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Detailed optical coherence tomography angiographic short-term response of type 3 neovascularization to combined treatment with photodynamic therapy and intravitreal bevacizumab

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ABSTRACT.

Purpose: **To explore the short-term vascular and structural changes of type 3 neovascularization using optical coherence tomography angiography (OCT-A) when treated with a combination of photodynamic therapy (PDT) and intravitreal bevacizumab (IVB), and to evaluate the course of different sequences of the combined therapies.**

Methods: **Thirty eyes of 29 treatment-naïve patients with a type 3 neovascularization were included in this prospective observational cohort study. They were all treated with PDT and IVB 2 weeks apart, starting either with PDT (PDT-first group) or IVB (IVB-first group). Optical coherence tomography angiography (OCT-A) imaging was performed at week 0, 2, 4 and 18, and best corrected visual acuity (BCVA) at week 0 and 18. Vascular, structural and functional features were graded and analysed over time.**

Results: **In all patients, at all follow-up visits, vascular and structural features were significantly more often decreased or resolved than unchanged or increased. Best corrected visual acuity (BCVA) significantly improved at 18 weeks. Vascular, structural and functional outcomes were all slightly better in the PDT-first group compared to the IVB-first group, although not statistically significant.**

Conclusion: **Combined treatment of PDT and IVB is effective in short-term for type 3 neovascularization based on vascular and structural features. Initial treatment with PDT tended to be more effective than with IVB.**

Key words: anti-VEGF – intraretinal cysts – intraretinal neovascularization – intravitreal bevacizumab – optical coherence tomography angiography – photodynamic therapy – retinal chorioidal anastomosis – type 3 neovascularization

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Introduction

Type 3 neovascularization is a distinct form of neovascular age-related macular degeneration (nAMD), which accounts for 12–15% of the newly diagnosed nAMD patients (Yannuzzi et al. 2008). Classification of the neovascularization types is based on their anatomical location (Fig. 1). Type 3 neovascularizations appear intraretinally, that is, within the deeper retina normally void of vessels (Yannuzzi et al. 2001; Gass et al. 2003; Freund et al. 2008).

Type 3 neovascularization is commonly diagnosed using a multimodal imaging approach: fundus examination, fluorescein angiography (FA), indocyanine green angiography (ICGA) and optical coherence tomography (OCT) (Ravera et al. 2016). This is not only time-consuming, but partially invasive by using intravenous dye for FA and ICGA. Such a multimodal imaging approach is therefore only used for diagnosis, not for treatment follow-up.

Recently, a new functional extension of OCT visualizing perfusion of the chorioretinal vasculature, called OCT angiography (OCT-A), became clinically available (Spaide et al. 2015a; Kashani et al. 2017). A volume scan pattern using this technique enables the construction of a perfusion map (Spaide et al. 2015a, b; Tsai et al.

