Comparison of the therapy effect of aflibercept and ranibizumab in patients with neovascular retinal pigment epithelium detachment identified by fluorescence angiography and optical coherence tomography angiography

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Abstract

Background To report on the current methods for choroidal neovascularization (CNV) detection and the clinical outcome of intravitreal therapies in patients with neovascular pigment epithelium detachment (PED). **Methods** Retrospective, interventional cohort study on 77 eyes of 59 patients. Inclusion criteria were a neovascular PED, identified by fluorescence angiography (FA) or/and optical coherence tomography angiography (OCTA) treated with aflibercept (16 eyes) or ranibizumab monotherapy (36 eyes) or with at least three injections of ranibizumab, with a therapy switch to aflibercept in case of persistent fluid (25 eyes). The therapy regimen was a pro re nata (PRN) scheme with an upload phase of three monthly injections. Outcome measures were sensitivity of CNV detection and evaluation of CNV activity at baseline on FA compared to OCTA, the change in highest retinal prominence (HRP) and PED size, assessed by spectral - domain OCT (SD-OCT), and the change in best-corrected visual acuity (BCVA) three months after therapy initiation in the monotherapy groups or after the switch. **Results** Sensitivity of CNV detection was slightly superior for FA (0.786) compared to OCTA (0.706), whereas CNV activity evaluation was superior on OCTA. HRP significantly decreased after aflibercept ($p < 0.001$) or ranibizumab monotherapy ($p < 0.001$), and after therapy switch to aflibercept ($p < 0.001$) in ranibizumab refractory patients. Corresponding BCVA improved in these groups, but without statistical significance ($p = 0.46$; $p = 0.11$; $p = 0.19$). PED size significantly decreased after aflibercept monotherapy ($p = 0.001$) or after therapy switch to aflibercept ($p < 0.001$), but not after ranibizumab. **Conclusions** The combination of FA and OCTA offers significantly improved visualisation, quantification, and predictability of CNV activity in neovascular PED. Aflibercept and ranibizumab are effective treatment options for neovascular AMD with PED, with a stronger effect of aflibercept on the PED itself. Furthermore, aflibercept appears to be a valuable tool for the management of patients unresponsive to ranibizumab.

Introduction

The term retinal pigment epithelium detachment (PED), a subtype of age-related macular degeneration (AMD) summarizes a heterogeneous group of different components underneath the retinal pigment epithelium (RPE) depending on the underlying pathomechanism. It is important to distinguish, whether there is additional sub- and/or intraretinal fluid on OCT and whether a PED is serous, drusenoid or angiographically vascularized (serous vascularized or fibrovascular determined by the predominant proportion), since vascularization implies the onset of an exudative disease justifying therapy with anti-vascular endothelial growth factor (VEGF) agents. Traditionally, fluorescein angiography (FA) is the gold standard for the diagnosis of choroidal neovascularization (CNV). Optical coherence tomography angiography (OCTA) is a newly developed non-invasive imaging technique that allows en face visualization of blood flow in retinal and choroidal vasculature (1). Many studies have been performed recently to investigate the ability of OCTA to analyse CNV features, secondary to different macular diseases, both before and after treatment. However, few studies so far compared FA and OCTA in their sensitivity of CNV identification and predictability of CNV activity in patients with PED (2-4).

Furthermore, although PEDs are a frequent finding in patients with AMD (5) little is known about the treatment modalities. Several authors have reported functional worsening during the natural course, with nearly 50% of patients with newly diagnosed untreated PED experiencing a loss of three lines during a mean observation period of one year (6, 7). We conducted our study in the context of the current controversy regarding possible differences between the two available anti-VEGF agents, either aflibercept or ranibizumab. The only available prospective randomized clinical trial for neovascular AMD with a direct comparison between these two drugs (i.e., the VIEW trials) showed no difference in visual acuity or change in fluid accumulation. A difference was found in the second year, where the number of injections in the PRN regimen part of the study was lower when using 2 mg aflibercept instead of 0.5 mg ranibizumab (8).

