Check for updates

Original research article

EJO European Journal of Ophthalmology

European Journal of Ophthalmology
2024, Vol. 34(2) 487–496
© The Author(s) 2023
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/11206721231187663
journals.sagepub.com/home/ejo
Sage

Brolucizumab for recalcitrant macular neovascularization in age-related macular degeneration with pigment epithelial detachment

Argyrios Chronopoulos[1], Elisa Huynh[1], Agharza Ashurov[1], James S Schutz[1], Jost B Jonas[2] and Lars-Olof Hattenbach[1]

Abstract

Purpose: To analyze anatomic and functional response to intravitreal brolucizumab in age-related macular degeneration recalcitrant to previous intravitreal anti-VEGF therapies.

Methods: In this monocentric, one arm, retrospective study, eyes affected by neovascular age-related macular degeneration (nAMD) resistant to other intravitreally injected anti-vascular endothelial growth factor inhibitors were switched to intravitreal brolucizumab. All patients underwent ophthalmological examinations at baseline and in regular follow-up intervals. Best registered visual acuity (BRVA), Goldmann tonometry, intraocular pressure (IOP), central retinal thickness (CRT) and pigment epithelial detachment (PED) characteristics were analyzed at initiation of anti-VEGF treatment, at treatment switch, and at the end of brolucizumab loading phase.

Results: The study included 20 eyes of 18 consecutively treated patients (age: 77 ± 6 years). All eyes had macular neovascularization with PED. Previous treatments included intravitreal aflibercept, bevacizumab, and ranibizumab and had not resulted in a significant improvement in BRVA (0.5 ± 0.5 logMAR vs 0.5 ± 0.6 logMAR) or mean CRT (320 ± 60 µm vs 313 ± 83 µm) up to treatment switch to brolucizumab. At the end of the brolucizumab loading phase, there was significant improvement for both BRVA (0.3 ± 0.2 logMAR, $P < 0.05$) and CRT (264 ± 55 µm, $P < 0.05$). Under previous anti-VEGF therapy, there was a significant increase/deterioration in both PED area (2.68 mm^2 to 5.18 mm^2, $P < 0.05$) and PED volume (0.39 mm^3 to 1.07 mm^3, $P < 0.05$); however, both parameters improved after switching to brolucizumab (3.81 mm^2 and 0.37 mm^3, $P < 0.05$).

Conclusion: Our results suggest a favourable anatomical and visual response after treatment switch to brolucizumab in patients with nAMD refractory to previous anti-VEGF agents.

Keywords

Brolucizumab, retinal pigment epithelial detachment, age-related macular degeneration, macular neovascularization, vascular endothelial growth factor, VEGF, ranibizumab, bevacizumab

Date received: 9 July 2022; accepted: 30 May 2023

Introduction

Intravitreal drugs directed against vascular endothelial growth factor (VEGF) have revolutionised treatment of neovascular age-related macular degeneration (nAMD).[1] Currently, there are three approved anti-VEGF drugs for the treatment of nAMD: ranibizumab (Lucentis®), aflibercept (Eylea®), and brolucizumab (BeoVu®). A fourth agent, bevacizumab (Avastin®), is used off-label. Clinical

[1]Department of Ophthalmology, Ludwigshafen City Hospital, Ludwigshafen am Rhein, Germany
[2]Department of Ophthalmology, Medical Faculty Mannheim, Ruprecht-Karls-University Heidelberg, Mannheim, Germany

Corresponding author:
Argyrios Chronopoulos, Department of Ophthalmology, Ludwigshafen Hospital, Bremserstrasse 79, Ludwigshafen am Rhein, Germany.
Email: aris_c@web.de

trials have consistently demonstrated that early, continuous treatment produces improvement in vision of three or more lines in 30–35% of nAMD patients; however, in a significant subgroup of patients neovascular activity persists or progresses with persistent subretinal (SRF) or intraretinal fluid (IRF), unresolved or new hemorrhages, progressive subretinal fibrosis and suboptimal vision recovery.[2,3] Such persistent disease activity affects up to 50% of nAMD patients after continuous anti-VEGF treatment for 1 year with suboptimal anatomical and functional results.[2–6] The consequences of persistent disease despite anti-VEGF treatment are prolonged treatments, decreased injection intervals, increased commuting and strain on relatives and caregivers, and increased risk of long-term vision loss.[7]

The effectiveness of anti-VEGF treatment is typically evaluated by the presence or absence of signs of disease activity such as intraretinal, subretinal, and sub-RPE fluid.[8] Anti-VEGF therapy has been shown to reduce the proportion of patients with pigment epithelial detachment (PED) and diminish PED volume as soon as one month after start of therapy.[9,10] However, the sub-RPE component, as surrogate for neovascular disease activity, is often treatment resistant.[11] The ability to quantify persistence of PED may provide insights into emerging therapeutics.[12]

Currently both brolucizumab registration trials (HAWK & HARRIER) as well as the OSPREY post-hoc analysis measured significant and faster reduction in central subretinal thickness (CST) as well as PED area and volume compared with baseline throughout a 56-week treatment period.[13,14] Furthermore, therapeutic benefit achieved with on-label treatment with brolucizumab allows for extended treatment intervals every 12 or even 16 weeks, reducing considerably the total number of injections and expense in the first year.[13,14]

The goal of this study is to analyze the functional and anatomic macular neovascularization and PED changes following treatment switch to intravitreal brolucizumab in patients with nAMD recalcitrant to previous intravitreal anti-VEGF therapies.

Materials and methods

This is a monocentric, hospital-based, interventional, retrospective study. Data from consecutive nAMD patients with macular neovascularization refractory to conventional anti-VEGF therapy who were switched to intravitreal brolucizumab were analyzed.

Inclusion criteria:

1. All patients with either type I or type II macular neovascularization were included in this study.
2. completion of at least one session (one loading dose) of three intravitreal anti-VEGF injections with either bevacizumab, ranibizumab or aflibercept.
3. refractory macular neovascularization identified using spectral-domain optical coherence tomography (SD-OCT), defined as persistent intraretinal fluid and/or subretinal fluid with PED (≥150 µm height) despite treatment and
4. completion of a loading dose of brolucizumab.

All data were extracted anonymously from our electronic medical records.

