BJO Online First, published on March 6, 2018 as 10.1136/bjophthalmol-2017-311614

Neuroretinal atrophy following resolution of macular oedema in retinal vein occlusion

Dominika Podkowinski,[1] Ana-Maria Philip,[1] Wolf-Dieter Vogl,[1] Jutta Gamper,[2] Hrvoje Bogunovic,[1] Bianca S Gerendas,[1] Bilal Haj Najeeb,[1] Sebastian M Waldstein,[1] Ursula Schmidt-Erfurth[1]

[1]Christian Doppler Laboratory for Ophthalmic Image Analysis, Vienna Reading Center, Department of Ophthalmology, Medical University of Vienna, Vienna, Austria
[2]Center for Medical Statistics, Informatics, and Intelligent Systems (CeMSIIS), Medical University of Vienna, Vienna, Austria

Correspondence to
Dr. Sebastian M Waldstein, Christian Doppler Laboratory for Ophthalmic Image Analysis, Vienna Reading Center, Department of Ophthalmology, Medical University of Vienna, Vienna 1090, Austria; sebastian.waldstein@meduniwien.ac.at

Received 14 November 2017
Revised 13 February 2018
Accepted 16 February 2018

ABSTRACT

Background/aims To characterise neuroretinal atrophy in retinal vein occlusion (RVO).

Methods We included patients with central/branch RVO (CRVO=196, BRVO=107) who received ranibizumab according to a standardised protocol for 6 months. Retinal atrophy was defined as the presence of an area of retinal thickness (RT) <260 µm outside the foveal centre. Moreover, the thickness of three distinct retinal layer compartments was computed as follows: (1) retinal nerve fibre layer to ganglion cell layer, (2) inner plexiform layer (IPL) to outer nuclear layer (ONL) and (3) inner segment/outer segment junction to retinal pigment epithelium. To characterise atrophy further, we assessed perfusion status on fluorescein angiography and best-corrected visual acuity (BCVA), and compared these between eyes with/without atrophy.

Results 23 patients with CRVO and 11 patients with BRVO demonstrated retinal atrophy, presenting as sharply demarcated retinal thinning confined to a macular quadrant. The mean RT in the atrophic quadrant at month 6 was 249±26 µm (CRVO) and 244±29 µm (BRVO). Individual layer analysis revealed pronounced thinning in the IPL to ONL compartment. Change in BCVA at 6 months was similar between the groups (BRVO, +15 vs +18 letters; CRVO, +14 vs +18 letters).

Conclusions In this exploratory analysis, we describe the characteristics of neuroretinal atrophy in RVO eyes with resolved macular oedema after ranibizumab therapy. Our analysis shows significant, predominantly retinal thinning in the IPL to ONL compartment in focal macular areas in 11% of patients with RVO. Eyes with retinal atrophy did not show poorer BCVA outcomes.

INTRODUCTION

Macular oedema secondary to central or branch retinal vein occlusion (CRVO/BRVO) is an important cause of vision loss in working-age patients.[1] Antivascular endothelial growth factor (anti-VEGF) therapy, which is the established standard treatment for macular oedema in RVO, often leads to restoration of visual acuity.[2] Following anti-VEGF treatment, macular oedema resolves and one would presume that retinal thickness returned to the normal level as prior to the acute event of RVO. However, retinal thinning beyond the normal range is sometimes observed. To the best of our knowledge, there are no systematic reports on retinal thinning in patients with RVO after resolution of macular oedema in the scientific literature.

To characterise this phenomenon further, we studied the incidence and characteristics of retinal atrophy in patients with RVO treated with ranibizumab based on spectral-domain optical coherence tomography (SD-OCT) imaging. Furthermore, we analysed the impact of such atrophy on best-corrected visual acuity (BCVA) outcomes. We performed a systematic post hoc analysis of two large multicentre trials using standardised treatment, imaging and follow-up.

PATIENTS AND METHODS

This was an exploratory post hoc analysis of a comprehensive clinical trial database. Patients with CRVO and BRVO enrolled in the CRYSTAL and BRIGHTER studies were included. CRYSTAL was a 24-month, phase IIIb, open-label, single arm, multicentre study assessing the efficacy and safety of an individualised, stabilisation criteria-driven PRN dosing regimen with ranibizumab 0.5 mg in patients with macular oedema secondary to CRVO.[3] BRIGHTER was a 24-month, phase IIIb, open-label, randomised, active-controlled, three-arm, multicentre study assessing the efficacy and safety of an individualised, stabilisation criteria-driven pro-re-nata (PRN) dosing regimen with ranibizumab 0.5 mg applied as monotherapy or with adjunctive laser photocoagulation in comparison with laser photocoagulation alone in patients with macular oedema secondary to BRVO.[4] These trials were performed in accordance with the Declaration of Helsinki, and all the participants provided written informed consent before inclusion. The multicentre trials are registered with ClinicalTrials.gov (identifiers NCT01599650 and NCT01535261). Image data were available for analysis at the Vienna Reading Centre (VRC), Vienna, Austria. The ethics committee at the Medical University of Vienna approved the conduct of the presented post hoc analysis.

Inclusion/exclusion criteria, treatment and imaging

Inclusion and exclusion criteria for the CRYSTAL and BRIGHTER studies were reported previously.[3 4] In our retrospective analysis, only patients randomised to the ranibizumab monotherapy arms with a complete monthly follow-up, available from baseline throughout month 6, were included.

