffered a decline of BCVA from .50 to .70 logMAR.

Peripapillary RNFL thickness changes

Comparisons for pRNFL thickness parameters are summarized in Table 2 (depicted in Fig. 3). The pRNFL thickness at baseline was similar in the affected and reference sectors (133.9 ± 35.2 μm vs 130.2 ± 28.4 μm, P = .711). During follow-up, the
pRNFL thickness significantly decreased in both the affected and the reference sectors, however, the decrease in the affected sector was more pronounced and thickness dropped from 133.9 ± 35.2 μm to 95.8 ± 21.8 μm (P = .010). This resulted in a significant decline of the internal reference ratio from 1.05 ± .23 to 0.82 ± .28 (P = .008), and a significant difference in the thickness at endpoint between the affected and reference sectors (95.8 ± 21.8 μm vs 124.9 ± 27.5 μm, P = .006). The global thickness significantly decreased from 101.2 ± 19.8 μm to 86.2 ± 13.4 μm (P = .004).

We additionally analyzed the pRNFL thickness changes in the fellow eyes of the 11 unilateral BRVO patients (Fig. 4). In the affected eyes, in additional to the affected sector (supero-temporal), pRNFL thickness significantly decreased after the follow-up in the supero-nasal, nasal, infero-temporal, and temporal sectors (P < .05). No significant thickness change was observed in the control eyes.

We compared the thickness between the affected and fellow eyes. At baseline, thickness was greater in the affected eyes in all sectors than in the control eyes. Besides, the differences in the nasal and temporal sectors were significant (P = .044,.004, respectively). However, thickness at endpoint in the affected sector (supero-temporal) of the affected eyes were significantly thinner than of the control eyes (P = .030).

**Thickness changes of individual macular layers**

Macular thickness change trends were completely different from the pRNFL (Table 3, visualized in Fig. 5). Thickness in the affected regions was significantly greater than in the reference regions of all layers at baseline. During the follow up, the affected regional thickness decreased in all layers, and significantly in the total retina, the mRNFL, the GCIPL, and the ORL. Meanwhile, the reference regional thickness was
stable in all individual layers. This resulted in the comparable thickness of the affected regions and the reference regions at endpoint in the total retina, the RNFL, the GCIPL, and the INL. The significant difference between the regional thickness was only found in the ORL at endpoint (P = .034).

The internal reference ratios of all individual layers decreased throughout the observational period, while the ratios at endpoint were greater in the outer retina than in the inner retina. The most significant changes occurred in the mRNFL and the GCIPL, with significantly decreased internal reference ratios from 1.41 ± .18 to 1.04 ± .21 (P < .001) and from 1.24 ± .12 to 1.05 ± .20 (P = .010), respectively. The average thickness changes were similar to the affected regional thickness changes, namely significantly decreasing in the total retina, the mRNFL, the GCIPL, and the ORL (P = .003, .002, .037, .004, respectively).

We did not observed any significant correlation between the thickness of the affected sectoral pRNFL and the affected regional RGC-related layers (mRNFL, GCIPL or GCC) at baseline or endpoint.

Discussion

In this study, we comprehensively analyzed the thickness changes of both the pRNFL and individual macular layers after BRVO. We observed distinctly different changing trends between the two retinal components.

The global pRNFL thickness decreased significantly after BRVO in our study. This is similar to some findings from previous publications.(13, 14) Besides, we introduced an internal reference for the sectoral thickness analysis on the basis of the horizontal symmetry of the pRNFL.(11, 12) Our results showed that pRNFL thickness were comparable between the affected sector and the reference sector shortly after
BRVO, followed by a significant decrease in the both sectors. Noticeably, the
decrease in the affected sector was much more drastic and led to a significant
thickness difference between the two sectors about 14 months after BRVO.
The comparison between the affected and control eyes revealed more details about
sectoral pRNFL thickness changes. We noticed the pRNFL thickness was greater in
the affected eyes than the control eyes in all sectors at baseline. After significant
general thickness decrease in the affected eyes, the differences disappeared in all
sectors except the supero-temporal sector. In this sector, pRNFL thickness became
significantly thinner in affected compared to control eyes.
Sectoral pRNFL thickness has been analyzed in two cross-sectional studies.(8, 15)
They found the affected sectoral pRNFL thickness was significantly thinner in the
affected eyes compared to the fellow eyes 12 and 20 months after BRVO. Choosing
fellow eyes as single controls has limitations: pRNFL thickness in the fellow eyes
may also affected by some systematic RVO pathogenic mechanism.(16) Besides,
since the lesions are only regional in BRVO cases, comparing to the fellow eyes
neglects the different regional changes of the eye with BRVO. Our results with
internal reference and fellow eye reference provided a comprehensive illustration
for pRNFL thickness change after BRVO.
The baseline thickness increased due to the general RNFL edema shortly after
BRVO. The edema was non-specific and involved non-affected sectors. During anti-
VEGF treatment, RNFL edema remitts with the resolution of BRVO. Moreover, anti-
VEGF treatment significantly reduces peripapillary blood flow volume and vessel
diameter.(17) These changes bring pRNFL thickness to “normal” levels in general.
However, the significant reduction in the thickness of the affected sector cannot be
explained by these changes. Thus, we speculate our findings indicate that pRNFL
thickness continued to decrease in the affected sector because of waning RGC axons.

