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Prognostic Factors for Long Term Visual Acuity Outcome after Ranibizumab Therapy in Patients with Neovascular Age-Related Macular Degeneration

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Abstract

Purpose: To evaluate whether Spectral Domain Optical Coherence Tomography (SDOCT) and Fluorescein Angiography (FA) findings are predictive of Visual Acuity (VA) outcome after ranibizumab for Neovascular Age-related Macular Degeneration (NVAMD).

Methods: Best corrected VA of 72 previously untreated eyes with NVAMD were retrospectively collected at baseline, after 3 injections and at 12, 24 and 36 months follow-up, if available. FA and SDOCT images at baseline were qualitatively and quantitatively analyzed using reading center software. The area of CNV lesion components on FA as well as the volume of the neurosensory retina, the outer nuclear layer, subretinal fluid, subretinal hyperreflective material and pigment epithelial detachment (PED) on SDOCT were calculated. VA as well as change in VA from baseline were correlated with all parameters.

Results: VA at baseline significantly correlated with final VA as well as change in VA during follow-up. A greater area of total CNV lesion, classic as well as occult CNV lesion components on FA correlated with lower VA during follow-up. Qualitative features that indicated better short-term outcomes included the presence of retinal angiomatous proliferation (RAP) and the absence of cystoid spaces on SDOCT. Eyes with a larger retinal volume demonstrated a greater short-term increase in VA, eyes with larger PED volume and area measurements on OCT demonstrated less VA increase after 12 months. Lower VA outcomes were seen in eyes with larger volume of subretinal hyperreflective material or larger area of PED, as well as lower volume of the outer nuclear layer. No prognostic value could be identified for CNV lesion types other than RAP, subretinal fluid, gender and age.

Conclusions: Several FA and SDOCT parameters showed prognostic value for VA outcome after ranibizumab in NVAMD. A larger, prospective dataset will be crucial for defining the relative importance of these parameters.

Keywords: Neovascular age related macular degeneration (NVAMD); Ranibizumab; Prognostic factors; Optical coherence tomography (OCT); Angiography

Introduction

Ranibizumab (Lucentis®, Novartis AG, Basel, Switzerland) is a recombinant, humanized, monoclonal antibody fragment that neutralizes vascular endothelial growth factor A (VEGF). VEGF triggers the growth of new vessels, and is an important factor for the development of choroidal neovascularization (CNV) [1-7] in neovascular age-related macular degeneration (AMD). Neovascular AMD is the leading cause of blindness in the elderly population above 65 years of age in the industrialized world [8,9] and the third major cause of blindness worldwide [10].

Intravitreal administration of ranibizumab can prevent vision loss or improve visual acuity (VA) in patients with neovascular AMD [11,12].

Optical coherence tomography (OCT) is a noninvasive imaging technique that has become an important diagnostic tool for management of patients with neovascular AMD [13-15]. OCT images allow identification of fine morphologic changes within the retina and facilitate quantification of various retinal and subretinal structures [16-19]. Advances in OCT technology, known as spectral domain OCT (SDOCT), have provided improved resolution, sensititvity, speed and the ability to generate three-dimensional depictions of the retina and deeper structures. OCT is increasingly used in clinical trials as well as in everyday practice to evaluate treatment outcome and guide re-treatment decisions for patients undergoing ranibizumab therapy [14,15].

Outcome after ranibizumab treatment in neovascular AMD varies between individuals. Several studies aimed to identify prognostic factors for VA and observed that age, VA at baseline and various OCT- and fluorescein angiography parameters may have predictive value [20-27]. Results however varied between studies, possibly due to differences in patient populations, as well as in imaging and image analysis methods. Many of the previous studies utilized automatically generated retinal thickness values provided by the Stratus OCT for subsequent analysis. These measurements have been demonstrated to be frequently inaccurate due to incorrect identification of the retinal

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boundaries, particularly in patients with CNV [28-30]. Furthermore, reliable automated quantification of CNV lesion components on fluorescein angiography or OCT is not yet possible with existing software algorithms.