All patients were treated with monthly intravitreal injections of ranibizumab 0.5 mg for 3 months. Subsequently, patients were seen monthly for BCVA measurement and structural analysis of disease activity. If a loss in BCVA was observed, monthly

To cite: Podkowinski D, Philip A-M, Vogl W-D, *et al*. *Br J Ophthalmol* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/bjophthalmol-2017-311614

ranibizumab injections were reinitiated until visual acuity stabilised as described in detail previously.[3 4] SD-OCT volume scans covering an area of 20° x 20°, centred on the fovea, were acquired at each visit by certified, masked investigators. Imaging was performed with SD-OCT by Cirrus HD-OCT (Carl Zeiss Meditec, Dublin, California, USA) and Spectralis OCT (Heidelberg Engineering, Dossenheim, Germany). A 6×6 mm macular cube scan pattern with a resolution of 200×200 for Cirrus and 512×49 for Spectralis (with eye-tracking function activated) was used. BCVA was measured at each visit using ETDRS charts.

Image processing

All SD-OCT images underwent fully automated computational image analysis at the VRC. First, OCT volumes were segmented into the individual retinal layers using the Iowa Reference Algorithm[5] and motion artefacts were removed.[6] To align scans acquired at different visits, a validated, automated registration algorithm was applied, allowing evaluation of identical retinal regions over time.[7] Total retinal thickness maps were computed for each visit and displayed as time series from baseline to month 6 as illustrated in figure 1A.

Definition and analysis of retinal atrophy

The retinal thickness maps were visually inspected for areas of excessive retinal thinning by two independent, masked investigators (DP, A-MP). The presence of retinal atrophy was defined as retinal thinning below 260 µm outside the foveal centre. This threshold was based on the reported normal foveal thickness of the Iowa Reference Algorithm.[8] Open adjudication was performed in case of disagreement between the graders. Additionally, we assessed the development of atrophy over

