EFFECT OF RANIBIZUMAB AND AFLIBERCEPT ON RETINAL PIGMENT EPITHELIAL DETACHMENT, SUBRETINAL, AND INTRA-RETINAL FLUID IN AGE-RELATED MACULAR DEGENERATION

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SUMMARY

Purpose: The aim of the study was to compare the effect of three initial doses of the anti-VEGF ranibizumab and aflibercept medication on serous pigment epithelial detachment (PED), subretinal fluid (SRF) and intraretinal fluid (IRF) in the macula of treatment naive neovascular AMD (nvAMD) patients.
Material and Methods: The cohort consists of 148 patients, of which 74 patients were treated with ranibizumab (51 females and 23 males) and 74 with aflibercept (46 females and 28 males). The data was recorded prospectively from the moment of diagnosis and start of treatment for a period of 3 months. At the moment of diagnosis and 3 months later, an OCT examination (Spectralis OCT, Heidelberg Engineering, Heidelberg, Germany) was performed. The OCT examination included a macular scan with 25 scans. Using the OCT instrument software, we measured the maximum anterior-posterior elevation of serous PED, the highest thickness of SRF and the largest diameter of the intraretinal cystic space. The statistical significance of differences between groups was evaluated using the t-test for continuous data and the Fisher exact test for categorical data. Changes in values of continuous variables over time were evaluated using the Wilcoxon paired test. Paired comparisons of binary parameters were determined by the McNemar test.
Results: Full regression of PED, SRF and IRF occurred in 3 (4.1%), 25 (39%) and 20 (51%) patients treated with ranibizumab, and in 5 (7.9%, p = 0.470), 28 (47%, p = 0.470) and 25 (57%, p = 0.827) patients treated with aflibercept, respectively. The average regression of PED, SRF and IRF was -60.4 µm (median -37.5 µm), -84.3 µm (median -85 µm) and -109.3 µm (median -81 µm) in patients treated with ranibizumab, and -46.3 µm (median -30 µm, p = 0.389), -127.7 µm (median -104 µm, p = 0.096) and -204.4 µm (median -163 µm, p = 0.005) in patients treated with aflibercept, respectively. We did not show a statistically significant difference in the regression rates of PED, SRF and IRF between the ranibizumab and aflibercept groups. (in patients with IRF after adjustment of the higher baseline IRF volumes in patients treated with aflibercept, p = 0.891).
Conclusion: We are convinced that ranibizumab and aflibercept have the same effect on serous PED, SRF and IRF in the macula in patients with treatment naive nvAMD during the initial loading phase.
Key words: age-related macular degeneration, ranibizumab, aflibercept, pigment epithelium detachment, subretinal fluid, intraretinal fluid

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INTRODUCTION

Age-related macular degeneration (AMD) is subdivided into the dry and wet form. The wet form represents only 10% of cases of this disease, but according to Bressler, 90% of the legal blindness from AMD is caused by the wet form [1].

The wet form of AMD, also called neovascular AMD (nvAMD), is based on the growth of the subretinal membrane (CNV), which leads to a decrease in visual acuity (VA) due to the anatomical changes in macula. Anatomical changes in macula in the nvAMD typically consist of retinal pigment epithelium detachment (PED), subretinal fluid (SRF) and intra-retinal fluid (IRF) [2,3].

Repeated intravitreal anti-vascular endothelial growth factor (anti-VEGF) injections are the current gold standard treatment for nvAMD [4–7]. Ranibizumab (Lucentis; Novartis Pharma AG, Basel, Switzerland) and Aflibercept (Eylea; Bayer HealthCare, Berlin, Germany) are the main treatments for this condition today. Aflibercept and Ranibizumab have shown comparable efficacy in terms of the best-corrected visual acuity (BCVA) and central retinal thickness improvement [7,8]. However, these two anti-VEGF medications present different pharmacological profiles [9]. There is an ongoing debate about potential differences of the medications' effect in a subset of patients. Therefore, comparative studies are needed.