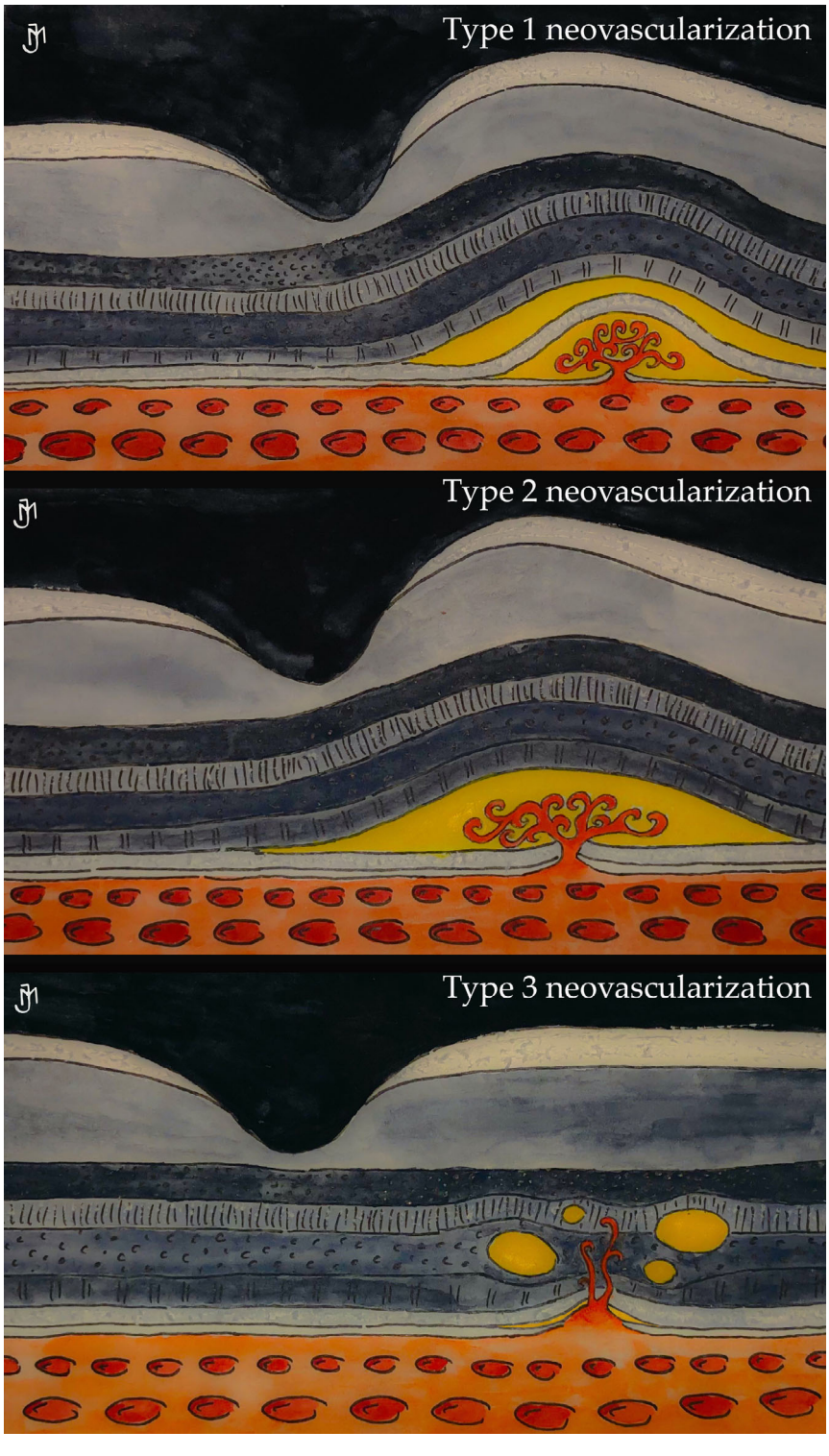

Fig. 1. A schematic image of type 1, type 2 and type 3 neovascularizations on a cross-sectional representation of the retina. Note that the type 3 neovascularization in this schematic presentation is a stage 3 lesion. Courtesy of J.E.A. Majoor, MD.

2017). Previous studies have shown that features of type 3 neovascularizations, such as the intraretinal neovascular complex as well as transretinal blood flow corresponding to a retinal choroidal anastomosis (RCA), are detectable and identifiable on OCT-A (Amarakoon et al. 2015; Dansingani et al. 2015; Kuehlewein et al. 2015; Tan et al. 2016; Querques et al. 2016; Bansal et al., 2018; de Jong et al. 2018). Hence, OCT-A could be used for examining the response to treatment in type 3 neovascularization.

The availability of a fast, noninvasive examination, like OCT-A, to study the vascular and structural response to treatment in type 3 neovascularization more vigorously is favourable. So far, small sample sizes, short follow-up periods and inconsistencies in follow-up measurements and treatment schedule made treatment consensus difficult (Tsai et al. 2017). Type 3 neovascularizations are thought to express vascular endothelial growth factor (VEGF), which is provoked by outer retina hypoxia (Tsai et al. 2017). Although monotherapy with VEGF inhibitors (anti-VEGF) shows positive results on visual acuity, the lesions remain active in most patients until the end of follow-up (Rosenfeld et al. 2006; Costagliola et al. 2007; Meyerle et al. 2007; Gupta et al. 2010; Tsai et al. 2017). To overcome the persistence of lesions after anti-VEGF monotherapy, a combination with photodynamic therapy (PDT) seems appropriate. Photodynamic therapy (PDT) may strengthen the success rate by closing retinal–retinal anastomosis (RRA) as well as RCA (Tsai et al. 2017). de Jong et al. (2018) showed that abnormal blood flow corresponding to the type 3 neovascularization tends to persist after treatment with the anti-VEGF agent bevacizumab (intravitreal bevacizumab; IVB) alone, whereas a combination with PDT rapidly resulted in complete resolution in most cases. Although these results show that combination therapy with PDT and IVB may be effective in resolving type 3 neovascularization, detailed analysis of the course of the lesion over time is warranted as well as analysis of the most effective sequence of this combination treatment.

Therefore, we aimed to explore the vascular and structural changes of type 3 neovascularization in short-term using OCT-A, when treated with a combination therapy of PDT and IVB. Furthermore, we determined and compared the course of both sequences of combining PDT and IVB.

Methods

Study design

This prospective observational cohort study was approved by the local internal review board of the Rotterdam Eye Hospital (REH) and the Medical

Research Ethical Committee of the Erasmus University Hospital (Rotterdam, the Netherlands), and adhered to the tenets of the Declaration of Helsinki. Informed consent was obtained from each participant before they were enrolled in the study.

Study population

Between September 2016 and June 2018, 30 eyes of 29 patients were enrolled in this study. Patients were included when diagnosed with new-onset type 3 neovascularization based on OCT, fundus examination, FA and ICGA without a history of treatment for nAMD (i.e. intravitreal anti-VEGF, peri-ocular steroids or PDT) within the last year. Diagnosis was performed by a medical retina specialist from the REH, and diagnosis of each case was confirmed before enrolment by one of them (M.V.). Diagnosis of type 3 neovascularization was based on the presence of known hallmarks on conventional imaging, that is, a focal intraretinal haemorrhage on fundus examination, focal leakage on FA, and a mid to late phase hotspot on ICGA. Type 3 neovascularization features based on OCT are presence of intraretinal hyperreflective focus and cystoid macula oedema (all stages), external limiting membrane (ELM) and ellipsoid zone disruption (stage 2 and 3), retinal pigment epithelial (RPE) disruption (stage 3), serous pigment epithelial detachment (PED) with or without subretinal fluid (SRF; stage 3) (Su et al. 2016).

Treatment strategy

Treatment strategy for these patients was a combination of PDT and IVB administered at 2 weeks apart. Treatment at baseline (week 0) was preferably within 1 week after diagnosis. The treatment sequence followed routine clinical care and was based on the patient's and hospital's logistics. If PDT was available within a week after diagnosis at the patient's convenience, the patient started with PDT at week 0 followed by IVB 2 weeks later (PDT-first group). Otherwise, the patient was first treated with IVB, followed by PDT at week 2 (IVB-first group). From week 6 onwards patients were treated with IVB on a pro re nata (PRN) schedule. Indication for PRN treatment was an increase in intraretinal or subretinal fluid on OCT and/or a visual acuity loss of at least five letters with evidence of fluid in the macular area on OCT. The spot size of PDT was adjusted to the hot spot on ICGA, using full fluence (50 J/cm^2) and full dose verteporfin (Visudyne, Novartis, Basel Switzerland; 6 mg/m^2) for 83 seconds.