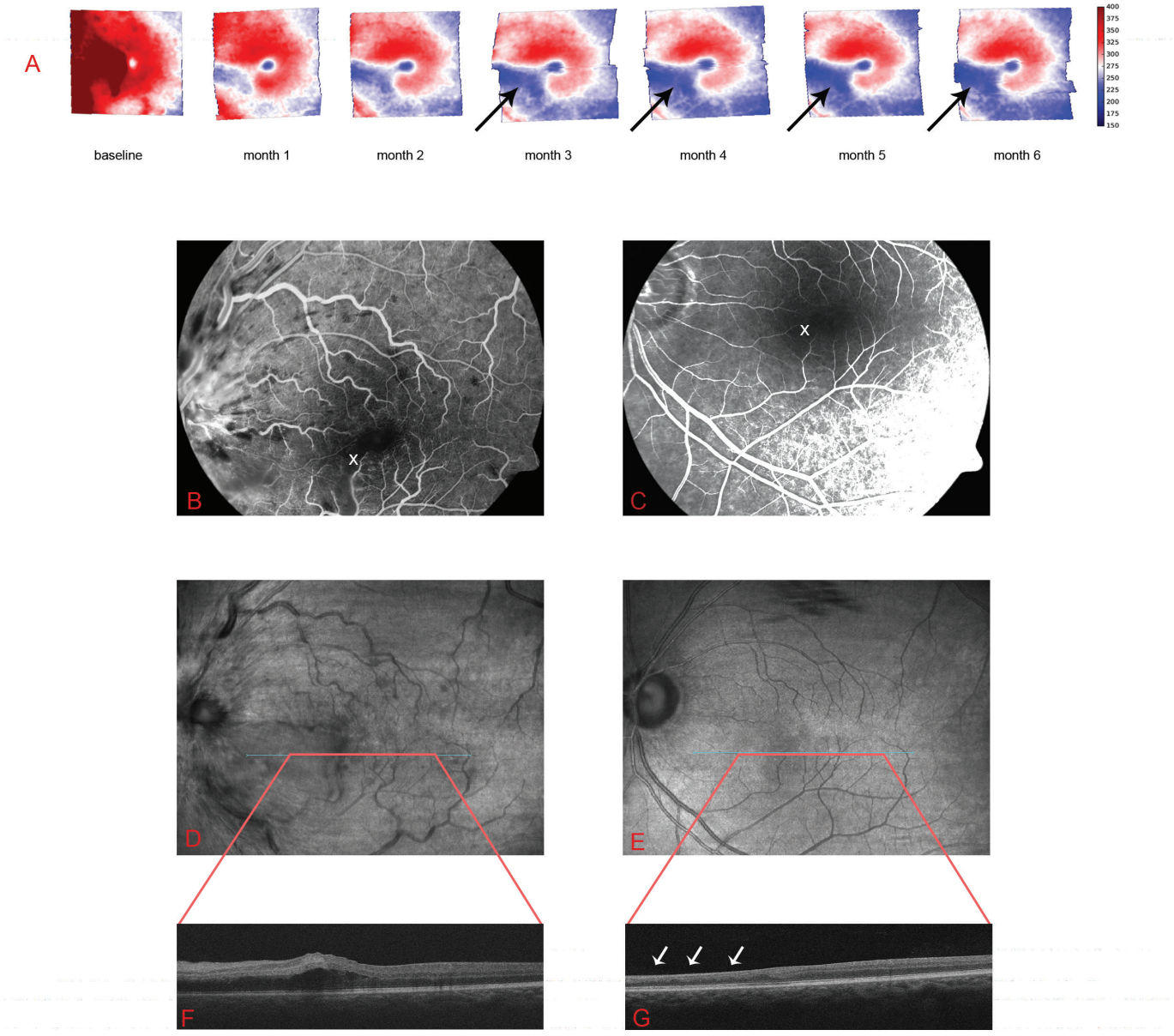

Figure 1 Example case for the development of retinal atrophy after central retinal vein occlusion. (A) Total retinal thickness map series from baseline to month 6 demonstrating the development of profound retinal thinning in the inferior nasal quadrant after month 1 (indicated by black arrows). (B) Early-phase fluorescein angiogram at baseline (white cross marks the macular quadrant in which retinal atrophy develops after resolution of macular oedema). (C) Fluorescein angiogram at month 3 demonstrating no evidence of capillary loss. OCT B-scans (F, G) through the area marked in (D, E) show the development of retinal atrophy (white arrows) (G), compared with an area of macular oedema at baseline (F).

time. Since retinal atrophy was observed to occur in patterns of macular quadrants, the retinal thickness maps were divided into four quadrants (superior nasal, superior temporal, inferior nasal, inferior temporal) and the quadrant with the mean thinnest retinal thickness at month 6 was selected for quantitative analysis.

Moreover, the thickness of three distinct retinal layer compartments was computed as follows: (1) retinal nerve fibre layer (RNFL) to ganglion cell layer (GCL), (2) inner plexiform layer (IPL) to outer nuclear layer (ONL) and (3) inner segment/outer segment (IS/OS) junction to retinal pigment epithelium (RPE).

Analysis of fluorescein angiography

Fluorescein angiography (FA) images acquired following a standardised protocol were graded at the Vienna Reading Centre (VRC) at baseline and at 3 months for CRVO and at baseline and at 6 months for BRVO. Capillary non-perfusion was evaluated in three macular subfields (central, inner, outer), according to the rings of the ETDRS grid, at each visit as described in detail previously according to standard reading centre protocol.[3 4] In the CRYSTAL study, the four inner and four outer subfields of the original ETDRS grid were summarised to be graded as two ring-shaped subfields in addition to the central subfield. In the BRIGHTER study, the four inner and four outer subfields of the original ETDRS grid were summarised to be graded as two half-ring-shaped subfields in addition to the central subfield.

In both studies, capillary loss in the respective subfields was graded by masked, certified readers as 'mild, moderate, severe or completely destroyed capillary bed' according to standard images representing approximately 30% stepwise loss in capillary perfusion. FA images were acquired by certified, masked examiners following a standard operating procedure. All FA cameras were certified by the VRC to allow comparability across study sites.[3 9]

Statistical analysis

All eyes were grouped based on the presence or absence of retinal atrophy at month 6, and the frequency of retinal atrophy was reported. The main outcome variable was the mean retinal thickness in the thinnest quadrant at month 6, compared between atrophy and non-atrophy groups for CRVO and BRVO, respectively, using two-sample t-tests. Secondary endpoints included BCVA, foveal thickness, morphological features such as subretinal fluid, intraretinal cystoid fluid and vitreomacular traction, as well as capillary non-perfusion at baseline and at month 6. Data are presented as mean±SD or counts and percentages.

A multiple linear regression model was calculated using change in BCVA at month 6 as dependent variable and baseline BCVA and all aforementioned parameters as predictors. Simple logistic regression models were designed to evaluate the influence of baseline BCVA, capillary loss, morphological OCT features and central retinal thickness as well as thicknesses in the four quadrants on the development of retinal atrophy. The capillary perfusion status was grouped for the regression model as 0–1, 2–3 and 4–5. Angiographies, which were not gradable, were excluded from the analysis.

All statistical analyses were performed using SPSS V.23.0 software (SPSS, Chicago, Illinois, USA) and R V.3.3.1 (R Core Team, Vienna, Austria). The formal significance level was set at P=0.05. Due to the exploratory nature of the analysis, no correction for multiplicity was performed.

RESULTS

Frequency and characteristics of retinal atrophy

Of all patients enrolled in the BRIGHTER and CRYSTAL studies randomised to the ranibizumab monotherapy arm (n=183, n=357), we included 107 (BRVO) and 196 (CRVO) in the current analysis with complete follow-up between baseline and month 6 available. The typical appearance of retinal atrophy following macular oedema is presented in figure 1B–F. All eyes with retinal atrophy showed sharply demarcated retinal thinning that was confined to one or two single, adjacent macular quadrants.

Central retinal vein occlusion

Fifty-nine of the patients with CRVO were imaged with Cirrus HD-OCT and 137 patients with the Spectralis OCT. Twenty-two patients (12.6%) with CRVO demonstrated retinal atrophy development at month 6. Mean retinal thickness in the thinnest quadrant at month 6 was significantly lower in the retinal atrophy group than in the non-atrophy group, as shown in figure 2 (250±26 µm vs 293±32 µm, P<0.001). The RNFL+GCL compartment, compartments 2 and 3 were statistically significantly thinner in the atrophy group (compartment 1: 72±14 µm vs 95±18 µm, P<0.001; compartment 2: 123±18 µm vs 141±19 µm, P<0.001; compartment 3: 54±4 µm vs 58±5 µm, P<0.001). Development of total retinal thickness as well as thickness of the individual compartments over time in the thinnest retinal quadrant at month 6 in eyes with and without retinal atrophy is demonstrated in figure 3.