Ranibizumab and aflibercept display different pharmacologic characteristics, which may have an effect on treatment responses in specific subgroups. Ranibizumab (Lucentis; Novartis Pharma AG, Basel, Switzerland) is a recombinant, humanized monoclonal antibody Fab fragment that neutralizes all isoforms of VEGF-A. Aflibercept (Eylea; Bayer Schweiz AG, Zurich, Switzerland) is a recombinant fusion protein composed of an Fc domain fused to the VEGF-binding domains of VEGF receptors 1 and 2. Aflibercept has several theoretical advantages compared to ranibizumab: 1. it has a much higher binding affinity for VEGF (0.5 pM dissociation constant for VEGF165 and VEGF121 (9)); 2. the vitreous half-life of aflibercept (18 days) is longer than ranibizumab (9 days), but slightly shorter than bevacizumab (21 days (10)) and 3. it binds related growth factors, such as placental growth factors 1 and 2 (PLGF1 and PLGF2) and VEGF-B (11). These receptors are unequally distributed in retinal and choroidal layers (12, 13), suggesting that the exudative phenotypes might potentially be influenced by different patterns of receptor activation. Thus, the different spectrum of anti-VEGF drugs might result in different responses depending on the phenotype. In fact, some reports have suggested that aflibercept may have a stronger effect on PEDs as described for bevacizumab refractory cases (14, 15).

As such, aflibercept appears to have theoretical pharmacological and clinical advantages in the treatment of neovascular AMD compared to ranibizumab. Another consideration is the fact that aflibercept, due to its higher VEGF-binding affinity may be useful in patients with persistent fluid treated with ranibizumab.

Therefore, the intention of our study was to evaluate whether this higher potency of aflibercept may lead to better efficacy in patients who might have developed resistance to other anti-VEGF agents (e.g. ranibizumab).

Methods

In this institutional, interventional, retrospective cohort study 77 eyes of 59 patients with neovascular active AMD with PED, treated with intravitreal anti-VEGF injections between 2011 and 2018 at the Department of Ophthalmology of the University of Berlin, Charité, Germany, are presented. All patients gave their informed consent and all procedures were in concordance with the tenets of the Declaration of

Helsinki. All patients were treated on label so that no ethics approval was needed for the retrospective chart review.

Diagnostic procedures included best-corrected visual acuity (BCVA) assessment in logMAR, anterior and posterior segment examination, spectral-domain optical coherence tomography (SD-OCT; Heidelberg Spectralis, Heidelberg Engineering, Heidelberg, Germany), optical coherence tomography angiography (OCTA; Heidelberg Spectralis, Heidelberg Engineering, Heidelberg, Germany), and fluorescein angiography (FA; Heidelberg Spectralis, Heidelberg Engineering, Heidelberg, Germany),

Baseline

The following OCT - parameters were assessed: highest retinal prominence (HRP), the distance from the RPE to the inner limiting membrane (ILM) at the highest point within the macula, in μm on the macular thickness map, the PED height in μm by manual measurement of the distance between the RPE and the Bruch's membrane at the highest concavity and the existence of intra- or subretinal fluid. Standard settings for OCT recordings were: $20^\circ \times 20^\circ$ volume scan, 49 sections at a distance of 122 μm . FA was performed for evaluation and classification of a CNV. FA was repeated periodically when visual loss occurred and/or in situations of poor response. For the OCTA examinations, 70 000 A-Scans were acquired and a $15^\circ \times 15^\circ$ scan angle protocol was used to gain a total of 261 B-scans with a resolution of 5.7 $\mu\text{m}/\text{pixel}$. The standard OCTA viewing module (Software version 6.9.5.0) and its associated automatic segmentation of the retinal layers was applied to derive the en face slabs for each vascular plexus. The presentation of CNVs was best visualized after manual segmentation adjustments were made.

Following CNV activity criteria were assessed: CNV shape, branching pattern and occurrence of anastomoses as in (1). Active CNV typically presents with tortuous vessels, numerous tiny capillaries and anastomoses and/or loops compared to inactive CNV with large, linear, mature vessels ("dead tree appearance") without any anastomoses/ loops. We further determined the CNV size in square millimetres.

At baseline patients were either treatment naïve (aflibercept and ranibizumab group) or had at least three injections of ranibizumab prior study inclusion (therapy switch group).

Treatment and Follow-up

Inclusion criteria were a PED with additional intra- or subretinal fluid, observed on OCT, and a full loading dose of three monthly intravitreal injections of the same drug (i.e., ranibizumab or aflibercept). Exclusion criteria were any ocular condition that was able to interfere with potential visual improvement (i.e. pigment epithelium tear at baseline) and poor image quality.