In contrast, we observed no thinning in macular GCC thickness. Our results showed the thickness of mRNFL and GCIPL were significantly thicker in the affected regions at baseline. During the follow-up, the affected regional thickness decreased significantly, while the reference regional thickness did not change. Consequently, the thickness in the two regions became comparable at endpoint. We consider that the difference at baseline was due to the local macular edema, while the comparable thickness at endpoint was the outcome of edema resolution.

There have been conflicting findings on GCC affection after BRVO. Alshareef et al. found GCIPL but not mRNFL was significantly thinner than in healthy controls 3 months after BRVO.(9) Lim et al. observed regional atrophy of macular GCC at 2 years after BRVO compared to the healthy fellow eyes.(15) A more recent study reported that regional retinal atrophy happened in 10.3% of BRVO patients during 6 months after BRVO, and the atrophic eyes suffered general decline in TRT, GCC thickness as well as ORT.(18) This percentage is similar to our finding: one patient (8%) demonstrated retinal atrophy in the affected region (TRT = 256.7 μm) in our study. These discrepancies in GCC thickness change might imply that GCC atrophy only develops in a minority of BRVO eyes. The outcome may vary depending on many factors, such as primary occlusion site, ischemic insult severity, reperfusion and duration of the disease.

Although our findings do not exclude RGC atrophy in the macular after BRVO, we were not able to show this and atrophy of distal RGC axons (pRNFL) seems more reliable and significant in morphological assessment. Taken together our findings, the thickness change trends of the pRNFL and RGC layers suggest anterograde
degeneration RGC as a possible mechanism after BRVO. Anterograde degeneration occurs when axonal degeneration occurs distal to the site of injury, while retrograde degeneration moves backward towards the cell soma and may result in damage to the soma of the neuron. (19) Anterograde RGC degeneration is not rare in ophthalmic diseases. It is associated with atrophy of the optic chiasm, optic tract, optic radiations, and primary visual cortex in some hereditary optic neuropathies. (20) Glaucoma presents both anterograde and retrograde degeneration. Separated by the primary injury site, the optic disc, the former type results in RGC axonal loss along the visual pathway, whereas the latter type leads to atrophic pRNFL and GCC loss. (21, 22) In glaucoma patients, retrograde RGC degeneration is well demonstrated by visual field and SD-OCT. Macular defects in glaucoma are typically in arcuate shape that appeared as a continuation of the pRNFL defect. (23, 24) Such changes are visualized in SD-OCT as thickness correlation between pRNFL and GCC.(25) In our study, however, no correlation was found between the pRNFL and GCC thickness, which is probably masked by concurrent edema. Considering the theoretical primary injury site in BRVO within the retina, and the different thickness changing trends between the two retinal compartments, we speculate that anterograde degeneration is the main pathomechanism of optic neuropathy secondary to RGC affection after BRVO.

The internal reference ratios at endpoint were greater in the INL and the ORL (1.15) than in the rest of the inner retina (1.04–1.05), which indicates a thickening trend of the INL and the ORL after BRVO. This finding is in line with some previous studies. Ebneter et al. noticed preserved ORL thickness with thinning in inner retina in BRVO animal models. (26) Alshareef et al. observed thicker ORL but thinner inner retina in BRVO eyes compared to fellow eyes and controls. (9) ORL are considered to be less
sensitive to hypoxic injury than inner retinal layers. (27) Thickening in the ORL may be a compensation for atrophy of inner retinal layers.