Branch retinal vein occlusion

Of the patients with BRVO, 36 were imaged with Cirrus HD-OCT and 71 with Spectralis OCT. In BRVO, 11 patients (10.3%) showed retinal atrophy development at month 6.

Mean retinal thickness in the thinnest quadrant at month 6 was significantly lower in the retinal atrophy group than in the non-atrophy group, as shown in figure 2 (BRVO: 245±29 µm vs 279±19 µm, P<0.001). The RNFL+GCL compartment was statistically significantly thinner in the atrophy group in BRVO (75±16 vs 88±12, P<0.001). Retinal compartments 2 and 3 were significantly thinner in retinal atrophy group (compartment 2: 118±16 µm vs 133±11 µm, P<0.01; compartment 3: 54±7 µm vs 58±5 µm, P=0.05). Development of total retinal thickness as well as thickness of the individual compartments over time in the thinnest retinal quadrant at month 6 in eyes with and without retinal atrophy is demonstrated in figure 3.

Secondary outcome variables in atrophy versus non-atrophy eyes

Tables 1 and 2 show secondary outcome variables compared between the non-atrophy and atrophy groups. BCVA at baseline was lower in the atrophy compared with the non-atrophy groups in both diseases (CRVO: 45±13 vs 55±14 letters (Snellen equivalent, 20/125 vs 20/80); BRVO: 52±11 vs 61±11 letters (Snellen equivalent, 20/100 vs 20/63)). BCVA change at month 6 was similar between atrophic and non-atrophic eyes.

The macular perfusion status based on FA was similar between the groups (tables 2 and 3).

Linear regression model for BCVA at month 6

The results of the linear model are displayed in table 4. Estimated coefficients, SEs and P values for testing the hypothesis of no effect on the BCVA at month 6 were calculated. Except BCVA at baseline and the mean retinal thickness at baseline of

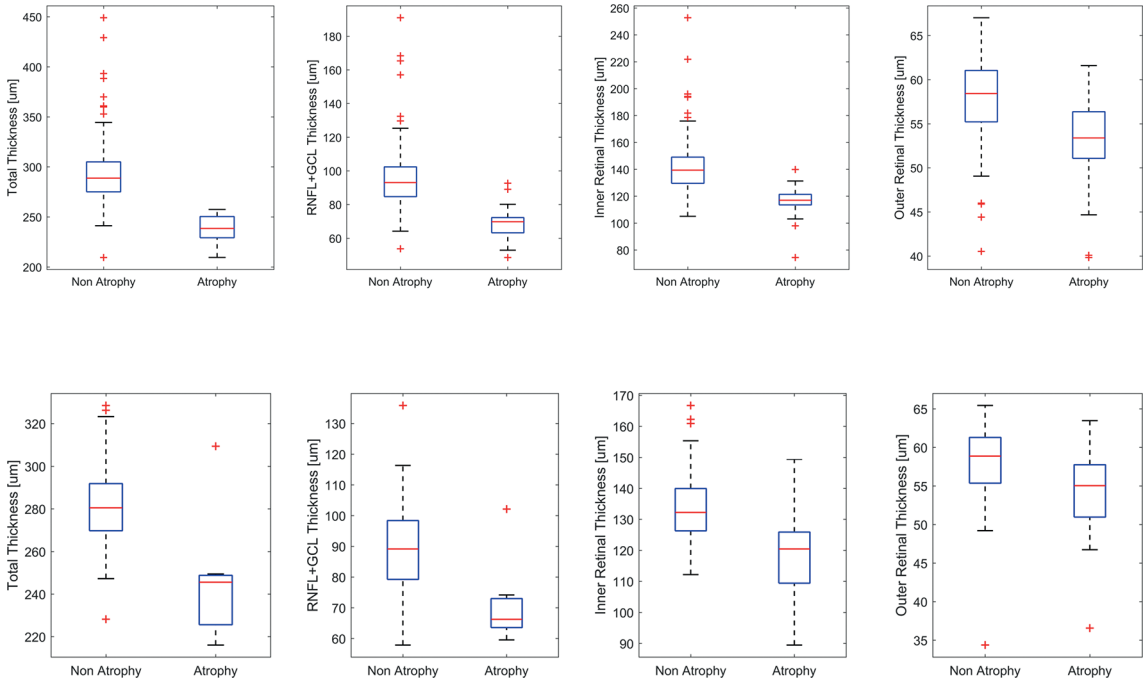

Figure 2 Box plots demonstrating mean total retinal thicknesses for central retinal vein occlusion (upper row) and branch retinal vein occlusion (lower row), mean retinal nerve fibre layer+ganglion cell layer (RNFL+GCL) thickness, mean thickness between the inner plexiform layer and the outer nuclear layer, and mean thickness between inner segment/outer segment junction and the retinal pigment epithelium in the thinnest quadrant at month 6 for atrophy and non-atrophy eyes, respectively.

the non-atrophic quadrants in retinal compartment 3, corresponding to IS/OS junction to RPE, none of the tested parameters showed a significant effect on BCVA at month 6 in BRVO. Similarly, in CRVO, the models showed BCVA at baseline and the mean retinal thickness at baseline of the three non-atrophic quadrants in retinal compartment 3 to have a statistically significant impact on BCVA at month 6.