Patients were either treated with three injections of 0.5 mg ranibizumab or 2 mg aflibercept in monthly intervals. Patients with bilateral disease were treated with the same drug on both eyes a minimum of 5 days apart. The rationale for using either ranibizumab or aflibercept was based on clinical judgment and

on the fact that aflibercept was first authorized in November 2012 for the treatment of wet AMD in Europe.

One month after the total of three injections, a follow up visit was performed (visit 1). In case of a dry macula or in case of a decreased PED without any sub- or intraretinal fluid, the patients were just observed monthly for the first twelve months after the last injection. Three re-injections in monthly intervals, as described in the IVAN trial (16, 17), were performed in case of 1. persistent or recurrent intraretinal or subretinal fluid on OCT; 2. new subretinal haemorrhage of the CNV; and 3. worsening of visual acuity with evidence of intra- or subretinal fluid on OCT or 4. an increase of the PED height. First line therapy was continued, if the fluid accumulation decreased. In cases of increased fluid after three consecutive injections, the treatment was switched between the two intravitreal agents. In our study, 22 patients were switched from ranibizumab to aflibercept. Only one patient was switched from aflibercept to ranibizumab, therefore this patient was excluded of this study. One month after the three subsequent injections, another follow-up visit was performed (visit 2).

Main outcome measures and statistics

According to the different treatment options patients were divided into three groups:

1. aflibercept monotherapy (16 eyes, 13 patients),
2. ranibizumab monotherapy (36 eyes, 24 patients),
3. therapy switch from ranibizumab to aflibercept in therapy refractory patients (25 eyes, 22 patients)

Main outcome measures were defined as sensitivity of CNV identification and assessment of CNV activity at baseline on OCTA compared to FA and reduction of HRP and PED size three months after therapy initiation (either ranibizumab or aflibercept) or three months after therapy switch from ranibizumab to aflibercept. Secondary outcome measures were the change in BCVA, safety and the percentage of eyes achieving complete resolution of fluid accumulation (intra-, subretinal and/or sub-RPE fluid) during the treatment period.

Statistics

Data were explored to identify outliers and to check normal distribution. All results are expressed in mean $\pm$ standard deviation (SD). Normally-distributed variables were compared with a Two-way ANOVA (repeated measures, Tukey's post hoc analysis). The comparability of all groups regarding their baseline characteristics was analysed using One-way ANOVA. The results were regarded as statistically significant if p was below 0.05. Statistics were performed with GraphPad Prism version 7 (GraphPad Software, La Jolla, California, USA)

Results

A total of 77 eyes from 59 patients (17 (28.8%) male and 42 (71.2%) female) with PED were included in the study with a mean age of 76 ± 7.4 years at primary onset. The PED was unilateral in 28 (47.5%) patients and bilateral in 31 (52.5%) patients. Of these 31 patients, 13 (41.9%) patients with bilateral disease, only one eye was included in this study due to the fact that the fellow eye had a Junius Kuhnt degeneration, a stable PED or an inactive CNV, which was just followed up.

Presence of CNV

A FA was performed at baseline in 32/59 (54.2%) patients. Patients with known allergies or a decrease in renal function did not receive a FA.

The angiographic type of CNV at baseline was

- type 1 in 24/32 (75%) patients
- mixed type 1 and 2 in 3/32 (9.3%) patients
- type 2 in 2/32 (6.3%) patients
- type 3 in 1/32 (3.1%) patients
- drusenoid PED with leakage on FA and sub- or intraretinal fluid in 2/32 (6.3%) patients.

OCTA was performed at baseline in 18/59 (30.5%) patients that were included at later time points of the study. The overall CNV detection rate on OCTA was 12/18 (66%) patients, with a higher incidence using the manual segmentation mode compared to the automatic segmentation algorithm. CNV detection on FA was superior to OCTA in 2/18 (11.1%) patients compared to one patient where the CNV was only visible on OCTA. Of note in 4/18 (22%) patients, OCTA images had significant motion artefacts leading to difficulties in layer segmentations and missing data, thus CNV presence could not be evaluated, whereas FA image quality was sufficient for CNV detection in all patients. Compared to FA with a sensitivity of 0.786 and specificity of 1, the sensitivity of OCTA was lower (0.706) with an identical specificity of 1. On OCTA a mean CNV size of 1.57mm^2 ($0.05\text{--}8.14\text{mm}^2$) could be detected and CNV's were classified as active according to the vessel morphology and branching pattern such as presence of anastomoses and loops (see Fig. 1) in 75% patients. Signs of beginning fibrotic conversion could be detected already in the remaining 25% of patients where CNV morphology showed signs of a "dead tree appearance" with large, linear, and more mature vessels lacking anastomoses or loops. On FA 92% of CNV's were classified as active according to leakage patterns, although, a definitive assessment of activity was more difficult to assess, because of the simultaneous pooling effect into the PED. Thus, prior to the introduction of OCTA in clinical routine the presence of additional sub- and/or intraretinal fluid on OCT has been considered as treatment criteria for neovascular activity along with CNV identification on FA.