Exclusion criteria

Patients with type III choroidal neovascularization were not considered in this analysis. Furthermore, cases with PED smaller than 150 µm height, history of previous retina surgery (e.g. vitrectomy) or concurrent systemic and/or ocular disease that could also lead to macular edema (e.g. diabetes mellitus, history of vein occlusion, polypoidal choroidal vasculopathy -PCV- or uveitis) were excluded from the analysis.

Types of macular neovascularization

The study included patients with exudative age-related macular degeneration (type I and type II) with the coexistence of a PED recalcitrant to previous treatment and switch over to intravitreal brolucizumab. Type III macular neovascularization was not included in this study.

Primary and secondary endpoints

The primary endpoints were difference in thickness of macular edema as well as PED height, area and volume between baseline (t1) and the end of brolucizumab loading dose phase (t3). The height of PED was again assessed and compared separately at the end of the follow-up period. Also, a comparison of PED area and volume was made in the course of anti-VEGF treatment with respect to different anti-VEGF agents (t2) and brolucizumab. The secondary endpoint was change in BRVA between baseline (t1), the end of anti-VEGF therapy before treatment switch to brolucizumab (t2) and one month after the end of brolucizumab loading dose (t3).

Assessment of macular neovascularization and PED

All optical coherence tomography (OCT) examinations were conducted using a Zeiss Cirrus 500/5000, (Cirrus®, Zeiss OCT, Zeiss Co., Germany). The assessment of PED was conducted as previously reported.[15] Briefly, all baseline OCTs were analyzed with the integrated algorithm on the Cirrus OCT "Advanced RPE analysis" which enables automatic calculation of the area and volume of PED within radiuses of 3 and 5 mm around the fovea. All measurements were averaged and compared between

the start of anti-VEGF therapy to the time of treatment switch to brolucizumab and to the end of the brolucizumab loading phase. Baseline images and follow-up images were checked for correct segmentation on the screen by two experienced investigators and verified by a third colleague (A. C., E. H. and A. A.). Error corrections, was conducted, when necessary with the built-in software.

Statistical analysis

All study parameters were analyzed for normal distribution with the Kolmogorov test. BRVA in logMAR tranformation and mean CRT were evaluated against baseline for each time-point using student's unpaired t-test for parametric data. P-values were calculated with a value of less than 0.05 indicating statistical significance. Statistical analysis was performed using Minitab® software.

Results

Patient demographics

We analyzed 18 consecutive patients (20 eyes, 10 right and 10 left eyes, 8 men, 10 women) who had macular neovascularization with PED recalcitrant to previous anti-VEGF treatments and who were then switched to intravitreal brolucizumab. The average patient age was 77 ± 7 years. The average treatment duration before switch to brolucizumab was 100 ± 91 weeks. Table 1 summarizes basic patient demographics as well as anatomical and treatment characteristics at baseline.

Anti-VEGF treatment strategy. From the 20 eyes included in this study, 10 eyes were on a monthly treatment with 4 eyes having received two loading doses with 2 different anti-VEGF agents (one eye with bevacizumab and aflibercept, two eye with bevacizumab and ranibuzimab, one with ranibizumab and aflibercept) and 6 eyes having received only one anti-VEGF agent before switch to brolucizumab (4 with bevacizumab, one with ranibizumab and one with aflibercept). Three eyes were on a treat and extend treatment with bevacizumab, ranibizumab and aflibercept respectively before switch to brolucizumab. The remaining 7 eyes were on a treat and extend protocol with two anti-VEGF agents before switch to brolucizumab. Eight eyes had two different rounds of intravitreal injections. Four eyes were switched from bevacizumab to brolucizumab, 7 eyes from ranibizumab to brolucizumab and 9 eyes were switched from aflibercept to brolucizumab. The average use of anti-VEGF before treatment switch to brolucizumab was 10 ± 8 injections for bevacizumab, 5 ± 3 injections for ranibizumab and 10.5 ± 9 injections for aflibercept. Nine eyes had been treated with bevacizumab (range 3 to 25 injections), 10 eyes had ranibizumab (range 3 to 12 injections) and 9 eyes had aflibercept (range 3 to 30).

Table 1. Patient demographics at brolucizumab treatment switch, the type of macular neovascularisation, the different types of intraretinal or subretinal fluid distribution as well as the type of PED.

Patient demographics at brolucizumab treatment switch	
	Patients (n = 18, eyes 20)
Mean age	77 ± 7 years
Sex	10 men, 10 women
Mean follow-up	13 ± 1 months
Baseline VA	0.5 ± 0.6 logMAR
Baseline CST	320 ± 60 µm
Concurrent ophthalmological diseases/treatments	Post cataract surgery 9, cataract 10, ocular hypertension 1, primary open angle glaucoma 1
Macula Neovascularization	
Type I	8
Type II	12
Fluid type	
IRF	15
SRF	10
SRF and IRF	5
PED	20
Type of PED	
Drusenoid	0
Fibrovascular	17
Serous	3

Central retinal thickness and vision

The mean CRT and BRVA at primary anti-VEGF indication was 320 ± 60 µm and 0.5 ± 0.6 logMAR respectively. Both parameters did not change significantly during the treatment phase before switch to brolucizumab, i.e. between the time of the first anti-VEGF injection (t1) and before the first brolucizumab was carried out (t2) (CRT: 320 ± 60 µm versus 313 ± 83 µm; $P > 0.05$; BRVA: 0.5 ± 0.5 logMAR versus 0.5 ± 0.6 logMAR, $P > 0.05$). Six weeks after the third brolucizumab intravitreal injection (t3), CRT decreased significantly to 262 ± 55 µm ($P = 0.035$) and BRVA improved to 0.3 ± 0.2 logMAR in comparison with other anti-VEGF agents (t3 vs t2). From the 20 eyes analyzed, 14 had no SRF or IRF, 2 eyes demonstrated SRF, 3 eyes demonstrated IRF and 1 eye demonstrated SRF and IRF. Eleven out of 20 eyes demonstrated improved vision (55%), 3 eyes reduced vision (15%) and 6 eyes stable vision (30%). These results were maintained until the end of the observation period with no significant change, neither functionally nor anatomically. These parameters were also significantly improved compared to the baseline and at the end of the study (Figures 1 and 2).