Study procedures and materials

Best corrected visual acuity (BCVA) was assessed using the Early Treatment Diabetic Retinopathy Study refraction protocol at 4 m distance at week 0 and 18. Full ophthalmic evaluation was performed at week 0, and at every clinical evaluation from week 6 onwards, including conventional SD-OCT.

Imaging by OCT-A was performed at weeks 0, 2, 4 and 18. At week 0 and 2, study measurements were scheduled before treatment. The study started with an experimental phase-resolved Doppler OCT system, which uses a swept-source laser (Axsun technologies Inc, Billerica, MA, USA) with a wavelength of 1040 nm operating at 100 kHz A-scan rate (Braaf et al. 2012). From patient 7 onwards, the study continued on a commercially available Spectralis SD-OCT system (Heidelberg Engineering, Heidelberg, Germany) for the acquisition of OCT-A images. The distance between B-scans was 6 μm, and pattern size (width $\times$ height) was either 10° $\times$ 5° ($\pm$3.0 mm $\times$ 1.5 mm) or 10° $\times$ 10° ($\pm$3.0 mm $\times$ 3.0 mm), resulting in 256 and 512 B-scans per OCT-A image, respectively. Scanning was performed by a single operator.

OCT-A grading

Two medical retina specialists (K.W. and J.M.) graded all OCT-A scans. They were masked for the treatment sequence, and the images were randomly presented. Baseline OCT-A images were graded on vascular (flow-based) features: intraretinal neovascularization (IRN), subretinal neovascularization (SRN), sub-RPE neovascularization (SRPEN) and RCA, and structural features: intraretinal cysts (IRC), SRF and PED. Vascular features are presented in Fig. 2. Changes over time were scored as increased, unchanged, decreased or resolved with respect to week 0 for all features at week 2, 4 and 18. If the two specialists disagreed, they were asked to discuss the OCT-A scan, to reach consensus. A decisive judgement was given by a third medical retina specialist (M.V.) in case no consensus was reached.

The vascular and structural features used as primary parameters for analysis of treatment response were IRN, RCA and IRC. All other vascular features, that is, SRN and SRPEN, and structural features, that is, SRF and PED, were considered secondary parameters.

Analysis

Statistical analysis was performed using SPSS Statistics Version 24 (IBM, Armonk, NY, USA). p values lower than 0.05 were considered statistically significant.

Combination therapy

Vascular and structural changes after combination therapy were analysed for each primary feature. Changes from week 0 to 2, week 0 to 4 and week 0 to 18 were only considered when the feature was present at baseline. For the primary vascular features (IRN and RCA combined) and the primary structural feature (IRC) at each follow-up visit, a binomial test was conducted to analyse whether the percentage of regressing lesions (decreased or resolved) differed significantly from 50%.

Functional change, that is, BCVA (LogMAR score), after combination therapy from week 0 to 18 was tested for significance by a Wilcoxon Signed-Ranks Test.

PDT-first versus IVB-first groups

The presence of vascular and structural baseline characteristics was compared between the PDT-first and IVB-first group, to analyse whether the groups were comparable at baseline. Differences were tested for each feature with a Fisher's test.

The percentage of resolved lesions from week 0 to 18 was compared between the PDT-first and IVB-first group for each primary feature using a one-way multivariate analysis of variance (MANOVA). The difference in functional progression, that is, BCVA improvement, between week 0 and 18

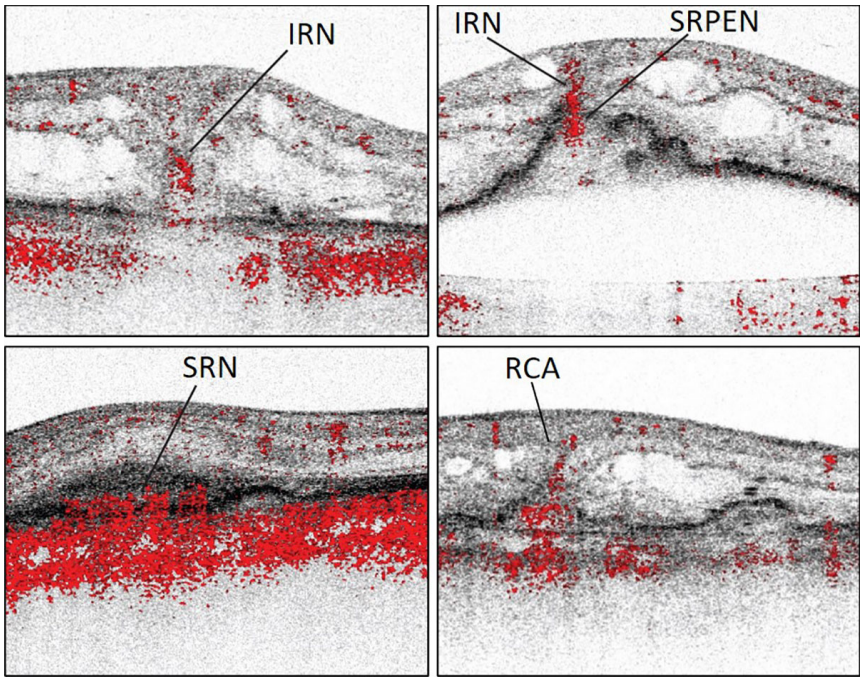

Fig. 2. Examples of vascular features derived from de Jong et al. (2018) Left: upper image shows an example of an intraretinal neovascularization (IRN), that is, abnormal flow located intraretinally, without a connection to the choroidal circulation. Lower image shows a subretinal neovascularization (SRN), that is, abnormal flow located subretinal, but above the retinal pigment epithelium. Right: upper image shows both IRN and a sub-RPE neovascularization (SRPEN), that is, sub-RPE located abnormal flow. Note that this is not a retinal choroidal anastomosis (RCA), as a large pigment epithelial detachment (PED) disturbs the connection with the choroid. Lower image is an example of a RCA, showing a clear connection of the IRN with the choroidal circulation.

was compared between the PDT-first and IVB-first group using a Mann–Whitney *U* test.