Highest retinal prominence

At baseline the one-way ANOVA analysis confirmed that the HRP was equally distributed in all groups with no significant difference in HRP between all groups ($p=0.97$) with mean values of all groups being close together. Therefore, legibility for comparison of all groups was given. Mean HRP decreased significantly from baseline to visit 1 after ranibizumab ($p<0.001$) or aflibercept monotherapy ($p<0.001$) and decreased further from visit 1 to visit 2, but without statistical significance ($p>0.99$ for ranibizumab, $p=0.94$ for aflibercept). Patients unresponsive to ranibizumab showed a significant decrease in HRP after therapy switch to aflibercept ($p<0.001$, see Fig. 2). The details are listed in table 1 and illustrated in Fig. 3. An additional excel file with all patient data relevant for the analysis is available as supplemental file (see Additional file 1).

Table 1. Mean HRP change in highest retinal prominence and pigment epithelium detachment size of 59 patients at baseline and during follow-up.

Size of the pigment epithelium detachment

At baseline one-way ANOVA analysis confirmed that PED size was equally distributed in all groups without significant difference in baseline PED size between all groups ($p=0.39$), although mean values may be quite far apart, so groups are comparable to a limited extend. Mean PED size decreased from baseline to visit 1 after ranibizumab and aflibercept therapy with statistical significance for aflibercept ($p<0.001$), but not for the ranibizumab monotherapy group ($p=0.5$). PED size further decreased after continuation of first line therapy but without statistical significance ($p=0.97$ for aflibercept, $p=0.16$ for ranibizumab). Patients unresponsive to ranibizumab showed a significant decrease in PED size after switch to aflibercept ($p<0.001$). The details are listed in table 1 and illustrated in figure 4.

The percentage of eyes without any persistent sub- or intraretinal fluid at the end of the study period (visit 1 or 2) was similar, whether aflibercept or ranibizumab has been injected. There was a significant effect of aflibercept on the PED itself, as the PED resolved in 31.2% of aflibercept treated patients compared to 14.4% of patients treated with ranibizumab (table 2).

Table 2. Assessment of percentage of eyes without any persistent fluid at the end of treatment period.

Visual function (BCVA)

At baseline the one-way ANOVA analysis confirmed that BVCA was not equally distributed in all groups with a significant difference in BCVA between all groups ($p=0.01$), therefore all conclusions regarding the change in BCVA represent a trend. The BCVA improved after ranibizumab monotherapy, after aflibercept monotherapy, and after therapy switch from ranibizumab to aflibercept, but without statistical significance in any group. BCVA decreased under ranibizumab therapy before the therapy switch to aflibercept (see table 3).

Table 3. Mean change in best corrected visual acuity of 59 patients with pigment epithelium detachment at baseline during follow-up.

Safety:

In our study, seven (11.8%) patients experienced a RPE rip, two patients under ranibizumab therapy and five patients under aflibercept therapy. Of these seven patients, six received anti-VEGF monotherapy and one patient had been switched from ranibizumab to aflibercept prior to the rip. The mean number of injections was three (range 1 - 6) with a mean PED height of 406.3 μ m (range 186 - 671 μ m) and a mean PED diameter of 3068.4 μ m (range 1635 - 4062 μ m) prior to the adverse event. During the follow-up period, the incidence of RPE rips was 13/59 (22%) patients in our cohort with eight patients after aflibercept and five patients after ranibizumab therapy with a mean number of 4.8 (1 - 23) injections and a mean PED height of 491 μ m and a mean PED diameter of 3088 μ m. Of note the higher mean PED height prior aflibercept therapy compared to ranibizumab monotherapy (433 vs. 366 μ m) might explain the higher incidence of RPE tears under aflibercept therapy. Five patients did not receive further anti-VEGF treatment, because of the missing prognosis for visual improvement. Two patients received further injections because of visual deterioration due to residual subretinal fluid.