We have not found a study that would prospectively and directly compare the effect of Ranibizumab and Aflibercept on serous PED, SRF and IRF in nvAMD patients. We know that the highest improvement of BCVA is achieved in the initial loading phase of treatment, i.e., the first three injections of Ranibizumab or Aflibercept [7,8,10,11], we decided to compare the effect of Ranibizumab and Aflibercept on the morphological changes in nvAMD patients during the initial, very important loading phase of the treatment. Moreover, by choosing this period, we were able to administer the same number of injections of both preparations over the same time frame.

The aim of the study was the evaluation of eventual statistically significant difference in the effect of Ranibizumab versus Aflibercept on serous PED, SRF and IRF in in the macula of patients with naive, age related neovascular degeneration during the loading phase of the treatment.

MATERIALS AND METHODS

The cohort consists of 148 patients (51 males and 97 females, average age of 74 and 72 years, respectively). The right and left eye were treated in 79 and 69 cases, respectively. 74 patients were treated with Ranibizumab (51 females and 23 males) and 74 with Aflibercept (46 females and 28 males).

Patients were prospectively followed up from January 2018. We continuously enrolled patients who were randomly assigned to treatment with Ranibizumab or Aflibercept at the discretion of the referring physician.

The data collection was independent on all treatment decisions; it did not affect patient's access to treatment and fully complied with all ethical, as well as legal requirements for data collection in the Czech Republic. All patients gave their written informed consent to the treatment, as well as to the data collection. The reported investigations were in accordance with the principles of the current version of the Helsinki Declaration.

Each visit included biomicroscopic examination of the eye fundus, determination of BCVA using the ETDRS (Early Treatment Diabetic Retinopathy Study) chart. The first visit involved fluorescein angiography (FA). At the moment of diagnosis and 3 months later, an OCT examination (Spectralis OCT, Heidelberg Engineering, Heidelberg, Germany) was performed. The OCT examination included a macular scan with 25 scans. We manually examined each of the 25 input OCT scans taken for each patient. Using the OCT instrument software, we measured the highest serous PED (greatest distance between RPE and Bruch's membrane) in µm, highest accumulation of SRF (greatest distance of RPE and outer side of neuroepithelium) and the diameter of the largest intra-retinal cystic space. (Figure 1) As OCT Spectralis is equipped with an eye-tracking system, it was possible to repeat the 25 scans at the same place 3 months later within a follow-up, after the 3 initial doses of the anti-VEGF medication. We repeated the measurement of the highest serous PED, the highest accumulation of SRF and the diameter of the largest intra-retinal cystic space.

Patients with a diagnosed wet form of AMD who complied with the Czech Society of Ophthalmology criteria

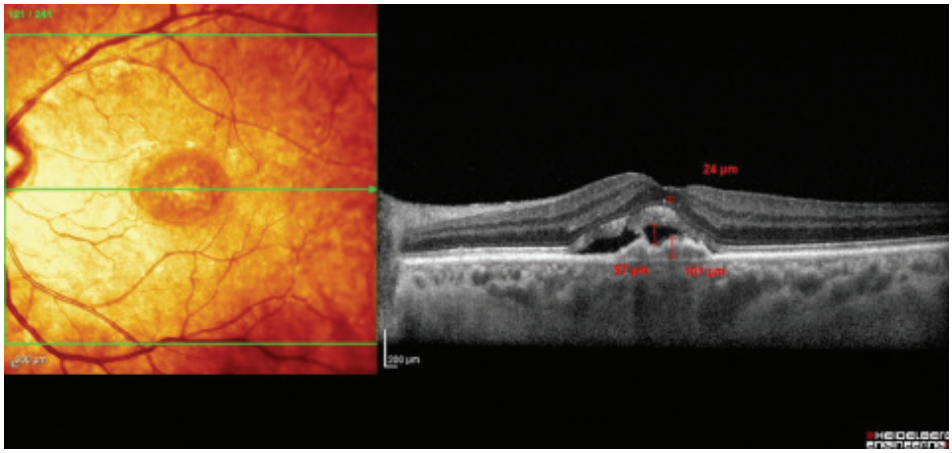


Figure1. Measurement of the highest accumulation of SRF, IRF, PED
SRF – subretinal fluid, IRF – intraretinal fluid, PED – retinal pigment epithelial detachment