This study aims to identify prognostic factors for visual outcome after ranibizumab therapy in eyes with neovascular AMD utilizing manual quantitative analysis of fluorescein angiography and high resolution SDOCT images.

Methods

Data collection

For this retrospective study, data from all patients receiving intravitreal injections of ranibizumab for neovascular AMD at the University of Cologne from June 2008 till March 2009 were collected and reviewed. During that time, patients were generally treated with 3 initial monthly injections of ranibizumab, followed by PRN (pro re nata) guided re-injections whenever signs for CNV activity were detected on funduscopy, OCT or angiography. To be included in the study, eyes were required to show active CNV lesions due to AMD and have SDOCT as well as fluorescein angiography images available at baseline. Patient characteristics such as age, gender, previous treatments, and concurrent diseases were collected.

A total of 624 patients received ranibizumab therapy within the 10 month period. 554 patients were excluded because 1) the study eye had been previously treated for CNV with bevacizumab and/or photodynamic therapy (PDT), 2) presence of other comorbid disease that could affect visual function, 3) absence of baseline SDOCT volume scans or fluorescein angiograms, and 4) failure of the patient to return for follow-up after 3 injections.

Seventy-two eyes of 70 consecutive patients met the inclusion criteria. Best corrected VA was collected at baseline before the first injection, after 3 monthly injections of ranibizumab, and at 12 months, 24 months and 36 months follow-up, if available. Fluorescein angiography images were collected at baseline (Spectralis HRA plus OCT, Heidelberg Engineering, Heidelberg, Germany) and after 3 injections of ranibizumab, if available. SDOCT images were collected at baseline and after 3 injections of ranibizumab (Spectralis HRA plus OCT, Heidelberg Engineering, Heidelberg, Germany). SDOCT volume scans (37 parallel 6 mm OCT B-scans (15° × 20°), 512 A-scans per B-scan, 20 images averaged) were used for analysis. This study adhered to the tenets set forth in the Declaration of Helsinki.

Fluorescein angiography analysis

Fluorescein angiography images at baseline were viewed and graded by a certified grader (SL) at the Cologne Image Reading Center and Laboratory (CIRCL, University of Cologne, Germany) using grading software written by Doheny Image Reading Center (DIRC, Doheny Eye Institute, Los Angeles) software engineers. This software is equipped with standard planimetric tools to allow calculation of the area of any closed-loop figure or structure drawn by the grader using a computer mouse (Figure 1).

CNV lesions were graded according to the modified Macular Photocoagulation Study (MPS) grading protocol utilized in the treatment of AMD with photodynamic therapy (TAP) and verteporfin in photodynamic therapy (VIP) studies [31,32]. Briefly, classic CNV was identified as an area of uniform early hyperfluoresence that showed extensive leakage in the mid and late phases. Occult CNV was classified as areas of stippled hyperfluoresence that appeared in the mid and late phases of the fluorescein angiography. Boundaries of the total area of classic CNV (drawn in the late venous phase of the transit), occult CNV (drawn in the late phase) and the total area of CNV lesion (defined as the area of classic plus occult CNV plus any contiguous areas of thick hemorrhage, blocked fluorescence, staining scar, or serous pigment epithelium detachment (PED) that could be obscuring the boundaries of the CNV) were marked. The area (mm^2) of the CNV lesion, classic CNV components and occult CNV components were calculated in all cases.

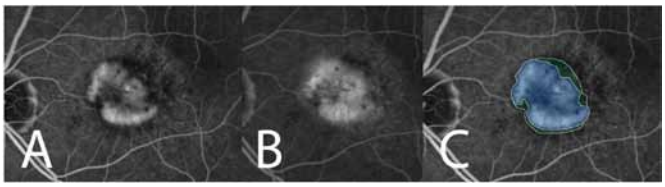

Figure 1: Quantitative analysis of fluorescein angiography images using the reading center GRADOR developed by Doheny Image Reading Center (DIRC, Doheny Eye Institute, Los Angeles) software engineers. CNV lesion components are manually delineated and the area of various CNV lesion components is calculated by the software. A: Early phase, B: Late phase, C: Graded image (blue: classic CNV lesion component, green: blocked fluorescence).