These layer changes, along with nerve fiber loss and RGC loss could also represent MME. MME is predominant in the INL, with the deeper retinal layers also affected by diffuse thickening. The mechanism is still not clear, but MME is believed to be a nonspecific finding possibly related to inflammatory transsynaptic degeneration, Müller cell loss and vitreous traction. It has been reported in demyelinating disease, optic neuropathy of variable etiology and after surgical ILM peeling. (10, 28)

Typically, this type of edema is not sensitive to anti-VEGF treatment. Indeed, we found MME in 25% of the eyes with macular edema following BRVO. We believed that there is selection bias in this estimated prevalence. Our inclusion criteria comprised a minimum observation length. Patients who did not have long follow-up were excluded. Many patients with mild BRVO might not have been referred at all, which also explains the small sample size of our study. The actual prevalence of MME in BRVO might be much lower than 25%. It should also be noted that the median time to macular edema resolution was 21 months in major BRVO and 18 months in macular BRVO, (29) which was longer than the median observation time in our study (14 months). Whether the persistent edema is the outcome of impaired fluid absorption or inadequate treatment is unclear. Prospective analysis with longer follow-up would be useful to evaluate the INL and the ORL thickness changes after BRVO in more detail.

This study has several limitations. Most significant are the small sample size and the retrospective design. Because of the limited sample size, we were not able to stratify the patients by macular edema resolution status. Thus, we cannot distinguish between vascular or degenerative edema of the macular layers. These
limitations motivate for more research on this topic.

Conclusions

In conclusion, topographical thinning predominantly seemed to occur in the pRNFL but less in macular layers, which suggests that anterograde degeneration could be the major mechanism causing optic neuropathy in BRVO. MME was presented in 25% of the eyes with macular edema following BRVO, which might represent a manifestation of retrograde maculopathy. This may explain why some cases of BRVO are not sensitive to anti-VEGF treatment. Our results emphasized the importance of pRNFL monitoring in BRVO treatment and considering degenerative MME in persistent edema following BRVO.

List of Abbreviations

RGC: retinal ganglion cell
BRVO: branch retinal vein occlusion
pRNFL: peripapillary retinal nerve fiber layer
mRNFL: macular retinal nerve fiber layer
GCIPL: ganglion cell-inner plexiform layer
MMR: microcystic macular edema
BCVA: best-corrected visual acuity
VEGF: vascular endothelial growth factor
GCL: ganglion cell layer
IPL: inner plexiform layer
GCC: ganglion cell complex
INL: inner nuclear layer
SD-OCT: spectral-domain optical coherence tomography

Declarations

Ethics approval and consent to participate
All procedures performed in studies involving human participants were in accordance with the ethical, standards of the local ethics committee of the University of Bern, Switzerland and with the 2013 Helsinki declaration. Given the retrospective design, the need for individual informed consent was waived.

Consent to publish
Not applicable.

Availability of data and materials
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests
MSZ is consultant for Novartis and Bayer and stockholder of Novartis. MRM received lecturer fees from Novartis and travel support from Bayer and is a consultant for Allergan, Lumithera and Zeiss. AE received lecturer fees and travel support from Bayer, grant and educational support from Novartis and is a consultant for Allergan. The remaining authors have no financial/conflicting interests to disclose.

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Authors’ Contributions
AE, MA, MSZ and MRM contributed to the study conception and design. Material preparation, data collection and analysis were performed by SY and XL. The first draft of the manuscript was written by SY and all authors commented on previous
versions of the manuscript. All authors read and approved the final manuscript.

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Not Applicable.

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Tables

Table 1: Baseline characteristics of the study population

| Characteristic                                      | Value       |
|----------------------------------------------------|-------------|
| Age, years old, means ± SD                         | 69.8 ± 11.6 |
| Male patients, n (%)                               | 6 (50)      |
| Right eyes, n (%)                                  | 8 (62)      |
| BCVA at baseline (in logMAR), means ± SD           | .42 ± .16   |
| Cup-to-disc ratio at baseline, means ± SD          | .45 ± .21   |
| Intraocular pressure at baseline, mmHg, means ± SD | 15.2 ± 3.6  |
| Macular edema presence at baseline, n (%)          | 11 (85)     |
| Number of anti-VEGF injections, means ± SD         | 8.5 ± 4.6   |
| Follow up interval, months, means ± SD             | 13.9 ± 5.8  |

BCVA = best-corrected visual acuity; VEGF = vascular endothelial growth factor.
Table 2: Comparisons between baseline and endpoint for the pRNFL thickness parameters

| pRNFL in 13 eyes     | Baseline        | P value* | Endpoint         | P value* |
|----------------------|-----------------|----------|------------------|----------|
| Global thickness (μm) | 101.2 ± 19.8    |          | 86.2 ± 13.4      |          |
| Affected sector thickness (μm) | 133.9 ± 35.2 | .711     | 95.8 ± 21.8      | .006     |
| Reference sector thickness (μm) | 130.2 ± 28.4 |          | 124.9 ± 27.5     |          |
| Inner reference ratio | 1.05 ± .23      |          | .82 ± .28        |          |