Furthermore, we analysed whether the number of PRN injections between week 6 and 18 differed between the PDT-first and IVB-first group using a Mann–Whitney *U* test.

Results

Thirty treatment-naïve eyes of 29 patients diagnosed with new-onset type 3 neovascularization were enrolled in the study (20 females, median age 82.5 years, range 62–95). Four patients were excluded for OCT-A analysis due to missing or poor quality baseline OCT A-scans, or an alternative treatment schedule (PDT and IVB were performed on the same day). One patient was lost to follow-up after week 2 and therefore excluded for BCVA analysis. Thirteen eyes were first treated with PDT (PDT-first group), and 17 eyes started with IVB (IVB-first group). Baseline characteristics are shown in Table 1. Figure 3 shows follow-up OCT-A images of a PDT-first patient and an IVB-first patient.

Combination therapy

Figure 4 shows the progression of the primary vascular and structural features at week 2, 4 and 18 with respect to week 0. This figure visualizes that at all follow-up visits, most vascular and structural features of the lesions were either decreased or resolved (92% at week 18). Binominal testing confirmed this observation ($p \leq 0.001$).

Figure 5 shows the BCVA at week 0 against the BCVA at week 18 for each patient. The mean BCVA was 0.34 and 0.28 LogMAR at weeks 0 and 18, respectively. A Wilcoxon Signed-Ranks Test indicated that the BCVA of at week 18 (median 0.18 LogMAR) was statistically significantly better compared to week 0 (median 0.32 LogMAR, $p = 0.038$).

PDT-first versus IVB-first groups

For the comparison between the PDT-first and IVB-first group in treatment response, we first compared the baseline characteristics (Table 2). Fisher's exact test showed no statistically significant differences between these two groups in any of the OCT-A features.

The fraction of resolved lesions was slightly higher in the PDT-first group at all follow-up moments, except for IRN at 2 and 18 weeks, and IRC 2 weeks after initial treatment (Fig. 6). MANOVA revealed no significant differences in the percentage of resolved lesions between the PDT-first and IVB-first groups at week 18 (Pillai's Trace = 0.052, $p = 0.70$).

Functional outcome, that is, BCVA, improved from week 0 to 18 in both the PDT-first group (median 0.38 to 0.14 LogMAR, mean 0.35 to 0.23 LogMAR) and the IVB-first group (median 0.32 to

Table 1. Baseline characteristics.

	PDT-first (n = 13)	IVB-first (n = 17)	p-value
Age (years)			
Median	82	83	1.000*
Range	62–91	69–95	
Gender (n)			
Male	5	5	0.602†
Female	8	12	
BCVA (LogMAR)	0.38	0.32	0.758*
CMT (μm)	421.7 ± 107.1	400.4 ± 106.2	0.710*
Staging lesion‡			
Stage 1	1	1	1.000†
Stage 2	0	0	
Stage 3	12	16	

BCVA = best corrected visual acuity; CMT = central macular thickness; IVB = intravitreal bevacizumab; PDT = photodynamic therapy.
* Mann–Whitney *U* test.
† Chi-Square test.
‡ Staging was based on the staging classifications of Su et al. (2016) and Kataoka et al. (2018).