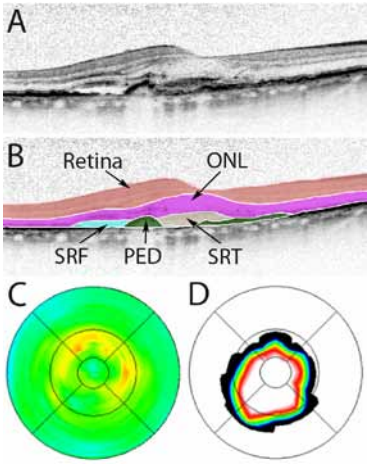

Figure 2: Quantitative analysis of spectral domain optical coherence tomography images (SDOCT) using the reading center software "3DOCTOR" developed by the Doheny Imaging Exploration and Software Engineering Laboratory (DIESEL). Boundaries of various retinal and subretinal spaces are manually drawn on each SDOCT scan. A: SDOCT B-scan, B: SDOCT B-scan after manually delineating the boundaries of various retinal and subretinal spaces. Volumes are calculated by the software for all graded spaces. C: Thickness map example for the neurosensory retina D: Thickness map example for pigment epithelial detachment.

CNV lesions were deemed to be "predominantly classic CNV" if classic CNV occupied at least 50% of the total CNV lesion area. Lesions that contained some classic CNV, but less than 50% of the lesion was composed of classic CNV, were classified as "minimally classic CNV". Lesions containing occult CNV, but no classic CNV, were graded as "occult with no classic CNV." Areas of retinal vascular communication to the lesion were identified (termed retinal angiomatous proliferation, RAP) [33,34]. Additionally, leakage on fluorescein angiography as evidence of persistent CNV activity after 3 ranibizumab injections, was noted.

SDOCT analysis

The software used for SDOCT analysis (termed "3D-OCTOR") was written by DIRC software engineers to facilitate viewing and manual grading of SDOCT images. The OCTOR software has been described and validated in previous reports [16,28]. This software, which effectively operates as a painting program and calculator, imports data exported from the SDOCT machine and allows the grader to use a computer mouse to manually draw boundaries of various structures and compartments (e.g. neurosensory retina, subretinal fluid (SRF) etc.) on each OCT B-scan (Figure 2). After interpolation, thickness values are calculated and converted into volumes (mm^3). Analogous to the SDOCT software, OCTOR provides a report showing the calculated thickness and volume values for the 9 Early Treatment of Diabetic Retinopathy Study (ETDRS) macular subfields for each compartment of interest (Figure 2).

SDOCT scans at baseline were analyzed by certified OCT graders (TR, SH, SL) at the CIRCL. Qualitative analysis included the presence of intraretinal cystoid spaces, SRF, and PEDs at baseline. Quantitative analysis was performed for all SDOCT volume scans that were generated using parallel B-scans spaced less than 125 microns apart and were of adequate quality (62 out of 72 cases). The foveal center point was manually determined for each case and the ETDRS grid was positioned to be centered on the fovea. Manually drawn boundaries included the internal limiting membrane (ILM), inner and outer borders of SRF and subretinal hyperreflective material (if present), the inner surface of the retinal pigment epithelium (RPE), and the estimated normal position of the RPE layer (in cases with RPE elevation). Additionally, the inner and outer borders of the outer nuclear layer (ONL) were drawn at baseline. All boundaries were drawn in accordance with the standard OCT grading protocol of the CIRCL [16]. After completion of the grading, the OCTOR software was used to calculate output parameters for all graded spaces: retina, ONL, SRF, subretinal hyperreflective material, and PED (Figure 2). Volume (mm^3) values of ETDRS subfield 9 (Foveal central subfield, FCS) were collected for the spaces retina and outer nuclear layer, the total volume (mm^3) as well as the total area (mm^2) within the ETDRS grid was calculated for SRF, subretinal hyperreflective material and PED.