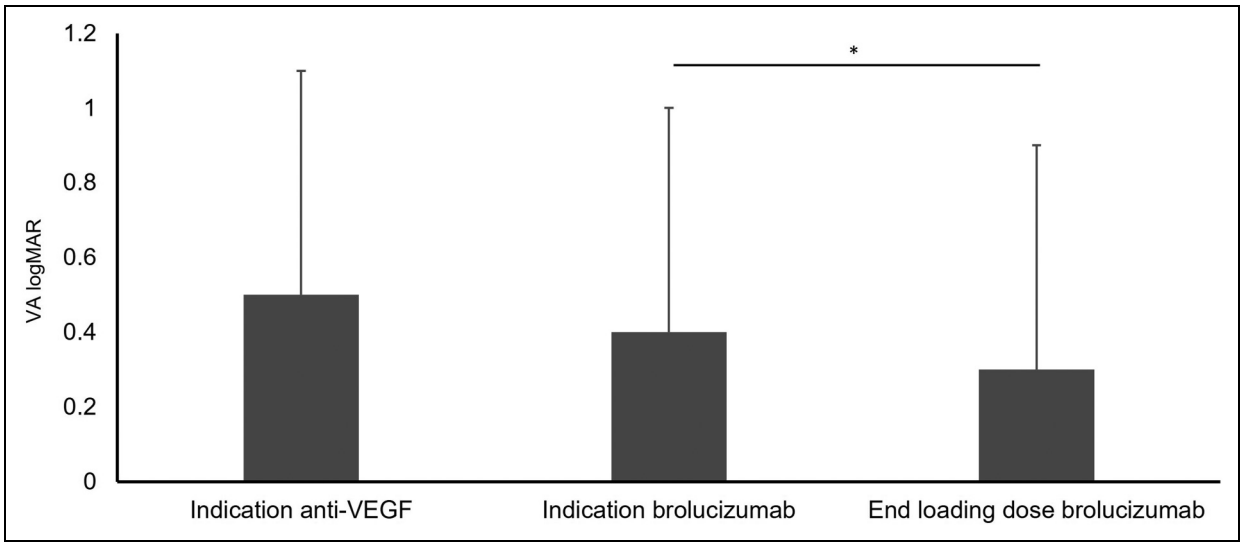


Figure 1. BRVA at baseline, at treatment switch to brolucizumab, and at first follow-up after the end of brolucizumab loading dose. Although BRVA did not improve significantly between baseline/indication to switch treatment, there was a significant change in function at the end of the loading phase with brolucizumab, BRVA 0.5 ± 0.6 logMAR to 0.3 ± 0.6 logMAR (* $p = 0.045$).

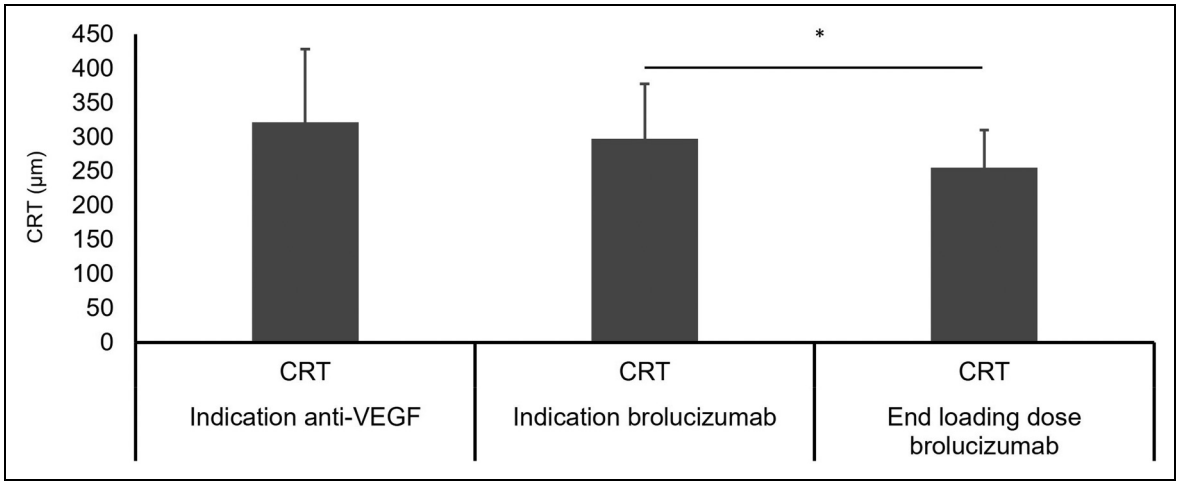


Figure 2. CRT at baseline, at treatment switch and at first follow-up after the end of brolucizumab loading dose. CRT did not improve significantly between baseline and indication to treatment switch, however, there is a significant reduction in CRT from 313 ± 83 µm to 262 ± 55 µm (* $p = 0.035$) at first follow-up after the end of brolucizumab loading dose.

PED hight, area and volume

We measured the PED height, area and volume of all included eyes once before treatment switch to brolucizumab and once at final follow-up. The mean follow-up time was 13 ± 1 months. The average PED height at treatment switch to brolucizumab was 400 ± 192 µm. At the end of follow up the PED height was significantly lower at 192 ± 129 µm ($p = 0.0001$). Between baseline and treatment switch to brolucizumab, macular PED area increased significantly in the 3 mm zone from 2.34 ± 1.86 mm^2 to 4.16 ± 1.83 mm^2 ($p = 0.0063$) and within the 5 mm zone from 3.02 ± 2.76 mm^2 to 6.2 ± 3.16 mm^2 ($p = 0.0075$); PED volume also increased significantly from 0.35 ± 0.49 mm^3 to 0.918 ± 0.56 mm^3 within the 3 mm zone ($p = 0.02$) and from 0.44 ± 0.59 mm^3 to 1.24 ± 0.8 mm^3 within the 5 mm zone ($p = 0.02$). There was an average increase in PED area from 1.82 to 3.16 mm^2 and in volume from 0.90 to 1.23 mm^3 (Figure 3A and 3B). In contrast, from the treatment switch to brolucizumab to the end of the loading phase, there was a reduction in both PED area and volume. In the central 3 and 5 mm zones, the reduction in PED area did not reach statistical significance, 4.16 ± 1.829 mm^2 to 3.09 ± 2.15 mm^2 and 6.2 ± 3.16 mm^2