for initiation of treatment with anti-VEGF medication were treated with three injections of Ranibizumab (0.5 mg) or Aflibercept (2 mg). Anti-VEGF therapy in the Czech Republic is indicated in patients with AMD who are 50 years old and above, with predominantly classic, minimally classic, or occult CNV reaching the subfoveal area, a BCVA

Table 1. Retinal pigment epithelial ablation

(A) Presence or disappearance of a feature					
RAN + AFL (N=148)	**After treatment: Present**	**After treatment: Disappeared**	**After treatment: Total**	**p-value[1]**	
Baseline: Present	**129 (94.2%)**	**8 (5.8%)**	**137 (100%)**	**p=0.046**	
Baseline: Not present	1 (9.1%)	10 (90.9%)	11 (100%)		
Baseline: Total	130 (87.8%)	18 (12.2%)	148 (100%)		
RANIBIZUMAB (N=74)	**After treatment: Present**	**After treatment: Disappeared**	**After treatment: Total**		
Baseline: Present	**71 (95.9%)**	**3 (4.1%)**	**74 (100%)**	p=0.248	
Baseline: Not present	0	0	0		
Baseline: Total	71	3	74		
AFLIBERCEPT (N=74)	**After treatment: Present**	**After treatment: Disappeared**	**After treatment: Total**		
Baseline: Present	**58 (92.1%)**	**5 (7.9%)**	**63 (100%)**	0.221	
Baseline: Not present	1 (9.1%)	10 (90.9%)	11 (100%)		
Baseline: Total	59 (79.7%)	15 (20.3%)	74 (100%)		
p-value[2] RAN vs AFL		p=0.470			
(B) Feature reduction					
CHANGE (difference of values before treatment and after treatment)	**Average**	**Median**	**Min**	**Max**	**p-value[3]**
RAN+AFL:All[3] (N=137)	**-53.9**	**-36**	**-463**	**130**	**<0.001**
RAN+AFL: Measurement[4] (N=129)	-49	-33	-463	130	<0.001
RAN: All[3] (N=74)	**-60.4**	**-37.5**	**-407**	**95**	**<0.001**
RAN: Measurement[4] (N=71)	-56.8	-36	-407	95	<0.001
AFL: All[3] (N=63)	**-46.3**	**-30**	**-463**	**130**	**<0.001**
AFL: Measurement[4] (N=58)	-39.5	-26.5	-463	130	0.001
p-value[4] RAN vs AFL					
All[3]		p=0.389			
Measurement[4]		p=0.237			

p -value[1] of McNemar test
p -value[2] of Fisher exact test
p -value[3] of Wilcoxon signed-rank test
p -value[4] of Mann-Whitney U-test
[3]patients without the feature after treatment were assigned the value 0 (i.e. maximal decrease)
4 patients with feature present and value measured before and after treatment (i.e. patients from whom the feature had not fully disappeared)
RAN – Ranibizumab, AFL – Aflibercept

score between 70–35 letters (20/40–20/200 Snellen equivalent), total macular lesion area < 8-disc area, submacular hemorrhage < 25% of the total macular lesion area.