Further, evidence of persistent CNV activity after 3 ranibizumab injections such as intraretinal or subretinal fluid was noted.

Statistical methods

Statistical analysis was performed using commercially available software (SigmaPlot for Windows version 11.0 Systat Software Inc., Germany). Snellen VA was converted to the logarithm of minimal angle of resolution (logMAR) VA for the purpose of statistical analysis. Change in VA was calculated from the difference between VA at baseline and VA at follow-up. Pearson correlation was used to correlate the fluorescein angiographic planimetric data and OCT thickness and volume measurements with logMAR VA as well as with the change in VA between baseline and follow-up visits.

The Mann-Whitney rank sum test was used for comparison between different CNV lesion types (minimal classic CNV, predominantly classic CNV, occult CNV without RAP, occult CNV with RAP) as well as qualitative OCT features (presence of intraretinal cystoid spaces, SRF or PED) and the presence or absence of persistent CNV activity after 3 injections of ranibizumab. P-values <0.05 were considered statistically significant.

Results

A summary of patient characteristics is provided in table 1.

Visual acuity

VA at baseline correlated with VA after 3 injections (R=0.7, p<0.001), 12 months (R=0.6, p<0.001), 24 months (R=0.6, p<0.01), and 36 months (R=0.5, p<0.02). Additionally, VA at baseline was inversely correlated with VA change after 3 injections (R=-0.3, p<0.05) and at 12 month follow-up (R=-0.5, p<0.01), indicating that eyes with lower VA (higher logMAR values) at baseline showed greater increase in VA (negative log MAR change value) during 1 year follow-up, however did not reach as good VA values as eyes with high VA values at baseline.

Fluorescein angiography

The total baseline CNV lesion area on FA correlated with VA after 3 injections (R=0.3, p<0.05) and at 12 months (R=0.4, p<0.01), with

Age [mean ± SD]		77 ± 8 years
Visual acuity [mean ± SD]		
Baseline (n=72)		0.53 ± 0.31 logMAR
After 3 injections (n=72)		0.44 ± 0.33 logMAR
12 months follow-up (n=33)		0.45 ± 0.32 logMAR
24 months follow-up (n=26)		0.55 ± 0.43 logMAR
36 months follow-up (n=22)		0.62 ± 0.47 logMAR
Number of injections since baseline [mean ± SD]		
12 months follow-up (n=33)		6.2 ± 1.6
24 months follow-up (n=26)		10.4 ± 3.0
36 months follow-up (n=22)		16.1 ± 4.8
CNV activity after 3 injections [n (%)]		27 (37.5%)
Type of choroidal neovascularization [n (%)]		
Predominantly classic lesion		15 (20.8 %)
Minimally classic lesion		7 (9.7 %)
Occult with no classic lesion		50 (69.4 %)
• without RAP		35 (70 %)
• with RAP		15 (30 %)
Presence of SDOCT parameters at baseline [n (%)]		
Pigment epithelial detachment		67 (93.1%)
Subretinal fluid		67 (93.1%)
Cystoid spaces		36 (50.0%)
Size of CNV lesion components on FA at baseline [area, mean ± SD]		
Total CNV lesion		5.49 ± 5.78 mm^2
Occult CNV lesion component		4.78 ± 5.22 mm^2
Classic CNV lesion component		0.29 ± 0.67 mm^2
Volume of SDOCT parameters at baseline [mean ± SD]		
Neurosensory retina	FCS	0.23 ± 0.08 mm^3
Outer nuclear layer	FCS	0.09 ± 0.03 mm^3
Subretinal fluid	FCS	0.04 ± 0.06 mm^3
	Total volume	0.40 ± 0.60 mm^3
	Area	4.95 ± 5.06 mm^2
Subretinal hyperreflective material	FCS	0.02 ± 0.04 mm^3
	Total volume	0.14 ± 0.30 mm^3
	Area	1.85 ± 2.76 mm^2
Pigment epithelial detachment	FCS	0.07 ± 0.10 mm^3
	Total volume	0.73 ± 1.28 mm^3
	Area	6.94 ± 5.88 mm^2