Data are presented as means ± standard deviations.
* P value between affected and reference sectors.
† P value between baseline and endpoint. P values of < .05 are listed in bold.

pRNFL = peripapillary retinal nerve fiber layer

Table 3 Comparisons between baseline and endpoint for macular thickness parameters

| Macular thickness in 12 eyes | Baseline        | P value* | Endpoint         | P value* |
|------------------------------|-----------------|----------|------------------|----------|
| Total retinal                |                 |          |                  |          |
| Fovea thickness (μm)         | 456.5 ± 130.4   |          | 315.3 ± 112.7    |          |
| Average thickness (μm)       | 369.5 ± 35.9    |          | 311.1 ± 41.9     |          |
| Affected region thickness (μm) | 424.9 ± 59.0  | < .001   | 335.9 ± 71.0     | .073     |
| Reference region thickness (μm) | 328.8 ± 32.2 |          | 301.5 ± 20.6     |          |
| Internal reference ratio     | 1.30 ± .20      |          | 1.11 ± .19       |          |
| mRNFL                        |                 |          |                  |          |
| Fovea thickness (μm)         | 30.6 ± 9.7      |          | 26.0 ± 4.7       |          |
| Average thickness (μm)       | 50.1 ± 8.6      |          | 41.4 ± 5.6       |          |
| Affected region thickness (μm) | 65.2 ± 11.1   | < .001   | 47.2 ± 9.3       | .735     |
| Reference region thickness (μm) | 46.9 ± 9.8    |          | 46.3 ± 9.4       |          |
| Internal reference ratio     | 1.41 ± .18      |          | 1.04 ± .21       |          |
| GCIPL                        |                 |          |                  |          |
| Fovea thickness (μm)         | 49.9 ± 12.0     |          | 38.7 ± 15.4      |          |
| Average thickness (μm)       | 70.7 ± 9.4      |          | 63.2 ± 12.9      |          |
| Affected region thickness (μm) | 79.6 ± 10.8   | < .001   | 67.1 ± 19.3      | .273     |
| Reference region thickness (μm) | 64.6 ± 9.3    |          | 62.9 ± 10.2      |          |
| Internal reference ratio     | 1.24 ± .12      |          | 1.05 ± .20       |          |
| INL                          |                 |          |                  |          |
| Fovea thickness (μm)         | 52.9 ± 25.4     |          | 35.2 ± 18.8      |          |
| Average thickness (μm)       | 45.1 ± 8.2      |          | 39.5 ± 10.9      |          |
| Affected region thickness (μm) | 54.9 ± 21.0   | .019     | 43.2 ± 16.4      | .257     |
| Reference region thickness (μm) | 38.2 ± 5.0    |          | 37.8 ± 9.8       |          |
| Internal reference ratio     | 1.45 ± .55      |          | 1.15 ± .38       |          |
| ORL                          |                 |          |                  |          |
| Fovea thickness (μm)         | 323.2 ± 124.4   |          | 215.5 ± 80.6     |          |
| Average thickness (μm)       | 203.3 ± 35.6    |          | 167.3 ± 27.3     |          |
| Affected region thickness (μm) | 224.6 ± 39.7   | .003     | 179.1 ± 42.6     | .034     |
| Reference region thickness (μm) | 179.1 ± 42.0  |          | 154.5 ± 13.1     |          |
| Internal reference ratio     | 1.28 ± .24      |          | 1.15 ± .20       |          |

Data are presented as means ± standard deviations.
* P value between affected and reference sectors.
† P value between baseline and endpoint. P values of < .05 are listed in bold.
mRNFL = macular retinal nerve fiber layer, GCIPL = ganglion cell-inner plexiform layer, INL = inner nuclear layer, ORL = outer retinal layers

Figures

Figure 1

Schematic representation of the 6 peripapillary sectors and 4 macular quadrants:
Figure 2

Representative example of persistent macular edema restricted to the INL and deeper retinal layers. Fusiform microcysts presented in fusiform microcysts restricted to the INL and irregular cysts in the deeper retinal layers.

Figure 3

pRNFL thickness change between baseline and endpoint. The global thickness and the thickness of the affected were significantly thinner than that of the reference sector (P = .006).
Comparison of the global and sectoral pRNFL thickness changes during the follow-up period. 

**Figure 4**

**Figure 5**

Thickness changes of individual macular layers between baseline and endpoint. A