Extensive subretinal haemorrhages were seen in two patients, both with type 1 CNV, which were treated by intravitreal injection of recombinant tissue plasminogen activator combined with gas injection (one patient) and further anti-VEGF injections (one patient). We did not observe any cases of endophthalmitis.

Discussion

Pigment epithelium detachment has been known to be less responsive to anti-VEGF treatment when compared with the response of macular edema arising from other subtypes of wet AMD according to the large clinical trials. The VIEW analyses demonstrated a slow and incomplete resolution of PED in contrast to other morphologic entities despite the usage of the most effective antiangiogenic substances and treatment regimen (18). Although reductions of retinal fluid were impressive, PED volume tended to remain unchanged or to regress only slowly which was also demonstrated in the CATT trial (19).

Our purpose was to evaluate the sensitivity of OCTA versus conventional FA regarding CNV detection and assessment of CNV activity. We found FA to be slightly superior to OCTA regarding CNV detection, in part due to the higher incidence of motion artefacts on OCTA compared to FA. On the other hand, OCTA allows a better evaluation of CNV activity due to the detailed visualisation of CNV morphology. On FA pooling into the adjacent PED makes CNV activity assessment more difficult.

We further analysed the therapy effect of aflibercept and ranibizumab in treatment naïve patients with PED with additional intra- or subretinal fluid and evaluated the outcome of a therapy switch to aflibercept in patients, refractory to ranibizumab. We could demonstrate, that ranibizumab and aflibercept achieved an equal significant reduction in retinal prominence in treatment naïve patients, but only aflibercept obtained a significant decrease in PED size. Therefore, we conclude that both medications had the same effect on intra- and subretinal fluid as hallmark of neovascular AMD, but only aflibercept reached a

statistically significant effect on fluid accumulation underneath the retinal pigment epithelium. A clear effect of ranibizumab on the PED size was seen, but aflibercept was more effective.

The observed gains seem to confirm the theoretical advantage of aflibercept in terms of its pharmacokinetics and its ability to bind not only to all isoforms of VEGF-A and VEGF-B but also to PIGF (9, 20). To date, it is still unknown whether PIGF antagonism plays a role in the treatment of neovascular AMD, as PIGF has been identified in the CNV process (11), and it stimulates VEGF production (21). Thus, it is conceivable that PIGF could also play a role in PED, as the RPE layer is anatomically more adjacent to the choroid.

Another important consideration is the observation that predominantly serous PEDs showed a significantly better response to anti-VEGF treatment. Similarly, others found that the degree of PED flattening was inversely correlated with hyperreflectivity under the pigment epithelium, which is considered the OCT equivalent of vascularization (22). Thus, the specific characteristics of PED may play an important role in treatment response, perhaps more important than the type of anti-VEGF medication chosen.

However, the clinical importance of PED flattening is not well understood. The natural course of PED, either serous or vascularized, shows an initial enlargement over months, which is followed by a slow decrease in size (7), finally resolving with remnant atrophy after years (23-25). Although unknown, this might depend on the pathway of anti-VEGF action; if PED flattening is related to a reduced exudative activity of the neovascular mass, the flattening might represent a healthier situation for the pigment epithelium. Although we know from long term observations, that a decrease in visual acuity is almost mandatory.

We further analysed patients unresponsive to ranibizumab with a therapy switch to aflibercept. In accordance to the literature (26-31), our results show a benefit of a therapy switch to aflibercept for patients' refractory to ranibizumab. Only one study showed visual acuity improvement after aflibercept injection according to a fixed regimen (28). All other papers demonstrated a stable or worse visual acuity despite reduced retinal prominence or PED height, with various injection regimens applied (PRN, fixed, treat and extend). In addition to the current literature, our retrospective study evaluated aflibercept efficacy in a large patient cohort with a PRN scheme, with three monthly injections in case of recurrent or recalcitrant fluid. Here, we could demonstrate a significant decrease in PED size and foveal prominence three months after the switch, whereas no short-term effect on BCVA improvement was seen.