Prediction model for retinal atrophy

Only BCVA at baseline showed a statistically significant, although small, predictive value for the development of retinal atrophy (CRVO: OR 0.95, P<0.01; BRVO: OR 0.94, P=0.02). All other tested variables showed no statistically significant influence on the development of retinal atrophy.

DISCUSSION

In this study, we characterise neuroretinal atrophy after the resolution of macular oedema in eyes with RVO treated with ranibizumab. We demonstrate significant retinal thinning beyond normal levels in approximately 11% of the studied population. In all cases, the thinned retinal areas appeared as punched-out, sharply demarcated regions corresponding to a macular quadrant, which may point towards a vascular pathological mechanism, as these quadrants correspond to retinal watershed zones.

In RVO, a previously healthy retina is affected by an acute vascular event, which must be differentiated clearly to other common causes of macular oedema such as diabetic maculopathy and age-related macular degeneration. In the specific circumstances of RVO, our findings may be best attributed to

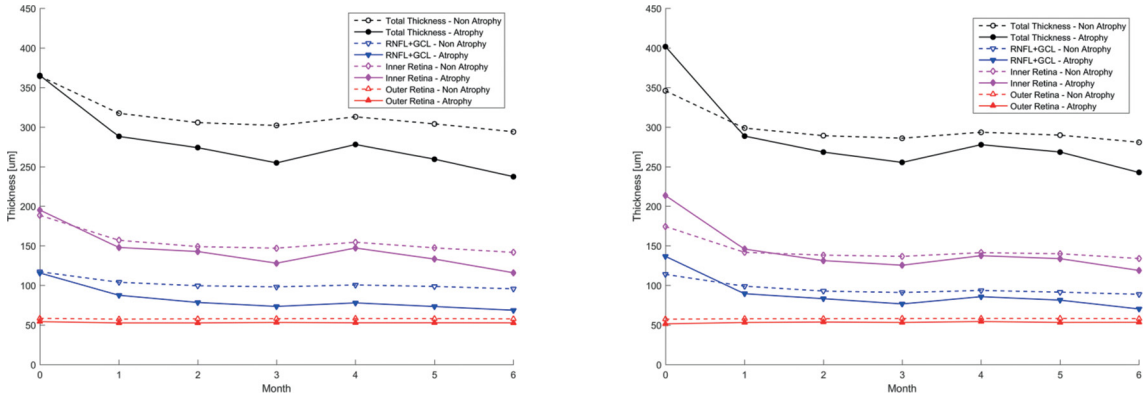

Figure 3 Development of mean total retinal thickness in the thinnest macular quadrant from baseline to month 6 for central retinal vein occlusion (left) and branch retinal vein occlusion (right). Retinal compartment 2: inner plexiform layer to the outer nuclear layer in the thinnest quadrant. Retinal compartment 3: inner segment/outer segment junction to the retinal pigment epithelium. In general, the trend towards development of thinning is already visible after month 1. GCL, ganglion cell layer; RNFL, retinal nerve fibre layer.

Table 1 Characteristics of non-atrophy versus atrophy eyes in branch and central retinal vein occlusion

Branch retinal vein occlusion	Non-atrophy	Atrophy	P value
N	96	11	
Baseline BCVA (mean±SD)	61±11	52±11	0.017
Snellen equivalent	20/63±20/640	20/100+20/640–	
BCVA change at month 6 (mean±SD)	15±11	18±13	0.414
Snellen equivalent (mean±SD)	20/500±20/640	20/400±20/500	
Central retinal thickness at baseline (mean±SD)	491.0±133	493.9±209	0.967
Vitreomacular traction at baseline	1.1%	0.0%	0.730
Subretinal fluid at baseline	53.8%	63.6%	0.761
Intraretinal cystoid fluid at baseline	100.0%	100.0%	1.000
Central retinal vein occlusion			
N	174	22	
Baseline BCVA (mean±SD)	55±14	45±13	<0.001
Snellen equivalent (mean±SD)	20/80±20/500	20/125±20/500	
BCVA change at month 6 (mean±SD)	14±11	18±18	0.256
Snellen equivalent (mean±SD)	20/500±20/640	20/400±20/400	
Central retinal thickness at baseline (mean±SD)	597.8±165	655.6±149	0.121
Vitreomacular traction at baseline	1.2%	4.3%	0.491
Subretinal fluid at baseline	71.3%	65.2%	0.488
Intraretinal cystoid fluid at baseline	100.0%	100.0%	1.000

BCVA, best-corrected visual acuity.

vascular injury-related hypoxia, which may occur due to venous congestion and ischaemia in the retinal capillary plexus. In retinal arterial occlusions, which may serve as a model of pathophysiology, loss of capillary perfusion in the affected areas leads to ischaemia and acute formation of oedema as a result of endothelial exudation.[10] As the retina, especially the neurosensory layers, is very sensitive to hypoxia, atrophy can develop over time after the acute event. Retinal atrophy caused by retinal arterial occlusion is well described and appears morphologically similar to our findings.[11 12] Potentially, in a subgroup of RVO eyes, the venous occlusion may lead to such severe alterations of the arterial vascular tree that hypoxia-mediated cell death occurs. It is noteworthy that eyes exhibiting atrophy showed relatively lower mean BCVA levels at baseline, which could be a sign of functional compromise by ischaemia. Furthermore, it is plausible that the degree of atrophy is related to the chronicity of macular oedema. It has been proposed that long-standing oedema in itself causes inner retinal loss.[13] The analysis by quadrants, which corresponds to retinal water shed zones, was chosen because the quadrant pattern showed the best representation of retinal atrophy seen on retinal thickness maps. Furthermore, this mode of analysis corresponds in general to the retinal blood supply, which highlights the primary disease mechanism in RVO.