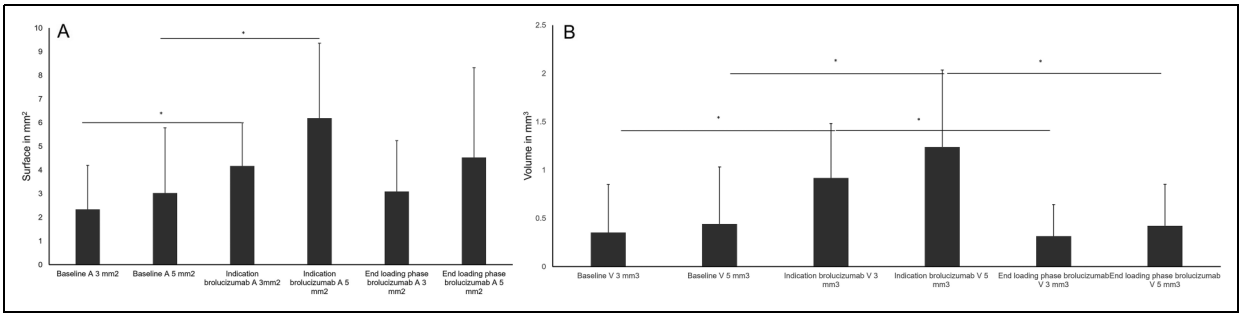


Figure 3A and B. PED area (3A) and volume (3B) increased significantly between indication to treat with anti-VEGF agents and indication to switch to brolucizumab. Following treatment switch, there is a gradual reduction in the surface and volume of the PED, with PED volume reaching statistical significance (A: area, V: volume, * < 0,05).

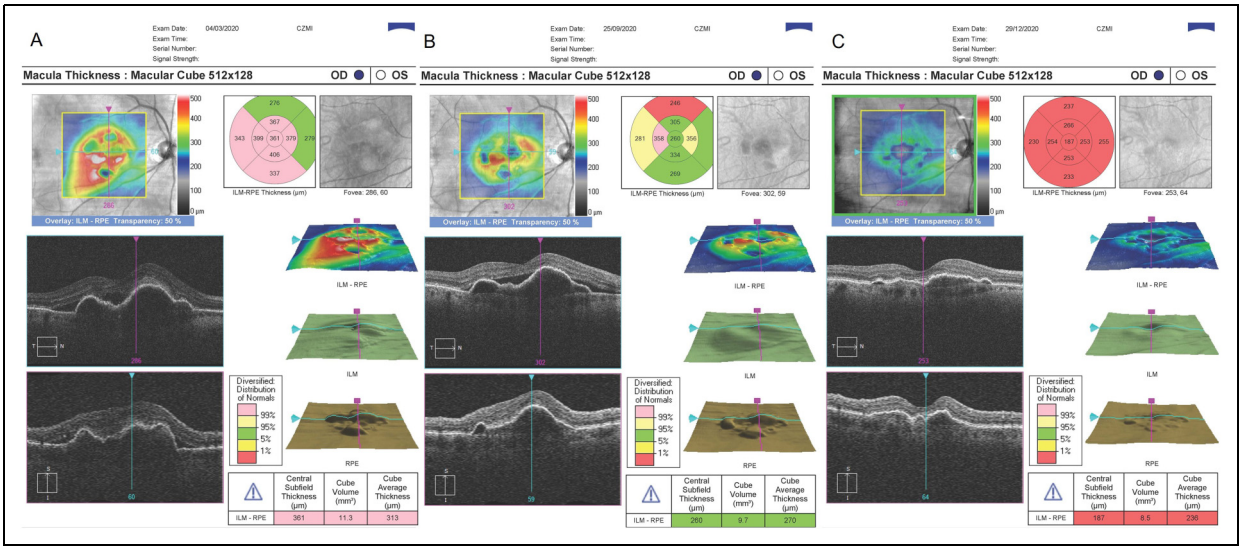


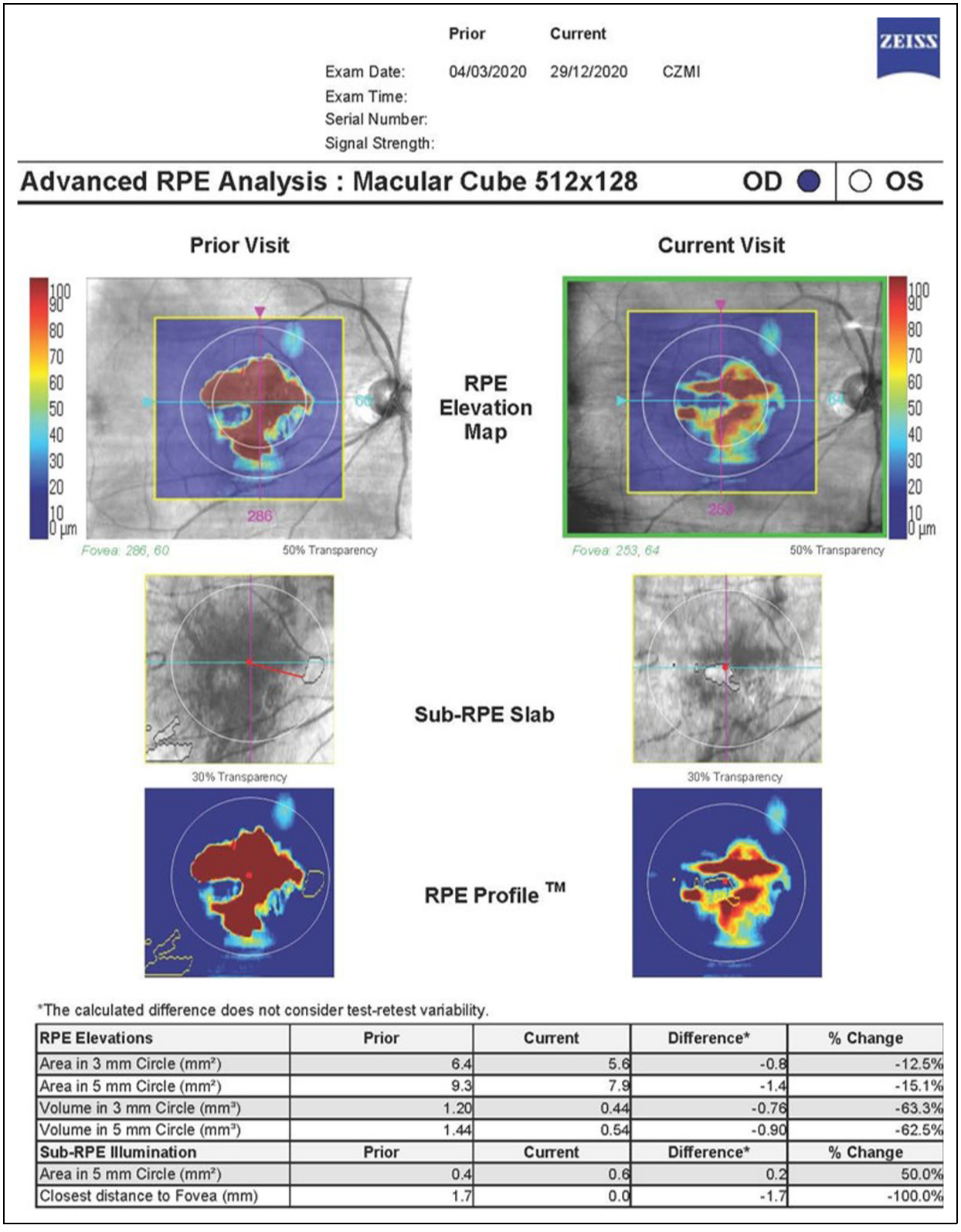
Figure 4. A characteristic example of poor responsiveness under older anti-VEGF agents (panel 4A and 4B) demonstrated on OCT. Following treatment switch (panel 4C), the subretinal fluid has also been resorbed and there is significant reduction of CRT and PED.