While these are interesting results, which are compatible with a stronger effect of aflibercept on PED's, the results may be confounded by the effect of time and/or the selection of refractory patients. Therefore with the long-term usage of anti-VEGF drugs the effect of tachyphylaxis has also to be addressed (32). Several authors found different percentages of patients not responsive to ranibizumab or bevacizumab ranging from 2% to up to 14% (33, 34). These authors also reported a significant change in the maximum PED height and central retinal prominence three months after switching from ranibizumab to another anti-VEGF drug, although their study cohort consisted of patients with all types of wet AMD and the

number of patients with exclusively PEDs was lower compared to our study (25, 35, 36). In summary, some patients might have a better response with fluid resolution through switching to another anti-VEGF drug because of tachyphylaxis.

Our short-term functional results showed no significant difference in visual acuity outcome for aflibercept or ranibizumab treated treatment naïve patients. We observed a lack of BCVA improvement also in patients unresponsive to ranibizumab with a therapy switch to aflibercept, as stated earlier. These findings are in accordance to the literature, where several authors demonstrated an anatomic benefit without visual acuity improvement (37-39). Only few authors demonstrated also a better functional outcome after switching from ranibizumab or bevacizumab to aflibercept (40, 41). However, previous reports have suggested that functional long-term prognosis of PED is generally poor, even under anti-VEGF treatment (25, 42). Some studies have reported an association of vascularized PED with poor functional outcomes (24, 43, 44), while others have found an association between poor functional outcomes and baseline PED height (23).

The major strength of our study is that patients, that switched between the two agents were analysed and therefore served as their own control group for purposes of comparison, which allowed a direct comparison of the response to the different drugs within the same parameters. Additionally, the implementation of treatment naïve patients with PED allowed an assessment of a not confounded effect of ranibizumab and aflibercept for their direct comparison.

Our study has several limitations, which include the inherent weaknesses of a retrospective study design and the relatively small study population. Some biases may arise from the lack of standardization of follow-up or they may be due to intraindividual differences in the response to different anti-VEGF agents.

Conclusion

In conclusion, our results show, that the combination of FA and OCTA offers significantly improved visualisation, quantification, and predictability of CNV activity in neovascular PED. We further conclude that aflibercept appears to be a valuable tool for the management of patients with refractory neovascular PED. These patients might have an anatomic improvement, with reductions of HRP, PED size and retinal exudation. Aflibercept would be preferable to extend the injection intervals.

List Of Abbreviations

AMD age-related macular degeneration

BM basal membrane

BCVA best-corrected visual acuity

CNV choroidal neovascularization

FA fluorescence angiography

HRP highest retinal prominence

ILM inner limiting membrane

OCT-A optical coherence tomography angiography

PED pigment epithelium detachment

PLGF placental growth factor

PRN pro re nata

RPE retinal pigment epithelium

SD-OCT spectral-domain optical coherence tomography

SD standard deviation

VEGF vascular endothelial growth factor

Declarations

Ethics approval and consent to participate

All patients gave their informed consent and all procedures were in concordance with the tenets of the Declaration of Helsinki. All patients were treated on label so that no ethics approval was needed for the retrospective chart review.

Consent for publication

Not applicable.

Availability of data and material

Data supporting our findings are contained in the manuscript and its supplementary information files.

Competing interests

The authors declare that they have no conflict of interest.

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Authors' contributions

AR performed the analysis and wrote and drafted the manuscript. DP participated in the analysis. TDN, BM and SW performed the patient examinations and together with AMJ revised the manuscript critically. SW designed the study and revised the manuscript critically. All authors read and approved the final manuscript.

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Tables

Table 1. Mean change in highest retinal prominence and pigment epithelium detachment size of 59 patients at baseline and during follow-up.

group	number of patients (number of eyes)	mean HRP + SD at baseline (μm)	mean HRP + SD at visit 1 (μm) (*p-value)	mean HRP + SD at visit 2 (μm) (**p-value)	mean PED size + SD at baseline (μm)	mean PED size + SD at visit 1 (μm) (*p-value)	mean PED size + SD at visit 2 (μm) (**p-value)
aflibercept monotherapy	13 (16)	656.1 ±151.1	466.8 ±129.2 (p < 0.001)	455.6 ±125.5 (p = 0.94)	433.8 ±166.5	253.8 ±208.1 (p < 0.001)	245.3 ±206.9 (p = 0.97)
ranibizumab monotherapy	24 (36)	667.7 ±172.9	524.6 ±150.5 (p < 0.001)	524.5 ±153.0 (p > 0.99)	366.5 ±267.9	336.8 ±213.0 (p = 0.5)	317.6 ±186.8 (p = 0.16)
switch ranibizumab to aflibercept	22 (25)	660.4 ±163.6	664.4 ±204.7 (p = 0.98)	515.9 ±164.9 (p < 0.001)	393.5 ±159.3	445.7 ±190.9 (p = 0.23)	303.7 ±200.9 (p < 0.001)

HRP= highest retinal prominence, PED=pigment epithelium detachment, SD = standard deviation

*Two-way-ANOVA of visit 1 - baseline, **Two-way-ANOVA of visit 1 - visit 2,

Table 2. Assessment of percentage of eyes without any persistent fluid at the end of treatment period.