The data was described using standard statistics – continuous variables were described by mean, median, minimum and maximum; absolute and relative frequencies were used for the description of the categorical variables. The statistical significance of the differences between the groups was evaluated using the t-test for continuous data and the Fisher exact test for categorical data. Adjustment for baseline IRF values was further applied using a multivariate linear regression model as different baseline IRF volumes could confuse the treatment effect – the higher baseline IRF volumes provides a higher potential for reduction in IRF. Changes in values of continuous variables over time were evaluated using the Wilcoxon paired test. Paired comparisons of binary parameters were determined by the McNemar test. The analysis was performed using R software by the Institute of Biostatistics and Analyses Ltd., Brno. The level of statistical significance was set at $\alpha = 0.05$ in all analyses.

RESULTS

Serous PED was diagnosed in 137 patients of the group at the beginning of treatment. Full regression and complete disappearance of PED was observed in 8 (6%) patients and anti-VEGF treatment was statistically significantly successful ($p = 0.046$). The average regression of PED after the treatment was -53.9 µm (median -36 µm) and the success rate was statistically significant ($p < 0.001$) (Table 1).

The table demonstrates the rate of regression of serous PED achieved in all patients but also in patients treated individually with Ranibizumab and aflibercept.

Of this cohort, 74 patients were in the Ranibizumab group and 63 in the Aflibercept group. Full regression of PED occurred in 3 (4.1%) patients treated with Ranibizumab and 5 (7.9%) patients treated with Aflibercept ($p = 0.470$). The average regression of PED after treatment was -60.4 µm (median -37.5 µm) and -46.3 µm (median -30 µm) in the Ranibizumab and Aflibercept groups ($p = 0.389$), respectively. There was no statistically significant difference in the rate of regression of serous PED achieved in patients treated with Ranibizumab and Aflibercept (Graph 1).

The difference between the preparations was not shown to be statistically significant ($p = 0.389$) even after adjustment for ablation baseline values.

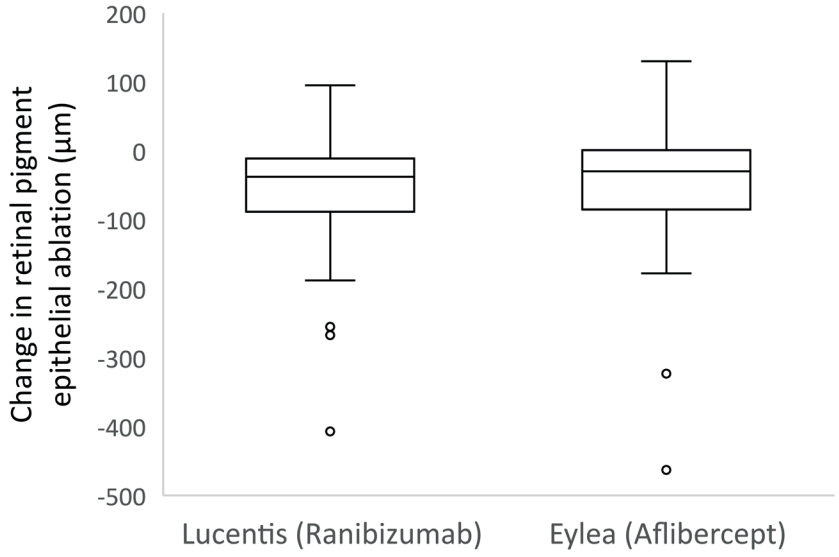
Baseline SRF was detected in 123 patients of the group. Full regression was observed in 53 patients (43%), a result that was statistically significant ($p < 0.001$). The average SRF regression after treatment was -105.3 µm (median -95 µm) and the resorption rate was statistically significant ($p < 0.001$) (Table 2).

The table demonstrates the rate of regression of subretinal fluid achieved in all patients but also in patients treated separately with Ranibizumab and aflibercept.

SRF was detected in 123 patients in the cohort. 64 of these patients were in the Ranibizumab group and 59 in the Aflibercept group. Full SRF regression was observed in 25 (39%) patients treated with Ranibizumab and 28 (47%) patients treated with Aflibercept ($p = 0.470$). The average SRF regression after treatment was -84.3 µm (median -85 µm) and -127.7 µm (median -104 µm) in the Ranibizumab and Aflibercept groups ($p = 0.096$), respectively. There was no statistically significant difference in the rate of SRF regression between the patients treated with Ranibizumab and Aflibercept (Graph 2).