LogMAR: Logarithm of the Minimum Angle of Resolution; SD: Standard Deviation; SDOCT: Spectral Domain Optical Coherence Tomography; CNV: Choroidal Neovascularisation; FA: Fluorescein Angiography; RAP: Retinal Angiomatous Proliferation; FCS: Foveal Central Subfield

Table 1: Characteristics of the Patients.

smaller lesions having better vision. No correlation could be observed for 24 and 36 months follow-up. Greater area of the classic CNV lesion component correlated with lower VA after 3 injections (R=0.3, p<0.05). Greater area of the occult CNV lesion component correlated with lower VA at 12 months (R=0.5, p<0.01). No association could be observed between change in VA and fluorescein angiography parameters.

Eyes with occult CNV and RAP demonstrated a significantly better increase in VA after 3 injections compared to eyes with occult CNV without RAP (p<0.01). No other differences were observed between CNV lesion types regarding VA or change in VA.

SDOCT

Thirty-six out of 72 eyes (50%) demonstrated cystoid spaces at baseline. VA after 3 injections (p<0.01) was significantly worse in eyes with intraretinal cystoid spaces at baseline compared to eyes without intraretinal cystoid spaces. Sixty-seven eyes (93.1%) demonstrated SRF and 67 eyes (93.1%) PED at baseline. The presence of SRF or PED at baseline did not show any predictive value for VA outcome.

The FCS retinal volume at baseline inversely correlated with change in VA after 3 injections (R=-0.3, p<0.05), indicating that eyes with a larger volume of the neurosensory retina showed a better short-term increase in VA (Table 2). Eyes with larger volume (R=0.5, p<0.01) and area of PED (R=0.7, p<0.001) at baseline showed less increase in VA at the 12 months visit.

The total volume and area of subretinal hyperreflective material at baseline correlated with VA after 3 injections (R=0.3, p<0.05). Total area of PED at baseline correlated with VA at 12 months (R=0.6, p<0.001), 24 months (R=0.5, p<0.05) and 36 months (R=0.6, p<0.05), indicating that eyes with larger PED areas at baseline showed poorer VA outcomes. The central volume of the ONL at baseline inversely correlated with VA after 3 injections (R=-0.4, p<0.001), at 12 months (R=-0.4, p<0.05), 24 months (R=-0.7, p<0.001) and 36 months (R=-0.6, p<0.01), indicating that eyes with a more atrophic ONL at baseline showed poorer VA outcomes even during long-term follow-up.

No statistically significant prognostic value for VA or change in VA at any follow-up time point was detected for age, gender and SRF. There was no significant difference regarding the VA outcome during follow-up between eyes with or without persistent CNV activity after 3 injections.

Discussion

Using manual subanalysis of high resolution SDOCT volume scans and quantitative analysis of fluorescein angiography, we could identify various parameters that appeared to be relevant prognostic markers for VA outcome after treatment with ranibizumab in patients with neovascular AMD.

Several studies have previously investigated the prognostic value of retinal imaging for VA outcome in patients with neovascular AMD undergoing anti-VEGF therapy [20-27]. Those studies provided partially conflicting results, which may be explained by differences in patient population, baseline characteristics, follow-up time or image analysis methodology.

Disagreement exists in the literature regarding the role of initial retinal thickness values. Various studies detected no correlation between retinal thickness values and VA at follow-up [20-23,25]. However, in the study reported by Einwallner et al. [21], retinal volume demonstrated a correlation with the change in VA between baseline and month 3. This is in agreement with our study, as initial retinal volume did not correlate with final VA (at the end of follow-up), but did correlate with the change in VA after 3 injections, suggesting that eyes with larger retinal volume values at baseline have a greater increase in VA shortly after the first 3 ranibizumab injections. The presence of cystoid spaces on SDOCT was not predictive for VA change, however was associated with worse VA values after 3 injections. A possible explanation is that the formation of cystoid spaces within the retina may disrupt the neurosensory network, leading to irreversible loss of retinal function.