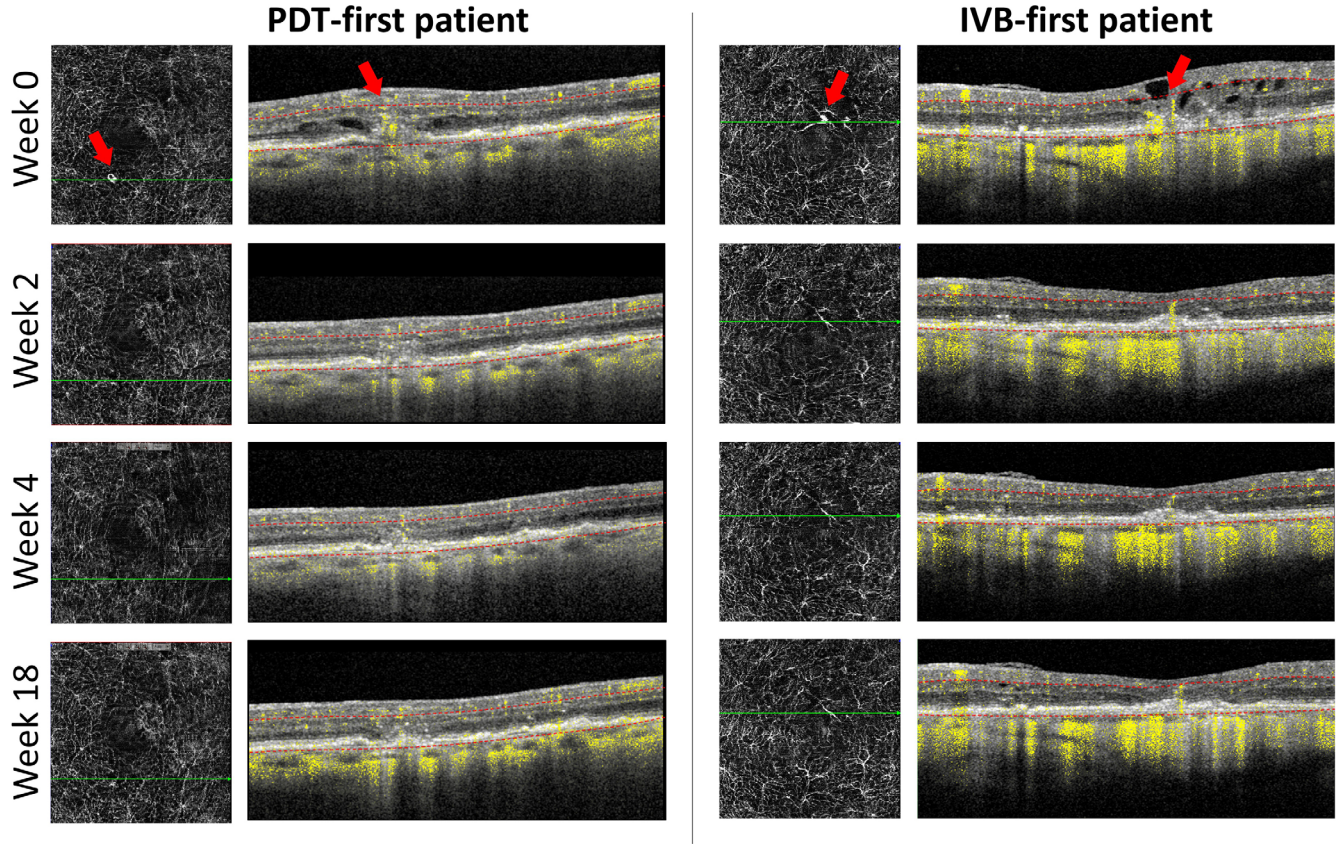

Fig. 3. Follow-up with optical coherence tomography angiography (OCT-A) of a photodynamic therapy (PDT)-first patient (left) and an intravitreal bevacizumab (IVB)-first patient (right). For both patients and for each week, the *en face* (left) is presented together with the most relevant cross-sectional B-scan (right), with the segmentation from the inner plexiform layer (IPL) to Bruch's membrane (BM) indicated with the red dotted lines in the B-scans. The green line in the *en face* images corresponds with the location of the B-scan. Inner plexiform layer (IPL) to BM was chosen for these patients to include the complete type 3 neovascularization in the image. Week 0 (baseline) OCT-A images show the initial type 3 neovascularization prior to treatment, indicated with arrows. Both examples had at baseline intraretinal cysts (IRC), a pigment epithelial detachment (PED) and a retinal choroidal anastomosis (RCA). Follow-up at week 2, 4 and 18 is shown beneath the week 0 OCT-A images. For the PDT-first patient, the IRC were decreased after 2 weeks, although this is not visible in this particular B-scan. They were resolved at week 4 and 18. Pigment epithelial detachment (PED) was decreased in all follow-ups, and the RCA was resolved in all follow-ups. For the IVB-first patient, the IRC were resolved at week 2 and 4, while at week 18 the IRC were decreased with respect to baseline. The small PED remained unchanged in all follow-ups. The RCA was decreased in all follow-ups with respect to week 0.

0.18 LogMAR, mean 0.33 to 0.32 LogMAR). However, the difference in progression between the treatment groups was not significant (Fig. 5).

Finally, the number of PRN injections between week 6 and 18 did not differ significantly between the PDT-first group (median = 1 injection, range 0–3) and the IVB-first group (median = 1 injection, range 0–4). The mean values were 1.2 and 1.5 for the PDT-first and IVB-first groups, respectively.

Discussion

In the current observational cohort study, we explored the short-term response to combination therapy with PDT and IVB in eyes with type 3 neovascularization using OCT-A. Analysis of vascular and structural parameters indicated that combination therapy resolved or decreased lesions in 92% of the patients, with improvement in BCVA. This study also indicates a slightly more effective treatment outcome with initial PDT treatment.

Our study showed that vascular features (either IRN or RCA) in some patients already disappeared after the first IVB or PDT treatment (week 2, 23% resolved), and an even greater percentage after the combination (week 4, 50% resolved). After 18 weeks, the resolution rate of the vascular features was 60%, with the majority of lesions occluded after combination therapy with IVB and PDT.

Interestingly, the structural feature IRC followed a different course over time. The resolution rate after the first treatment was 42%, increasing to 73% after the combination therapy, and declining to 48% at week 18. A high percentage of resolved IRCs was seen in week 2 in the IVB-first group (Fig. 6). This can be explained because IVB is known to inhibit vascular permeability, and therefore reduces vascular leakage (Shweiki et al. 1992; Fogli et al. 2018), irrespective of closure of the neovascular network. After 4 weeks, the PDT-first patients were treated with IVB as well, resulting in very high resolution rates (89%) of the IRCs. Inhibiting vascular permeability after closure of the leaking vessel by PDT seem to strengthen the effect on IRC resolution. After 18 weeks, the resolution rates of the vascular features and the IRCs are more similar.