The difference between the products was not proven statistically significant ($p=0.096$) even after adjusting for the baseline subretinal fluid values ($p=0.249$, not stated in Table 2).

IRF was detected in 84 patients of the cohort. Full re-



Graph 1. Change in retinal pigment epithelial ablation

gression and complete disappearance of the IRF was observed in 45 (53%) patients and the anti-VEGF treatment was statistically significantly successful ($p < 0.001$). The average IRF regression after treatment was -160.9 µm (median -139 µm) and the regression rate was statistically significant ($p < 0.001$). (Table 3).

Table 2. Subretinal fluid

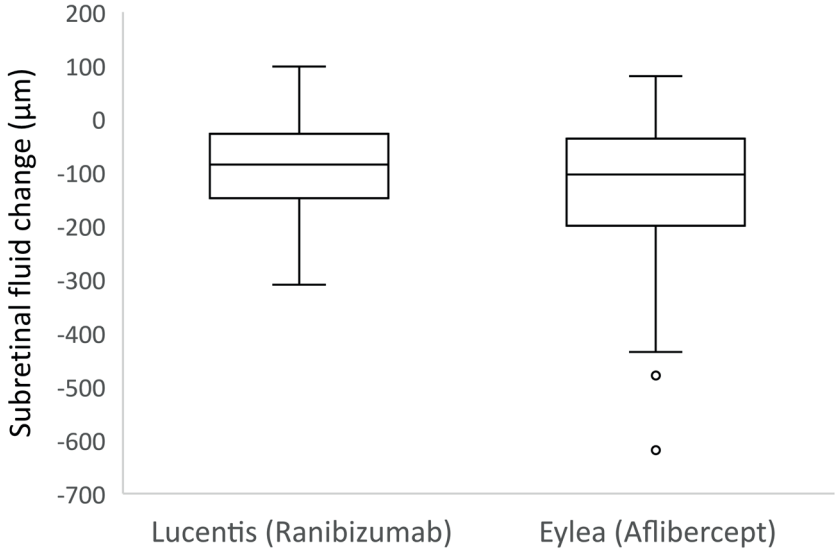
(A) Presence or disappearance of a feature					
RANIBIZUMAB + AFLIBERCEPT (N=148)	**After treatment: Present**	**After treatment: Disappeared**	**After treatment: Total**	**p-value[1]**	
Baseline: Present	**70 (56.9%)**	**53 (43.1%)**	**123 (100%)**	**<0.001**	
Baseline: Not present	7 (28%)	18 (72%)	25 (100%)		
Baseline: Total	77 (52%)	71 (48%)	148 (100%)		
RANIBIZUMAB (N=74)	**After treatment: Present**	**After treatment: Disappeared**	**After treatment: Total**		
Baseline: Present	**39 (60.1%)**	**25 (39.1%)**	**64 (100%)**	**<0.001**	
Baseline: Not present	4 (40%)	6 (60%)	10 (100%)		
Baseline: Total	43 (58.1%)	31 (41.9%)	74 (100%)		
AFLIBERCEPT (N=74)	**After treatment: Present**	**After treatment: Disappeared**	**After treatment: Total**		
Baseline: Present	**31 (52.5%)**	**28 (47.5%)**	**59 (100%)**	**<0.001**	
Baseline: Not present	3 (20%)	12 (80%)	15 (100%)		
Baseline: Total	33 (44.6%)	40 (55.4%)	74 (100%)		
p-value[2] RAN vs AFL		p=0.368			
(B) Feature reduction					
CHANGE (difference of values before and after treatment)	**Average**	**Median**	**Min**	**Max**	**p-value[3]**
RAN+AFL: All[3] (N=122*)	**-105.3**	**-95**	**-619**	**98**	**<0.001**
RAN+AFL: Measurement[4] (N=69)	-58.9	-35	-368	98	<0.001
RAN: All[3] (N=63)	**-84.3**	**-85**	**-310**	**98**	**<0.001**
RAN: Measurement[4] (N=38)	-45.1	-30	-187	98	<0.001
AFL: All[3] (N=59*)	**-127.7**	**-104**	**-619**	**80**	**<0.001**
AFL: Measurement[4] (N=31)	-75.8	-45	-368	80	<0.001
p-value[4] RAN vs AFL					
All[3]		0.096			
Measurement[4]		0.426			