to 4.53 ± 3.8 mm^2 with an average change of -1.07 and -1.66 mm^2 respectively, but there was a significant reduction in PED volume from 0.92 ± 0.56 and 0.42 ± 0.42 mm^3 to 0.32 ± 0.32, $p = 0.01$ and 0.24 ± 0.8 mm^3, $p = 0.01$, with an average reduction of -0.6 and -0.82 mm^3 respectively (Figure 3A and 3B). Characteristic examples of the PED improvement are demonstrated in Figures 4 and 5.

Discussion

Switching to intravitreal brolucizumab in patients with nAMD and macular neovascularization with PED recalcitrant to previous anti-VEGF therapy led to significant anatomic and to some extent functional improvement. PED area and volume, which had worsened significantly during previous anti-VEGF treatments, improved under brolucizumab.

Intravitreal anti-VEGF therapy has markedly enriched the armamentarium for the treatment of nAMD, enabling not only anatomic and functional stabilisation but also improvement in vision.[16] Nevertheless, persistent disease activity and suboptimal vision recovery remain a problem for many patients under continued anti-VEGF treatment. Furthermore, the treatment for PED is unpredictable and results in unsatisfactory outcomes despite multiple anti-VEGF agents available. PEDs (serous, fibrovascular, and hemorrhagic) associated with exudative AMD demonstrate variable responsiveness to anti-VEGF treatment and can lead to significant morbidity by their sub-RPE component, as surrogate for neovascular



*The calculated difference does not consider test-retest variability.

RPE Elevations	Prior	Current	Difference*	% Change
Area in 3 mm Circle (mm²)	6.4	5.6	-0.8	-12.5%
Area in 5 mm Circle (mm²)	9.3	7.9	-1.4	-15.1%
Volume in 3 mm Circle (mm³)	1.20	0.44	-0.76	-63.3%
Volume in 5 mm Circle (mm³)	1.44	0.54	-0.90	-62.5%
Sub-RPE Illumination	**Prior**	**Current**	**Difference***	**% Change**
Area in 5 mm Circle (mm²)	0.4	0.6	0.2	50.0%
Closest distance to Fovea (mm)	1.7	0.0	-1.7	-100.0%

Figure 5. PED analysis of the same patient showing significant improvement between baseline and end of brolucizumab loading phase (current visit). There is a marked reduction in both PED area and volume, with more marked volume reduction in the 3- and 5-mm circles (63.5% and 62.5% respectively).

disease activity, which can often prove treatment resistant.[11,17–21] Epidemiological studies have estimated the percentage of poor-, non- or stop-responders to be 8% to 50%, depending on the anti-VEGF agent used.[22–24] This combined with strict strategies of "no fluid tolerance" has led to suboptimal results with burdensome and cost-intensive fixed treatment strategies, patient fatigue, and reduced patient compliance.[7,25–27] Our real-world pilot study on patients switched to intravitreal brolucizumab for nAMD recalcitrant to previous treatment has confirmed the good anatomic results of previous studies on this particular patient group.[28] Furthermore, our analysis on PED metrics has demonstrated good responsiveness of PED to treatment with brolucizumab which projects possibly on the effectiveness of the brolucizumab molecule on the neovascular component of the lesion.[10,11]

Intravitreal brolucizumab has only recently been introduced into nAMD therapy. It is a humanised monoclonal single-chain variable fragment that binds to and inhibits vascular endothelial growth factor A (VEGF-A).[29] Its small size allows better penetration into retinal tissue.[30,31] Brolucizumab binds VEGF-A in a 2:1 ratio and has a higher binding affinity to VEGF-A isoforms than bevacizumab or ranibizumab.[29,32] With its high solubility, brolucizumab can be concentrated up to 120 mg/ml, which allows for concentrations of up to 6 mg in a single 0,05 ml intravitreal injection.[33] The registration trials HAWK and HARRIER demonstrated non-inferiority of brolucizumab to aflibercept in terms of visual outcomes with no significant difference in BCVA gain at week 48 that was maintained until week 96.[14] Brolucizumab demonstrated superior anatomic outcomes, resulting in fewer eyes with intra-retinal, sub-retinal, or sub-RPE fluid and increased reduction in central subfield thickness (CST) on OCT.[3,14,34] In addition more than 50% of patients were able to be maintained on a 4-month treatment interval, an improvement in socioeconomic burden. A major adverse effect of intravitreally applied brolucizumab is intraocular inflammation including occlusive retinal vasculitis, potentially limiting its wider use.[35] In our study however no safety concerns were noted.

Nonetheless, the clinical response to intravitreal anti-VEGF treatment is variable, and despite individualised treatment protocols, retinal fluid persists in many eyes with nAMD.[8,36] Previous studies have already investigated the effect of higher concentrations or more frequent treatment intervals with ranibizumab or aflibercept with sustained improvement at year one meaning that some patients with persistent fluid may require a different treatment regimen.[37–39] The MERLIN study set out to investigate the efficacy and safety of brolucizumab (6 mg) intravitreal treatment every 4 weeks in a patient cohort with persistent retinal fluid compared to aflibercept (2 mg) also every 4 weeks.[40] Although frequent intraocular inflammation incidents led to termination of the study, its primary and secondary goal with visual acuity outcomes noninferior to aflibercept under brolucizumab and superior anatomic outcomes were met.[40] Specifically, there was a greater and sustained reduction in central macular subfield thickness and a greater proportion (40.2%) of patients with fluid-free retina from baseline to week 52.[40] Our results in a similar cohort with pre-treated patients and persistent retinal fluid confirm the superior anatomical improvement also in nAMD cases with PED.