The predictive value of cystoid spaces for a worse VA outcome and the association of larger retinal volumes with a greater short term increase in VA may seem contradictory. This however, may indicate that eyes with cystoid retinal edema and consecutively lower baseline VA may demonstrate a greater short-term increase in VA following initial anti-VEGF therapy, however still ultimately have lower VA scores in the long term follow-up. This is in agreement with observations regarding the prognostic value of baseline VA for

		VA after 3 injections	**VA at 12 months**	**VA at 24 months**	**VA at 36 months**
Neurosensory Retina	FCS	n.s.	n.s.	n.s.	n.s.
Outer nuclear layer	FCS	R=-0.4, p<0.001	R=-0.4, p<0.05	R=-0.7, p<0.001	R=-0.6, p<0.01
Subretinal fluid	Total Volume Area	n.s. n.s.	n.s. n.s.	n.s. n.s.	n.s. n.s.
Subretinal hyperreflective material	Total Volume Area	R=0.3, p<0.05 R=0.3, p<0.05	n.s. n.s.	n.s. n.s.	n.s. n.s.
PED	Total Volume	n.s.	n.s.	n.s.	n.s.
	Area	n.s.	R=0.6, p<0.001	R=0.5, p<0.05	R=0.6, p<0.05
		Change from baseline to visit after 3 injections	**Change from baseline to 12 months**	**Change from baseline to 24 months**	**Change from baseline to 36 months**
Neurosensory Retina	FCS	R=-0.3, p<0.05	n.s.	n.s.	n.s.
Subretinal fluid	Total Volume Area	n.s. n.s.	n.s. n.s.	n.s. n.s.	n.s. n.s.
Subretinal hyperreflective material	Total Volume Area	n.s. n.s.	n.s. n.s.	n.s. n.s.	n.s. n.s.
PED	Total Volume Area	n.s. n.s.	R=0.5, p<0.01 R=0.7, p<0.001	n.s.	n.s.

FCS: Foveal Central Subfield; n.s.: not significant; PED: Pigment Epithelial Detachment; VA: Visual Acuity

Table 2: Correlation between quantitative spectral domain optical coherence tomography (SDOCT) parameters (volume, mm3) and visual acuity as well as change in VA from baseline.

long-term functional outcomes after treatment for neovascular AMD [20,22,24,26]. Our results are consistent with these reports, as eyes with lower VA at baseline showed a higher gain in VA during follow-up, whereas eyes with better initial VA maintained higher VA scores over time. A possible explanation is that eyes with lower VA have a greater potential to gain vision over time, though, potentially irreversible damage to the retina may hinder complete recovery in many patients.

Ahlers and Einwallner found a significant correlation between manual SRF measurements and VA change after 3 injections of ranibizumab [21,23]. In contrast, the presence of SRF did not show any prognostic value in the studies reported by Hirami and Singh [22,26]. In our study, we also could not confirm a significant correlation between the volume or the presence of SRF and VA outcome at various follow-up time points. The lack of a significant correlation for SRF presence may be explained by the very high frequency (93%) of SRF in the eyes of our patient cohort. Thus, we may not have been sufficiently powered to detect a significant difference.