Group	without sub ± intraretinal fluid	without detectable PED
1	68.7%	31.2%
2	55.5%	14.4%
3	64%	12%

Table 3. Mean change in best corrected visual acuity of 59 patients with pigment epithelium detachment at baseline during follow-up.

group	number of patients (number of eyes)	mean BCVA + SD at baseline (logMAR)	mean BCVA + SD at visit 1 (logMAR) (*p-value)	mean BCVA + SD at visit 2 (logMAR) (**p-value)
<u>aflibercept monotherapy</u>	<u>13 (16)</u>	<u>0.52 ±0.31</u>	<u>0.48 ±0.39</u> (p = 0.47)	<u>0.46 ±0.39</u> (p = 0.94)
<u>ranibizumab monotherapy</u>	<u>24 (26)</u>	<u>0.71 ±0.33</u>	<u>0.64 ±0.35</u> (p = 0.16)	<u>0.65 ±0.32</u> (p = 0.97)
<u>switch ranibizumab to aflibercept</u>	<u>22 (25)</u>	<u>0.47 ±0.28</u>	<u>0.52 ±0.32</u> (p = 0.54)	<u>0.47 ±0.32</u> (p = 0.54)

BCVA= best corrected visual acuity; logMAR = logarithm of minimal angle of resolution, SD = standard deviation

*Two-Way-ANOVA of visit 1 - baseline, **Two-Way-ANOVA of visit 2 - visit 1

Figures

Figure 1

Multimodal imaging of a type 1 choroidal neovascularization (CNV) in serous pigment epithelium detachment (PED). (A): Early and late phase fluorescence angiography demonstrate a type 1 membrane (yellow arrow) at the nasal border of a PED with extensive pooling (black arrow) at the late phase. (B): Optical coherence tomography (OCT) B-scan shows a serous PED with a notch nasally superior (black arrow), indicating the presence of the CNV. (C): Visualization of the type 1 CNV underneath the retinal pigment epithelium (RPE) by en face OCT-angiography (OCTA, upper panel) and corresponding OCT with blood flow depicted in yellow and automatic segmentation algorithm of the avascular complex between

the outer plexiform complex (OPL) and the basal membrane (BM) visualized as dashed red lines (lower panel). (D): Higher magnification image of the CNV, marked by a dashed square on OCTA, confirming an active type 1 CNV with a widely anastomosed vascular network and tiny capillaries. CNV borders are manually outlined in turquoise and the CNV size in mm² was calculated by the device software.

Figure 2

Treatment response of ranibizumab refractory patients after therapy switch to aflibercept assessed by optical coherence tomography (OCT) (A): 64-year-old man with a fibrovascular pigment epithelium detachment (PED) and subretinal fluid (SRF) with no change in PED height and increase in SRF after three ranibizumab injections at visit 1 (three months). After three aflibercept injections a complete resolution of PED and SRF was seen at visit 2 (six months). (B): 72-year-old woman with a serous PED and minimal SRF centrally showing an increase in PED height after three ranibizumab injections at visit 1 and a complete resolution of PED and SRF after switching to aflibercept at visit 2.

Figure 3

Boxplot graph representing changes in highest retinal prominence (HRP) at baseline and during follow-up of anti-VEGF therapy in patients with retinal pigment epithelium detachment (PED). Figure shows the difference in change in HRP in μm for group 1 (aflibercept monotherapy), group 2 (ranibizumab monotherapy), and group 3 (therapy switch from ranibizumab to aflibercept).

Figure 4

Boxplot graph representing changes in pigment epithelium detachment (PED) size at baseline and during follow-up of anti-VEGF therapy in patients with PED. Figure shows the difference in change in PED size in μm for group 1 (aflibercept monotherapy), group 2 (ranibizumab monotherapy), and group 3 (therapy switch from ranibizumab to aflibercept).

Supplementary Files

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