The REBA study of efficacy and safety of brolucizumab for nAMD in treatment naïve as well as pretreated patients with persistent intra- or SRF demonstrated significant anatomical and visual improvement, one of the first demonstrations of significant decrease in PED height.[28] Our study demonstrated similar results, particularly in the response of PED to brolucizumab with significant decrease of height, volume and area.

While our study involved anti-VEGF pretreated patients and brolucizumab as a switching agent with the traditional loading-dose in clinical settings, a variety of heterogeneous treatments patterns are used and no clinical data are currently available that demonstrate whether or not anti-VEGF pretreated patients also benefit from a loading dose. The FALCON study is designed to investigate whether patients with unsatisfactory response to previous anti-VEGF treatments benefit from a loading dose at switch to brolucizumab treatment.[41]

Treatment benefit of nAMD largely depends on early diagnosis and effective monitoring. This also includes the definition and introduction into clinical practice of useful disease markers. OCT and probably OCT-A are unprecedented in providing in vivo high-resolution visualisation of retinal, RPE and choriocapillaris pathology.[42,43] The incidence of pigment epithelial detachments in nAMD has been estimated between 63% to 80%.[11,44] PEDs have been associated with choriocapillaris neovascular activity in nAMD and are perhaps the most relevant parameter reflecting progressing disease activity.[11] Sub-RPE lesion activity precedes subsequent subretinal and IRF formation. The treatment response of PED under brolucizumab in our study may be related to its improved deeper bioavailability, making it possibly the treatment of choice for early intervention.

Our study has the inherent limitations of a retrospective data analysis. Our cohort is relatively small. The measurement of vision was performed based on patient chart using habitual correction which might have underestimated the best corrected visual acuity. The fact that almost half of the patients also had cataract could have also influenced the final measured vision. Furthermore, all our patients had already undergone multiple intravitreal injections with suboptimal results and persistent disease activity so the effect of brolucizumab, although very favorable, should be analyzed with caution. It is known that the more nAMD progresses, the less eyes stabilise

anatomically and that vision gains with time are modest. The elevation of the RPE layer is known to be directly associated with the neovascular activity at the level of choriocapillaris; hence, a PED is the surrogate of neovascular disease.[11] However, due to the lack of a control group, the observed regression of PEDs might have reflected the natural course of the disease and might have occurred independently of treatment, particularly since spontaneous regression of PEDs has been described.[45,46]

The relationship between fluid distribution in nAMD (intraretinal, subretinal) and vision is important for understanding the anatomical signs that indicate treatment efficacy and need for further treatment.[47] The post hoc analysis of the HARBOR study demonstrated that residual IRF is associated with worse vision, regardless of location/severity, whereas residual SRF is not associated with worse vision. The relationship of VA to PEDs, however, has been proved challenging. Although anti-VEGF intravitreal therapy is efficacious in the treatment of nAMD with PED to prevent significant vision loss, the available retrospective and prospective studies seem to support only improved anatomical outcomes, possibly also anti-VEGF dose dependent but without correlated functional improvement.[48–50] The treatment dosing (e.g. higher concentration) could also play a role as demonstrated in the post hoc analysis of the HARBOR study; however, the final BCVA between groups was similar.[48] In our analysis, most of the eyes demonstrated improved PED size but also improved SRF and IRF. This should also be appreciated in the interpretation of the functional results in our cohort. Finally, although we demonstrate PED volume reduction, it is still unknown whether brolucizumab is potent enough to lead to permanent shrinkage of the neovascular component.

In conclusion, our data demonstrate efficacy of brolucizumab manifested by macular neovascularization and PED improvement in patients with persistent nAMD activity. Several studies have demonstrated that switching between anti-VEGF agents in treatment resistant eyes usually leads to anatomical improvement whereas changes in vision are less pronounced and in some cases not correlated to the anatomical improvement. Hence the notion that treatment should focus on visual acuity and not on complete resolution of PED.[51] The existence of a PED is a further challenging factor in the treatment of nAMD. Although our data demonstrate PED improvement in area and volume, efficacy in reducing also the size of the neovascular component has yet to be demonstrated. As brolucizumab becomes incorporated in routine nAMD treatment, more data will define long term effectiveness and potential to reduce treatment burden.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iD

Argyrios Chronopoulos https://orcid.org/0000-0002-1135-4360
Agharza Ashurov https://orcid.org/0000-0002-6055-1571

References

1. Han X, Chen Y, Gordon I, et al. A systematic review of clinical practice guidelines for age-related macular degeneration. *Ophthalmic Epidemiol* 2023; 30: 1–8. DOI: 10.1080/09286586.2022.2059812
2. Martin DF, Maguire MG, Ying GS, et al. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. *N Engl J Med* 2011; 364: 1897–1908. DOI: 10.1056/NEJMoa1102673
3. Dugel PU, Koh A, Ogura Y, et al. HAWK And HARRIER: phase 3, multicenter, randomized, double-masked trials of brolucizumab for neovascular age-related macular degeneration. *Ophthalmology* 2020; 127: 72–84. DOI: 10.1016/j.ophtha.2019.04.017
4. Heier JS, Brown DM, Chong V, et al. Intravitreal aflibercept (VEGF trap-eye) in wet age-related macular degeneration. *Ophthalmology* 2012; 119: 2537–2548. DOI: 10.1016/j.ophtha.2012.09.006
5. Martin DF, Maguire MG, Fine SL, et al. Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two-year results. *Ophthalmology* 2012; 119: 1388–1398. DOI: 10.1016/j.ophtha.2012.03.053
6. Ying GS, Kim BJ, Maguire MG, et al. Sustained visual acuity loss in the comparison of age-related macular degeneration treatments trials. *JAMA Ophthalmol* 2014; 132: 915–921. DOI: 10.1001/jamaophthalmol.2014.1019
7. Prenner JL, Halperin LS, Rycroft C, et al. Disease burden in the treatment of age-related macular degeneration: findings from a time-and-motion study. *Am J Ophthalmol* 2015; 160: 725–731.e721. DOI: 10.1016/j.ajo.2015.06.023
8. Wykoff CC, Clark WL, Nielsen JS, et al. Optimizing anti-VEGF treatment outcomes for patients with neovascular age-related macular degeneration. *J Manag Care Spec Pharm* 2018; 24: S3–S15. DOI: 10.18553/jmcp.2018.24.2-a.s3
9. Lai TT, Hsieh YT, Yang CM, et al. Biomarkers of optical coherence tomography in evaluating the treatment outcomes of neovascular age-related macular degeneration: a real-world study. *Sci Rep* 2019; 9: 529. DOI: 10.1038/s41598-018-36704-6
10. Schmidt-Erfurth U and Waldstein SM. A paradigm shift in imaging biomarkers in neovascular age-related macular degeneration. *Prog Retin Eye Res* 2016; 50: 1–24. DOI: 10.1016/j.preteyeres.2015.07.007
11. Schmidt-Erfurth U, Waldstein SM, Deak GG, et al. Pigment epithelial detachment followed by retinal cystoid degeneration leads to vision loss in treatment of neovascular age-related macular degeneration. *Ophthalmology* 2015; 122: 822–832. DOI: 10.1016/j.ophtha.2014.11.017