Besides the resolution rates of these vascular and structural features, visual acuity had significantly improved at 18 weeks. This is consistent with the

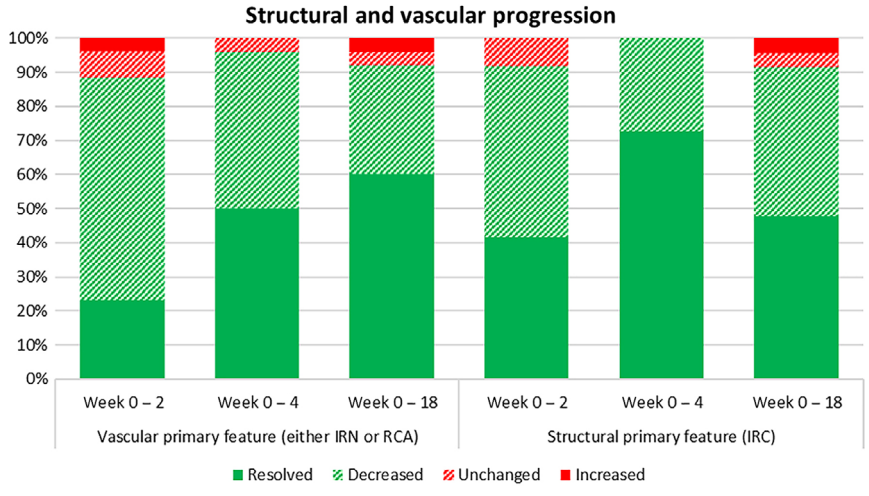

Fig. 4. Fraction of increased, unchanged, decreased or resolved structural and vascular primary features at week 2, 4 and 18 with respect to baseline (week 0). The vascular primary feature was either intraretinal neovascularization (IRN) or retinal choroidal anastomosis (RCA), and the structural primary feature was defined as intraretinal cysts (IRC), plotted together in this bar chart.

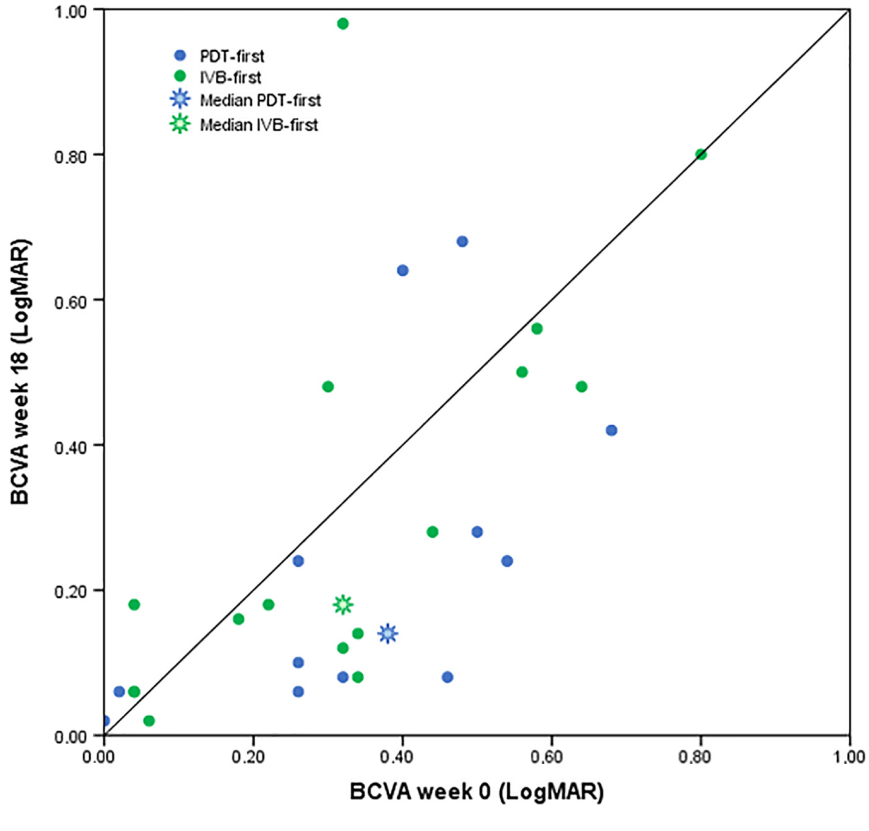

Fig. 5. Plot of the best corrected visual acuity (BCVA) in LogMAR at week 0 versus week 18 for each patient, coded by treatment group.

results of Saito et al. (2008), who also reported an improved visual acuity after combination therapy with IVB and PDT. Few of our patients (n = 5) suffered a clear deterioration in visual acuity at week 18 (loss of VA more than 0.1 logMAR, Fig. 5), but we found that the majority of the vascular and structural outcomes in these patients had improved. This shows that even if vascular and structural abnormalities are restored, visual acuity may not. Although it is important to treat the vascular and structural features related to the neovascularization to prevent further decline of visual function, there is no clear relation between the course of vascular or structural features and whether the visual acuity improves, stabilizes or deteriorates. Kim et al. (2017) suggested that a poorer visual outcome is related to the presence of a PED at baseline. PED was present in almost all patients in our cohort (Table 2), showing an overall improved visual acuity (Fig. 5). Kim et al. (2017) treated patients with anti-VEGF monotherapy, therefore combined therapy with PDT and IVB might be favourable when a PED is present at baseline.

As stated before, initial PDT treatment showed a more effective outcome. Figure 6 shows that initial treatment with PDT resulted in slightly higher resolution percentages in almost all vascular and structural parameters at all follow-up visits, although not statistically significant. Also improvement of visual acuity seemed superior in the PDT-first patients (see Fig. 5). A possible explanation for the more promising results in the PDT-first group is related to its effect on the endothelial cells of the abnormal blood vessels of the type 3 neovascularization. Verteporfin binds selectively to active endothelial cells in the abnormal blood vessels, triggering a photochemical reaction when activated by laser energy. The activated verteporfin molecule leads to selective microvascular occlusion (Newman 2016). If patients are treated with IVB first, we can hypothesize that the number of potentially verteporfin-binding endothelial cells has already been diminished by the IVB, since bevacizumab inhibits the activity of VEGF molecules that bind to receptors on the surface of endothelial cells. On the other hand, if patients start with PDT, the leaking blood vessel will be sealed and bevacizumab may strengthen this effect by further inhibiting angiogenesis and vascular permeability.