In contrast, larger volume of subretinal hyperreflective material was observed to be a prognostic factor for VA outcome after 3 injections, indicating that larger amounts of subretinal hyperreflective material at baseline correlated with lower VA values. Recently, Byun et al reported that nonresponders to bevacizumab had thicker subretinal hyperreflective material values than responders [27]. The impact of subretinal hyperreflective material on VA has already been demonstrated previously by our group using Stratus OCT images, indicating that larger amounts of subretinal material correlate with lower VA values [35]. Subretinal hyperreflective material corresponds to fibrovascular tissue, thick hemorrhage or photoreceptor debris in the subretinal space. This material may disturb the interaction between the surviving photoreceptors and the RPE more severely than SRF, and have an impact on the transport of metabolic factors. Over time, disciform scar formation may induce a loss of the overlying photoreceptor layer, resulting not only in a decrease in VA, but also in a subsequent irreversible loss of the potential to recover vision after treatment.

Increased volume of the sub-RPE space did not show a similar effect on VA in short term follow-up, although a significant association was observed between larger area measurements of PED and VA values during long-term follow-up as well as between larger area and volume measurements of PED and increase in VA after 12 months. These findings highlight the importance of identifying the location (subretinal vs sub-RPE) of the neovascular tissue on OCT.

Sayanagi et al. analyzed the association between VA and the photoreceptor status, and demonstrated that the presence of an intact inner segment/ outer segment junction band on OCT is relevant for VA outcome [36]. Disruption of the inner segment/ outer segment junction may indicate photoreceptor degeneration due to underlying neovascular tissue or intraretinal fluid accumulation. Retinal degeneration over time results in atrophy and thinning of the ONL. In our study, the baseline ONL volume appeared to be of prognostic significance, as eyes with a thinner or more atrophic ONL at baseline demonstrated lower VA values at every follow-up time point and showed the strongest correlation of all analyzed parameters on SDOCT.

Fluorescein angiography-derived measures, such as the total area of the CNV lesion, have been shown to be of prognostic value in prior studies [24]. Our findings confirmed that a greater area of the total CNV lesion and additionally a greater area of classic CNV and occult CNV lesion components are associated with worse VA outcome after 3 injections and at 12 months. When evaluating different CNV lesion subtypes, only the presence of RAP lesions in eyes with occult CNV proved to be of prognostic value in our data set. Twenty-seven eyes (37.5%) in our study demonstrated evidence of persistent CNV activity on either OCT or fluorescein angiography at the first visit following 3 injections of ranibizumab. We did not find a significant difference in the long term VA outcome between eyes with or without persistent CNV activity after 3 ranibizumab injections. Thus, eyes which rapidly respond to ranibizumab therapy do not seem to have an ultimate visual functional advantage over the eyes with a slower initial response.

Our study is not without limitations, including its retrospective design, the use of Snellen VA, and the small study population. A significant number of patients were lost to follow-up at our clinic because they returned to their referring ophthalmologist. However, our study also has several strengths. The utilization of high-resolution SDOCT images allows a more detailed interpretation of the complex morphologic changes occurring in neovascular AMD, including assessment and quantification of the ONL. The use of standardized protocol manual segmentation of OCT and angiographic images in a reading center using certified graders also allows the imaging parameters to be extracted in a reliable fashion [16].

Manual delineation of various features on SDOCT images as performed in this study may not be feasible in clinical practice. However, knowledge of the potential implication of prognostic parameters may help clinicians to judge the benefits of anti-VEGF treatment for the individual patient and to balance it against the risks of repeated intravitreal injections. As no effective alternative treatments are available to date, this information however may not change clinical management.

In summary, using manual grading software and high resolution imaging, we identified several SDOCT and fluorescein angiography parameters (area of CNV lesion, as well as the area of the occult and classic part of the CNV lesion on angiography, presence of RAP, presence of intraretinal cystoid spaces, volume of the neurosensory retina, subretinal hyperreflective material, PED and ONL layer) to be prognostic outcome parameters for VA after ranibizumab therapy in eyes of patients with neovascular AMD. A larger, prospective dataset will be crucial for defining the relative importance of these parameters.

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Financial Interest

S.R. Sadda and A.C. Walsh are co-inventors of Doheny intellectual property related to OCT that has been licensed by Topcon Medical Systems and have also served as consultants for Heidelberg Engineering, Inc. However, it is not related to the subject matter of this manuscript.

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