Individual layer analysis showed particular affection of the IPL–ONL compartment corresponding to the deep retinal capillary plexus. Recent studies using OCT angiography showed mild changes in the superficial capillary plexus and severe affection of the deep capillary plexus in eyes with RVO.[14] These results are supportive of our findings; however, they do not explain why retinal atrophy only develops in a minority of eyes, and only in a specific area of the retina, even in eyes with CRVO.

Furthermore, it should be noted that blood supply in our defined compartments potentially may not correspond ideally to the anatomical plexus division. In this study, we investigated the photoreceptor–RPE complex independently for its functional importance and possible influence on visual outcome and therefore separated it from compartments 1 and 2.

Table 2 Perfusion status of non-atrophy versus atrophy groups in branch and central retinal vein occlusion at baseline

	Central mm		3 mm		6 mm	
	Non-atrophy (%)	Atrophy (%)	Non-atrophy (%)	Atrophy (%)	Non-atrophy (%)	Atrophy (%)
Branch retinal vein occlusion						
Fluorescein angiography at baseline						
0 no capillary loss	6.3	0.0	3.1	0.0	11.5	0.0
1 questionable capillary loss	18.8	18.2	15.6	0.0	15.6	0.0
2 mild	21.9	0.0	25.0	18.2	15.6	27.3
3 moderate	7.3	18.2	9.4	27.3	12.5	18.2
4 severe loss	6.3	9.1	4.2	9.1	3.1	9.1
5 completely destroyed	1.0	0.0	0.0	0.0	0.0	0.0
6 not gradable	38.0	54.5	42.7	45.5	41.7	45.5
Central retinal vein occlusion						
Fluorescein angiography grading at baseline						
0 no capillary loss	18.3	13.0	15.4	9.1	23.1	13.6
1 questionable capillary loss	13.0	9.1	24.9	13.6	20.1	18.2
2 mild	10.1	4.5	13	13.6	11.8	13.6
3 moderate	10.7	9.1	7.1	13.6	3.6	4.5
4 severe loss	4.1	0.0	0.6	0.0	0.0	0.0
5 completely destroyed	1.8	9.1	0.0	0.0	0.0	0.0
6 not gradable	42	50.0	39.1	50.0	41.4	50.0

mm, millimetre.

Table 3 Perfusion status of non-atrophy versus atrophy groups in branch retinal vein occlusion at month 6 and central retinal vein occlusion at month 3

	Central mm		3 mm		6 mm	
	Non-atrophy (%)	Atrophy (%)	Non-atrophy (%)	Atrophy (%)	Non-atrophy (%)	Atrophy (%)
Branch retinal vein occlusion						
Fluorescein angiography grading at baseline						
0 no capillary loss	15.5	10.0	7.1	10.0	28.6	10.0
1 questionable capillary loss	19.0	0.0	19.0	0.0	13.1	0.0
2 mild	22.6	50	39.3	40.0	23.8	10.0
3 moderate	7.1	10.0	16.7	30.0	16.7	60.0
4 severe loss	8.3	0.0	2.4	20.0	2.4	20.0
5 completely destroyed	2.4	10.0	0.0	0.0	0.0	0.0
6 not gradable	25.0	20.0	15.6	0.0	15.5	0.0
Central retinal vein occlusion						
Fluorescein angiography grading at baseline						
0 no capillary loss	23.6	33.3	38.5	28.6	49.7	42.9
1 questionable capillary loss	15.5	4.8	16.8	9.5	18.6	14.2
2 mild	16.8	4.8	20.5	9.5	12.4	4.8
3 moderate	5.0	4.8	5.6	4.8	0.6	4.8
4 severe loss	6.8	4.8	0.6	9.5	0.6	0.0
5 completely destroyed	0.0	4.8	0.0	0.0	0.0	0.0
6 not gradable	32.3	42.9	18.0	38.1	18	33.3

mm, millimetre.

Interestingly, the initial magnitude of oedema in the area proceeding to develop atrophy was not predictive of future retinal thinning. In our study, we detected retinal thinning in the IS/OS junction to RPE. This compartment's blood supply is guaranteed by the choroid; therefore, it may be speculated why the retinal thinning occurs. In our opinion, this could eventually be caused by a paracrine or autocrine dysregulation of growth factors, for example, VEGF in the retina, as well as the choroid and therefore leads to a thinning in retinal compartment 3.