p -value[1] of McNemar test
p -value[2] of Fisher exact test
p -value[3] of Wilcoxon signed-rank test
p -value[4] of Mann-Whitney U-test
[3]patients without the feature after treatment were assigned the value 0 (i.e. maximal decrease)
[4]patients with feature present and value measured before and after treatment (i.e. patients from whom the feature had not fully disappeared)
RAN – Ranibizumab, AFL – Aflibercept
** measurement after treatment lacking for 1 patient*

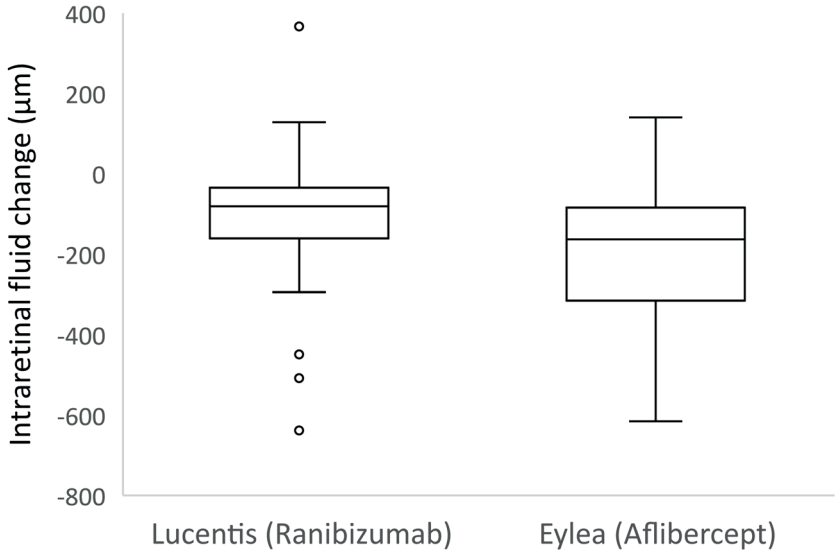
The table demonstrates the rate of regression of intra--retinal fluid achieved in all patients but also in patients treated separately with Ranibizumab and aflibercept.

IRF was diagnosed in 84 patients in the cohort – 39 patients in the Ranibizumab group and 45 in the Aflibercept group. Full IRF regression was observed in 20 (51%) patients treated with Ranibizumab and 25 (57%) patients treated with Aflibercept (p = 0.827). The average IRF regression after treatment was -109.3 µm (median -81 µm) and -204.4 µm (median -163 µm) in the Ranibizumab and Aflibercept groups (p = 0.005), respectively. There was a statistically significant IRF reduction in both groups. Aflibercept treatment led to statistically significantly greater IRF reduction (median -163 vs. median -81, p = 0.005). However, the higher baseline IRF volumes in patients treated with Aflibercept played a part, providing a higher potential for reduction. There was no statistically significant difference in the reduction of the IRF between Ranibizumab and Aflibercept after the adjustment (p = 0.891) (Table 4).

Only intra-retinal fluid showed a statistically significant difference in baseline feature size between the Ranibizumab and Aflibercept groups. However, the baseline intra--retinal fluid was statistically significantly higher in the Aflibercept group than in the Ranibizumab group (p < 0.001). Thus, there was no statistically significant difference in the IRF regression rate between Ranibizumab- and aflibercept-treated patients (Table 3, Table 4, Graph 3).