12. Querques G, Georges A, Ben Moussa N, et al. Appearance of regressing drusen on optical coherence tomography in age-related macular degeneration. *Ophthalmology* 2014; 121: 173–179. DOI: 10.1016/j.ophtha.2013.06.024
13. Ehlers JP, Zahid R, Kaiser PK, et al. Longitudinal assessment of ellipsoid zone integrity, subretinal hyperreflective material, and subretinal pigment epithelium disease in neovascular age-related macular degeneration. *Ophthalmol Retina* 2021; 5: 1204–1213. DOI: 10.1016/j.oret.2021.02.012
14. Dugel PU, Singh RP, Koh A, et al. HAWK and HARRIER: ninety-six-week outcomes from the phase 3 trials of brolucizumab for neovascular age-related macular degeneration. *Ophthalmology* 2021; 128: 89–99. DOI: 10.1016/j.ophtha.2020.06.028
15. Chronopoulos A, Kakkassery V, Strobel MA, et al. The significance of pigment epithelial detachment in central serous chorioretinopathy. *Eur J Ophthalmol* 2021; 31: 556–565. DOI: 10.1177/1120672120904670
16. Schmidt-Erfurth U, Chong V, Loewenstein A, et al. Guidelines for the management of neovascular age-related macular degeneration by the European society of retina specialists (EURETINA). *Br J Ophthalmol* 2014; 98: 1144–1167. DOI: 10.1136/bjophthalmol-2014-305702
17. Chen E, Kaiser RS and Vander JF. Intravitreal bevacizumab for refractory pigment epithelial detachment with occult choroidal neovascularization in age-related macular degeneration. *Retina* 2007; 27: 445–450. DOI: 10.1097/01.iae.0000249574.89437.40
18. Freeman WR, Kozak I, Yuson RM, et al. Prognosti implications of pigment epithelial detachment in bevacizumab (avastin)-treated eyes with age-related macular degeneration and choroidal neovascularization. *Retina* 2011; 31: 1812–1818. DOI: 10.1097/IAE.0b013e31821987a4
19. Major JC Jr., Wykoff CC, Croft DE, et al. Aflibercept for pigment epithelial detachment for previously treated neovascular age-related macular degeneration. *Can J Ophthalmol* 2015; 50: 373–377. DOI: 10.1016/j.jcjo.2014.12.012
20. Patel KH, Chow CC, Rathod R, et al. Rapid response of retinal pigment epithelial detachments to intravitreal aflibercept in neovascular age-related macular degeneration refractory to bevacizumab and ranibizumab. *Eye (Lond)* 2013; 27: 663–667. DOI: 10.1038/eye.2013.31
21. Pauleikhoff D, Loffert D, Spital G, et al. Pigment epithelial detachment in the elderly. Clinical differentiation, natural course and pathogenetic implications. *Graefes Arch Clin Exp Ophthalmol* 2002; 240: 533–538. DOI: 10.1007/s00417-002-0505-8
22. Suzuki M, Nagai N, Izumi-Nagai K, et al. Predictive factors for non-response to intravitreal ranibizumab treatment in age-related macular degeneration. *Br J Ophthalmol* 2014; 98: 1186–1191. DOI: 10.1136/bjophthalmol-2013-304670
23. Lux A, Llacer H, Heussen FM, et al. Non-responders to bevacizumab (Avastin) therapy of choroidal neovascular lesions. *Br J Ophthalmol* 2007; 91: 1318–1322. DOI: 10.1136/bjo.2006.113902
24. Krebs I, Glittenberg C, Ansari-Shahrezaei S, et al. Non-responders to treatment with antagonists of vascular endothelial growth factor in age-related macular degeneration. *Br J Ophthalmol* 2013; 97: 1443–1446. DOI: 10.1136/bjophthalmol-2013-303513
25. Ehlken C, Helms M, Bohringer D, et al. Association of treatment adherence with real-life VA outcomes in AMD, DME, and BRVO patients. *Clin Ophthalmol* 2018; 12: 13–20. DOI: 10.2147/OPTH.S151611
26. Gadkari AS and McHorney CA. Unintentional non-adherence to chronic prescription medications: how unintentional is it really? *BMC Health Serv Res* 2012; 12: 98. DOI: 10.1186/1472-6963-12-98
27. Thompson AC, Thompson MO, Young DL, et al. Barriers to follow-up and strategies to improve adherence to appointments for care of chronic eye diseases. *Invest Ophthalmol Vis Sci* 2015; 56: 4324–4331. DOI: 10.1167/iovs.15-16444
28. Bilgic A, Kodjikian L, March de Ribot F, et al. Real-world experience with brolucizumab in wet age-related macular degeneration: the REBA study. *J Clin Med* 2021; 10: 2758. DOI: 10.3390/jcm10132758
29. Tadayoni R, Sararols L, Weissgerber G, et al. Brolucizumab: a newly developed anti-VEGF molecule for the treatment of neovascular age-related macular degeneration. *Ophthalmologica* 2021; 244: 93–101. DOI: 10.1159/000513048
30. Ahmad ZA, Yeap SK, Ali AM, et al. Scfv antibody: principles and clinical application. *Clin Dev Immunol* 2012; 2012: 980250. DOI: 10.1155/2012/980250
31. Nguyen QD, Das A, Do DV, et al. Brolucizumab: evolution through preclinical and clinical studies and the implications for the management of neovascular age-related macular degeneration. *Ophthalmology* 2020; 127: 963–976. DOI: 10.1016/j.ophtha.2019.12.031
32. Szabo E, Phillips DJ, Droste M, et al. Antitumor activity of DLX1008, an anti-VEGFA antibody fragment with low picomolar affinity, in human glioma models. *J Pharmacol Exp Ther* 2018; 365: 422–429. DOI: 10.1124/jpet.117.246249
33. Holz FG, Dugel PU, Weissgerber G, et al. Single-chain antibody fragment VEGF inhibitor RTH258 for neovascular age-related macular degeneration: a randomized controlled study. *Ophthalmology* 2016; 123: 1080–1089. DOI: 10.1016/j.ophtha.2015.12.030
34. Dugel PU, Jaffe GJ, Sallstig P, et al. Brolucizumab versus aflibercept in participants with neovascular age-related macular degeneration: a randomized trial. *Ophthalmology* 2017; 124: 1296–1304. DOI: 10.1016/j.ophtha.2017.03.057
35. Singer M, Albini TA, Seres A, et al. Clinical characteristics and outcomes of eyes with intraocular inflammation after brolucizumab: post hoc analysis of HAWK and HARRIER. *Ophthalmol Retina* 2022; 6: 97–108. DOI: 10.1016/j.oret.2021.05.003
36. Arnold JJ, Markey CM, Kurstjens NP, et al. The role of subretinal fluid in determining treatment outcomes in patients with neovascular age-related macular degeneration–a phase IV randomised clinical trial with ranibizumab: the FLUID study. *BMC Ophthalmol* 2016; 16: 31. DOI: 10.1186/s12886-016-0207-3
37. Brown DM, Chen E, Mariani A, et al. Super-dose anti-VEGF (SAVE) trial: 2.0 mg intravitreal ranibizumab for recalcitrant neovascular macular degeneration-primary end point. *Ophthalmology* 2013; 120: 349–354. DOI: 10.1016/j.ophtha.2012.08.008
38. Wykoff CC, Brown DM, Chen E, et al. SAVE (Super-dose anti-VEGF) trial: 2.0 mg ranibizumab for recalcitrant