Of note, our study did not show any significant correlation between angiographically determined capillary perfusion status and the development of retinal atrophy. Due to the acute nature of the retinal occlusions, several of the FAs could not be graded, for example, due to the presence of profound retinal haemorrhage. Some eyes showed loss of capillary perfusion at baseline. Future studies using OCT angiography will be able to deliver a more precise analysis of the perfusion status, although OCT angiography is also affected by blockage due to haemorrhage.[15]

Our results did not show any correlation between visual acuity and retinal atrophy during anti-VEGF treatment. The functional test used here, BCVA, mainly tests foveal areas, whereas we observed atrophy mainly outside foveal regions. This may

Table 4 Multiple linear regression models for best-corrected visual acuity change at month 6

	Estimate	SE	P value
Branch retinal vein occlusion			
(Intercept)	12.84	14.1	0.364
BCVA at baseline	0.428	0.084	<0.01
Mean thickness of the three non-atrophic quadrants in RNFL+GCL	0.059	0.022	0.010
Mean thickness of the three non-atrophic quadrants in retinal layer compartment 2	−0.022	0.024	0.364
Mean thickness of the three non-atrophic quadrants in retinal layer compartment 3	0.342	0.223	0.128
Mean thickness in the thinnest quadrant RNFL+GCL	0.012	0.028	0.656
Mean thickness in the thinnest quadrant in retinal layer compartment 2	−0.014	0.019	0.451
Mean thickness in the thinnest quadrant in retinal layer compartment 3	0.253	0.200	0.208
Central retinal vein occlusion			
(Intercept)	4.649	10.91	0.670
BCVA at baseline	0.841	0.072	<0.001
Mean thickness of the three non-atrophic quadrants in RNFL+GCL	0.161	0.049	0.001
Mean thickness of the three non-atrophic quadrants in in retinal layer compartment 2	−0.005	0.028	0.852
Mean thickness of the three non-atrophic quadrants in retinal layer compartment 3	−0.045	0.268	0.866
Mean thickness in the thinnest quadrant RNFL+GCL	−0.130	0.054	0.018
Mean thickness in the thinnest quadrant in retinal layer compartment 2	−0.002	0.026	0.924
Mean thickness in the thinnest quadrant in retinal layer compartment 3	0.259	0.258	0.316

Retinal layer compartment 3: between inner segment/outer segment junction and retinal pigment epithelium.
BCVA, best-corrected visual acuity; GCL, ganglion cell layer; RNFL, retinal nerve fibre layer.

explain the lack of correlation between BCVA and retinal atrophy. Microperimetric evaluation of retinal sensitivity may be required to reveal the functional deficits that would be expected to occur in the presence of structural retinal damage. However, layer thicknesses in the non-atrophic areas showed a statistically significant influence on BCVA at month 6 in our study. Recent studies showed an association of specific morphological features on OCT and BCVA outcome as well as the development of ischaemia on FA.[16–18] The presence of hyper-reflective changes in the inner nuclear layer, similarly to the changes seen in paracentral acute middle maculopathy, may be precursors for the development of macular atrophy. Similarly, low-reflectivity changes in the RNFL have been reported to be predictive of retinal non-perfusion. Although in our study the development of atrophy was not related to retinal non-perfusion on FA, further investigations combining these predictive factors may be of value and may provide predictive factors for the development of atrophy.

When interpreting our results, it has to be considered that patients with non-acute, pre-existing retinal occlusions could have been included. Therefore, retinal atrophy could have also been caused by long-existing ischaemia. As atrophy developed over time and was not visible at baseline, this cause however seems unlikely, although it must be noted that eyes affected by atrophy already showed reduced BCVA levels at baseline. Moreover, an association between the development of atrophy and treatment with anti-VEGF seems unlikely, as the drug is administered into the vitreous and retinal atrophy affected only a single quadrant of the imaged retina, whereas oedema was reduced in all of the quadrants. However, our study lacks a control group of untreated patients that would allow definitive clarification of the association with anti-VEGF therapy. Nevertheless, a potential influence of anti-VEGF therapy can only be ruled out by a study using an untreated control group or a control group of patients receiving steroids. Neither of these was available for analysis in our paper. Further studies are needed to clarify the role of anti-VEGF in ischaemic diseases.

There are some limitations to this study, including its retrospective nature and limited follow-up duration. We analysed data acquired by masked operators under standardised conditions during prospective trials, which limits the bias conferred by retrospective studies. The prevalence of atrophy depends on the definition of retinal thinning, that is, on the employed threshold in retinal thickness. Other definitions of atrophy, for example, by comparing hemisphere thicknesses in BRVO eyes, may provide different rates of atrophy presence. However, this approach is not feasible in CRVO eyes. A possible measurement bias caused by the use of two different OCT devices, which may lead to small differences in retinal thicknesses, was mitigated by using independent automated layer segmentation as demonstrated previously.[19]

In conclusion, we characterised retinal atrophy following the resolution of macular oedema in patients treated with anti-VEGF for RVO. About 10% of the patients analysed in this study presented atrophy in at least one macular quadrant at month 6. Atrophy occurred in all individual retinal compartments analysed. We hypothesise that the observed retinal thinning may be caused by the vascular injury resulting from the vaso-occlusion, which evoked retinal hypoxia; however, future studies are required to investigate the underlying pathophysiology.

Contributors DP designed the study, analysed the data, and drafted and revised the paper. She is the guarantor. A-MP analysed the data and revised the manuscript draft. W-DV implemented the algorithm necessary for data analysis and revised the paper draft. JG planned and performed the statistical analysis of the paper and revised the paper draft. HB analysed the data, provided the visualisation of the data and revised the paper draft. BSG designed the study protocol and revised the paper draft. BHN analysed the data and revised the paper draft. SMW designed the study and coordinated the analysis, including the statistical analysis of the data, and drafted and revised the paper. UMS-E initiated the project, designed the study and revised the manuscript.