This study evaluated in detail the progression of typical type 3 neovascularization related parameters on both *en face* and cross-sectional B-scans, which can be used in future studies. The statistical power of this study is limited due to its explorative nature and the relatively small study population, to truly compare the different sequences of the combination therapy. Larger cohorts are necessary to confirm or

Table 2. Comparison between PDT-first and IVB-first groups on presence of baseline characteristics (*n*, %).

	PDT-first (total = 11)	IVB-first (total = 15)	p-value[a]
IRN	3 (27%)	6 (40%)	0.683
SRN	0 (0%)	1 (7%)	1.000
SRPEN	1 (9%)	4 (27%)	0.358
RCA	8 (73%)	9 (60%)	0.683
IRC	9 (82%)	15 (100%)	0.188
SRF	1 (9%)	2 (13%)	1.000
PED	11 (100%)	13 (87%)	0.492

IRC = intraretinal cysts; IRN = intraretinal neovascularization; IVB = intravitreal bevacizumab; PDT = photodynamic therapy; PED = pigment epithelial detachment; RCA = retinal choroidal anastomosis; SRF = subretinal fluid; SRN = subretinal neovascularization; SRPEN = sub-RPE neovascularization.
[a] Chi-Square test.

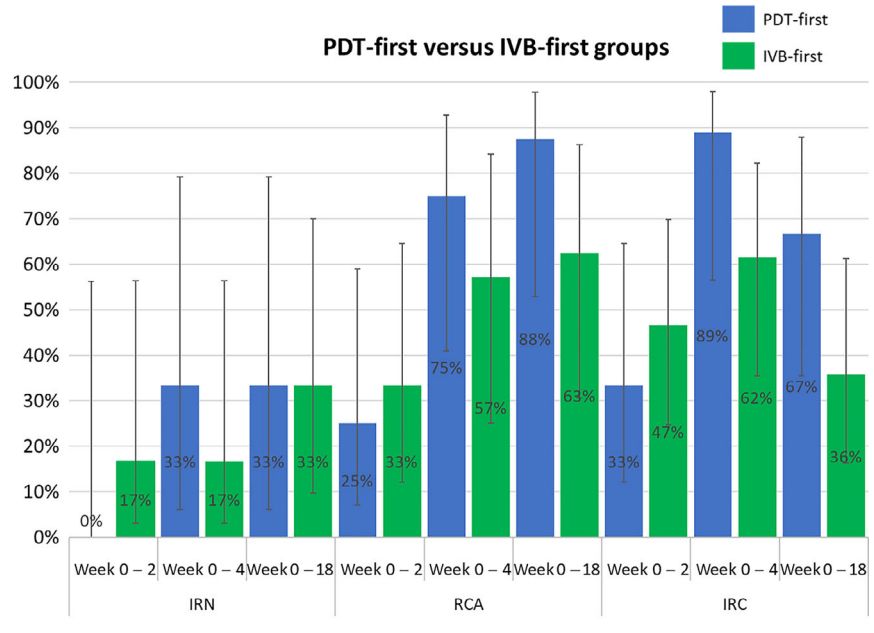

Fig. 6. Comparison between photodynamic therapy (PDT)-first and intravitreal bevacizumab (IVB)-first group on fraction of resolved features at 2, 4 and 18 weeks with respect to week 0 for the vascular primary features: intraretinal neovascularization (IRN) and retinal choroidal anastomosis (RCA), and structural primary feature: intraretinal cysts (IRC). Features were only considered when they were present at baseline. Intraretinal neovascularization (IRN) was present at baseline in three PDT-first (27%) and in six IVB-first (40%) eyes, RCA was present at baseline in eight PDT-first (73%) and in nine IVB-first (60%) eyes, and IRC was present in nine PDT-first (82%) and 15 IVB-first (100%) eyes (Table 2). The error bars show the 95% confidence interval.

reject the theory that starting with PDT is most effective. Furthermore, this study did not include treatment with IVB alone, which is a widely accepted treatment regimen for type 3 neovascularization. This could be the subject for future research, together with a longer follow-up period, enabling the registration of recurrence rates as well. Another difficulty in the current study was the considerable variation between the two graders for the OCT-A images (agreement data not shown), which was overcome by presenting consensus data. The follow-up scores were also subjective and could be improved by automated quantification of the flow on OCT-A images. However, since images were presented randomly, the specialists were not biased by the knowledge of the treatment status of the patient. Furthermore, two different OCT-A devices were used in this study. Since the analysis only included subjective grading of presence or absence of several flow- and structure-related parameters, we believe this did not influence the results.

In conclusion, this study shows the efficacy of combined PDT and IVB therapy on type 3 neovascularization in short-term. It showed improvement of vascular and structural features on OCT-A combined with increase of BCVA, and possibly a more effective outcome when starting with PDT. To optimize the treatment regimen for patients with a type 3 neovascularization, future studies should focus on the analysed parameters in larger cohorts with a longer follow-up and other treatment options, such as different anti-VEGF agents.

References

Amarakoon S, de Jong JH, Braaf B, Yzer S, Missotten T, van Velthoven ME & de Boer JF (2015): Phase-resolved doppler optical coherence tomographic features in retinal angiomatous proliferation. Am J Ophthalmol **160**: 1044–1054.e1041.