neovascular age-related macular degeneration: 1-year results. *Ophthalmic Surg Lasers Imaging Retina* 2013; 44: 121–126. DOI: 10.3928/23258160-20130313-04

39. Jaffe GJ, Kaiser PK, Thompson D, et al. Differential response to anti-VEGF regimens in age-related macular degeneration patients with early persistent retinal fluid. *Ophthalmology* 2016; 123: 1856–1864. DOI: 10.1016/j.ophtha.2016.05.016
40. Khanani AM, Brown DM, Jaffe GJ, et al. MERLIN: phase 3a, multicenter, randomized, double-masked trial of brolucizumab in participants with neovascular age-related macular degeneration and persistent retinal fluid. *Ophthalmology* 2022; 129: 974–985. DOI: 10.1016/j.ophtha.2022.04.028
41. Holz FG, Schmitz-Valckenberg S, Wolf A, et al. A randomized, open-label, multicenter study of switching to brolucizumab with or without a loading dose for patients with suboptimal anatomically controlled neovascular age-related macular degeneration-the FALCON study. *Graefes Arch Clin Exp Ophthalmol* 2022; 260: 2695–2702. DOI: 10.1007/s00417-022-05591-z
42. Geitzenauer W, Hitzenberger CK and Schmidt-Erfurth UM. Retinal optical coherence tomography: past, present and future perspectives. *Br J Ophthalmol* 2011; 95: 171–177. DOI: 10.1136/bjo.2010.182170
43. Keane PA, Patel PJ, Liakopoulos S, et al. Evaluation of age-related macular degeneration with optical coherence tomography. *Surv Ophthalmol* 2012; 57: 389–414. DOI: 10.1016/j.survophthal.2012.01.006
44. Coscas F, Coscas G, Souied E, et al. Optical coherence tomography identification of occult choroidal neovascularization in age-related macular degeneration. *Am J Ophthalmol* 2007; 144: 592–599. DOI: 10.1016/j.ajo.2007.06.014
45. Ghazza A, Trouve L and Meyer L. Natural history of a drusenoid pigment epithelial detachment in age-related macular degeneration: spontaneous regression. *J Fr Ophtalmol* 2021; 44: 108–111. DOI: 10.1016/j.jfo.2020.02.022
46. Milewski SA and Judson PH. Spontaneous resolution of hemorrhagic retinal pigment epithelial detachment. *Ann Ophthalmol* 1992; 24: 91–92.
47. Sadda S, Holekamp NM, Sarraf D, et al. Relationship between retinal fluid characteristics and vision in neovascular age-related macular degeneration: HARBOR post hoc analysis. *Graefes Arch Clin Exp Ophthalmol* 2022; 260: 3781–3789. DOI: 10.1007/s00417-022-05716-4
48. Sarraf D, London NJ, Khurana RN, et al. Ranibizumab treatment for pigment epithelial detachment secondary to neovascular age-related macular degeneration: post hoc analysis of the HARBOR study. *Ophthalmology* 2016; 123: 2213–2224. DOI: 10.1016/j.ophtha.2016.07.007
49. Khanani AM, Eichenbaum D, Schlottmann PG, et al. Optimal management of pigment epithelial detachments in eyes with neovascular age-related macular degeneration. *Retina* 2018; 38: 2103–2117. DOI: 10.1097/IAE.0000000000002195
50. Mariani A, Deli A, Ambresin A, et al. Characteristics of eyes with secondary loss of visual acuity receiving variable dosing ranibizumab for neovascular age-related macular degeneration. *Graefes Arch Clin Exp Ophthalmol* 2011; 249: 1635–1642. DOI: 10.1007/s00417-011-1734-5
51. Ashraf M, Banaee T, Silva FQ, et al. Switching anti-vascular endothelial growth factors in refractory neovascular age-related macular degeneration. *Ophthalmic Surg Lasers Imaging Retina* 2018; 49: 166–170. DOI: 10.3928/23258160-20180221-03
52. Mettu PS, Allingham MJ and Cousins SW. Incomplete response to anti-VEGF therapy in neovascular AMD: exploring disease mechanisms and therapeutic opportunities. *Prog Retin Eye Res* 2021; 82: 100906. DOI: 10.1016/j.preteyeres.2020.100906