Funding Austrian Federal Ministry of Economy, Family and Youth, National Foundation for Research, Technology and Development.

Disclaimer The funding organisation had no role in the design or conduct of this research.

Competing interests UMS-E reports consultancy for Bayer, Boehringer and Novartis. BSG reports consultancy for Roche. SMW reports consultancy for Bayer and Novartis, as well as research support by Bayer and Genentech. All other authors have no financial interest to disclose.

Patient consent Detail has been removed from this case description/these case descriptions to ensure anonymity. The editors and reviewers have seen the detailed information available and are satisfied that the information backs up the case the authors are making.

Ethics approval Ethics Committee of the Medical University of Vienna.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Klein BE, Klein R, Linton KL. Prevalence of age-related lens opacities in a population. The Beaver Dam Eye Study. *Ophthalmology* 1992;99:546–52.
2 Campochiaro PA, Heier JS, Feiner L, *et al*. Ranibizumab for macular edema following branch retinal vein occlusion: six-month primary end point results of a phase III study. *Ophthalmology* 2010;117:1102–12.
3 Larsen M, Waldstein SM, Boscia F, *et al*. Individualized ranibizumab regimen driven by stabilization criteria for central retinal vein occlusion: twelve-month results of the CRYSTAL study. *Ophthalmology* 2016;123:1101–11.
4 Tadayoni R, Waldstein SM, Boscia F, *et al*. Individualized stabilization criteria–driven ranibizumab versus laser in branch retinal vein occlusion. *Ophthalmology* 2016;123:1332–44.
5 Haeker M, Abramoff M, Kardon R, *et al*. *Medical image computing and computer-assisted intervention—MICCAI 2014*. . Boston, USA: International Conference on Medical Image Computing and Computer-Assisted Intervention, 2014:9. 800–7.
6 Montuoro A, Wu J, Waldstein S, *et al*. Motion artefact correction in retinal optical coherence tomography using local symmetry. *Med Image Comput Comput Assist Interv* 2014;17:130–7.
7 Vogl WD, Waldstein SM, Gerendas BS, *et al*. Spatio-temporal signatures to predict retinal disease recurrence. 2015;24:152–63.
8 Terry L, Cassels N, Lu K, *et al*. Automated retinal layer segmentation using spectral domain optical coherence tomography: evaluation of inter-session repeatability and agreement between devices. *PLoS One* 2016;11:e0162001.
9 Tadayoni R, Waldstein SM, Boscia F, *et al*. Individualized stabilization criteria-driven ranibizumab versus laser in branch retinal vein occlusion: six-month results of brighter. *Ophthalmology* 2016;123:1332–44.
10 Christoffersen NL, Larsen M. Pathophysiology and hemodynamics of branch retinal vein occlusion. *Ophthalmology* 1999;106:2054–62.
11 Ritter M, Sacu S, Deák GG, *et al*. In vivo identification of alteration of inner neurosensory layers in branch retinal artery occlusion. *Br J Ophthalmol* 2012;96:201–7.
12 Kaur C, Foulds WS, Ling EA. Blood-retinal barrier in hypoxic ischaemic conditions: basic concepts, clinical features and management. *Prog Retin Eye Res* 2008;27:622–47.
13 Romero-Aroca P. Managing diabetic macular edema: the leading cause of diabetes blindness. *World J Diabetes* 2011;2:98–104.
14 Coscas F, Glacet-Bernard A, Miere A, *et al*. Optical coherence tomography angiography in retinal vein occlusion: evaluation of superficial and deep capillary plexa. *Am J Ophthalmol* 2016;161:160–71.
15 Adhi M, Filho MA, Louzada RN, *et al*. Retinal capillary network and foveal avascular zone in eyes with vein occlusion and fellow eyes analyzed with optical coherence tomography angiography. *Invest Ophthalmol Vis Sci* 2016;57:OCT486–94.
16 Ko J, Kwon OW, Byeon SH. Optical coherence tomography predicts visual outcome in acute central retinal vein occlusion. *Retina* 2014;34:1132–41.
17 Rahimy E, Sarraf D, Dollin ML, *et al*. Paracentral acute middle maculopathy in nonischemic central retinal vein occlusion. *Am J Ophthalmol* 2014;158:372–80.
18 Hasegawa T, Yamashita M, Maruko I, *et al*. Optical coherence tomographic predictor of retinal non-perfused areas in eyes with macular oedema associated with retinal vein occlusion. *Br J Ophthalmol* 2017;101:569–73.
19 Rashid A, Waldstein S, Gerendas B, *et al*. Reproducibility of retinal thickness measurements across spectral-domain optical coherence tomography devices using Iowa Reference Algorithm. 2016 (accessed 19 Dec 2016).

Neuroretinal atrophy following resolution of macular oedema in retinal vein occlusion

Dominika Podkowinski, Ana-Maria Philip, Wolf-Dieter Vogl, Jutta Gamper, Hrvoje Bogunovic, Bianca S Gerendas, Bilal Haj Najeeb, Sebastian M Waldstein and Ursula Schmidt-Erfurth

Br J Ophthalmol published online March 6, 2018