Bansal R, Hemanth V, Mulkutkar S, Singh R, Gupta V, Dogra MR & Gupta A (2018): OCT angiography demonstrates retinal angiomatous proliferation and chorioretinal anastomosis of type 3 neovascularization. Int Ophthalmol **38**: 2149–2151.

Braaf B, Vermeer KA, Vienola KV & de Boer JF (2012): Angiography of the retina and the choroid with phase-resolved OCT using interval-optimized backstitched B-scans. Opt Express **20**: 20516–20534.

Costagliola C, Romano MR, dell'Omo R, Cipollone U & Polisena P (2007): Intravitreal bevacizumab for the treatment of retinal angiomatous proliferation. Am J Ophthalmol **144**: 449–451.

Dansingani KK, Naysan J & Freund KB (2015): En face OCT angiography demonstrates flow in early type 3 neovascularization (retinal angiomatous proliferation). Eye (Lond) **29**: 703–706.

Fogli S, Del Re M, Rofi E, Posarelli C, Figus M & Danesi R (2018): Clinical pharmacology of intravitreal anti-VEGF drugs. Eye (Lond) **32**: 1010–1020.

Freund KB, van Ho I, Barbazetto IA et al. (2008): Type 3 neovascularization: the expanded spectrum of retinal angiomatous proliferation. Retina **28**: 201–211.

Gass JDM, Agarwal A, Lavina AM & Tawansy KA (2003): Focal inner retinal hemorrhages in patients with drusen: an early sign of occult choroidal neovascularization and chorioretinal anastomosis. Retina **23**: 741–751.

Gupta B, Jyothi S & Sivaprasad S (2010): Current treatment options for retinal angiomatous proliferans (RAP). Br J Ophthalmol **94**: 672–677.

de Jong JH, Braaf B, Amarakoon, S, et al. (2018): Treatment effects in retinal angiomatous proliferation imaged with OCT angiography. Ophthalmologica, **241**: 1–11.

Kashani AH, Chen CL, Gahm JK, Zheng F, Richter GM & Rosenfeld PJ, Shi Y & Wang RK (2017): Optical coherence tomography angiography: A comprehensive review of current methods and clinical applications. Prog Retin Eye Res **60**: 66–100.

Kataoka K, Takeuchi J, Nakano Y, Fujita A, Kaneko H, Ito Y & Terasaki H (2018): Characteristics and classification of type 3 neovascularization with B-scan flow overlay and en face flow images of optical coherence tomography angiography. Retina, **40**: 1–12.

Kim JM, Kim JH, Chang YS, Kim JW, Kim CG & Lee DW (2017): Treatment of bilateral retinal angiomatous proliferation with anti-vascular endothelial growth factor: 12-month outcome. Kor J Ophthalmol **31**: 240–248.

Kuehlewein L, Dansingani KK, de Carlo TE et al.(2015): Optical coherence tomography angiography of type 3 neovascularization secondary to age-related macular degeneration. Retina **35**: 2229–2235.

Meyerle CB, Freund KB, Iturralde D et al. (2007): Intravitreal bevacizumab (Avastin) for retinal angiomatous proliferation. Retina **27**: 451–457.

Newman DK (2016): Photodynamic therapy: current role in the treatment of chorioretinal conditions. Eye (Lond) **30**: 202–210.

Querques G, Miere A & Souied E (2016): Optical coherence tomography angiography features of type 3 neovascularization in age-related macular degeneration. Dev Ophthalmol **56**: 57–61.

Ravera V, Bottoni F, Giani A, Cigada M & Staurenghi G (2016): Retinal angiomatous proliferation diagnosis: a multiimaging approach. Retina **36**: 2274–2281.

Rosenfeld PJ, Brown DM, Heier JS, Boyer DS, Kaiser PK, Chung CY & Kim RY (2006): Ranibizumab for neovascular age-related macular degeneration. N Engl J Med **355**: 1419–1431.

Saito M, Shiragami C, Shiraga F, Nagayama D & Iida T (2008): Combined intravitreal bevacizumab and photodynamic therapy for retinal angiomatous proliferation. Am J Ophthalmol **146**: 935–941.e931.

Shweiki D, Itin A, Soffer D & Keshet E (1992): Vascular endothelial growth factor induced by hypoxia may mediate hypoxia-initiated angiogenesis. Nature **359**: 843–845.

Spaide RF, Fujimoto JG & Waheed NK (2015a): Image artifacts in optic coherence angiography. Retina **35**: 2160–2180.

Spaide RF, Klancnik JM & Cooney MJ (2015b): Retinal vascular layers imaged by fluorescein angiographyand optical coherence tomography angiography. JAMA Ophthalmology **133**: 45–50.

Su D, Lin S, Phasukkijwatana N, Chen X, Tan A, Freund KB & Sarraf D (2016): An updated staging system of type 3 neovascularization using spectral domain optical coherence tomography. Retina **36**: S40–S49.

Tan ACS, Dansingani KK, Yannuzzi LA, Sarraf D & Freund KB (2016): Type 3 neovascularization imaged with cross-sectional and en face optical coherence tomography angiography. Retina, **37**: 1–13.

Tsai ASH, Cheung N, Gan ATL, Jaffe GJ, Sivaprasad S, Wong TY & Cheung CMG (2017): Retinal angiomatous proliferation. Surv Ophthalmol **62**: 462–492.

Yannuzzi LA, Negrao S, Iida T et al. (2001): Retinal angiomatous proliferation in age-related macular degeneration. Retina **21**: 416–434.

Yannuzzi LA, Freund KB & Takahashi BS (2008): Review of retinal angiomatous proliferation or type 3 neovascularization. Retina **28**: 375–384.

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