Graph 2. Subretinal fluid change



Graph 3. Intraretinal fluid change

Table 3. Intraretinal fluid

(A) Presence or disappearance of a feature					
RANIBIZUMAB + AFLIBERCEPT (N=148)	**After treatment: Present**	**After treatment: Disappeared**	**After treatment: Total**	**p-value[1]**	
Baseline: Present	**39 (46.4%)**	**45 (53.6%)**	**84 (100%)**	**<0.001**	
Baseline: Not present	4 (6.3%)	60 (93.8%)	64 (100%)		
Baseline: Total	43 (29.1%)	105 (70.9%)	148 (100%)		
RANIBIZUMAB (N=74)	**After treatment: Present**	**After treatment: Disappeared**	**After treatment: Total**		
Baseline: Present	**19 (48.7%)**	**20 (51.3%)**	**39 (100%)**	**<0.001**	
Baseline: Not present	2 (5.7%)	33 (94.3%)	35 (100%)		
Baseline: Total	21 (28.4%)	53 (71.6%)	74 (100%)		
AFLIBERCEPT (N=74)	**After treatment: Present**	**After treatment: Disappeared**	**After treatment: Total**		
Baseline: Present	**20 (44.4%)**	**25 (55.6%)**	**45 (100%)**	**<0.001**	
Baseline: Not present	2 (6.9%)	27 (93.1%)	29 (100%)		
Baseline: Total	22 (29.7%)	52 (70.3%)	74 (100%)		
p-value[2] RAN vs AFL		p=0.827			
(B) Feature reduction					
CHANGE (difference of values before treatment and after treatment)	**Average**	**Median**	**Min**	**Max**	**value[3]**
RAN+AFL: All[3] (N=83*)	**-160.9**	**-139**	**-638**	**367**	**<0.001**
RAN+AFL: Measurement[4] (N=38)	-63	-56	-315	367	<0.001
RAN: All[3] (N=38)	**-109.3**	**-81**	**-638**	**367**	**<0.001**
RAN: Measurement[4] (N=18)	-16.4	-32.5	-237	367	0.043
AFL: All[3] (N=45*)	**-204.4**	**-163**	**-615**	**140**	**<0.001**
AFL: Measurement[4] (N=20)	-105	-99.5	-315	140	0.001
p-value[4] RAN vs AFL					
All[3]		0.005			
Measurement[4]		0.013			

p -value[1] of McNemar test
p -value[2] of Fisher exact test
p -value[3] of Wilcoxon signed-rank test
p -value[4] of Mann-Whitney U-test
[3]patients without the feature after treatment were assigned the value 0 (i.e. maximal decrease)
[4]patients with feature present and value measured before and after treatment (i.e. patients from whom the feature had not fully disappeared)
RAN – Ranibizumab, AFL – Aflibercept
** measurement after treatment lacking for 1 patient*

There was only a statistically significantly larger reduction of intra-retinal fluid in the Aflibercept group (p = 0.005). After adjusting for the baseline values, the difference in the reduction of the intra-retinal fluid between Ranibizumab and Aflibercept was not statistically significant (p = 0.891), not stated in Table 3).

DISCUSSION

The MARINA [4], ANCHOR [6], VIEW 1, and VIEW 2 [7] trials showed the efficacy of Ranibizumab and Aflibercept administered as a continuous monthly regimen of injections over a period of 24 months for patients with nvAMD. Initially, the primary endpoint of the studies on the effect of Ranibizumab and Aflibercept on the course of nvAMD was always the changes of BCVA. The description of morphological changes in the macula was usually limited to the rate of macular thickness change associated with the development of macular oedema.

This trend has changed slightly over time. Changes in macular morphology have been reported in the treatment of nvAMD. HARBOR Study 1-Year Results in the Ranibizumab group (0.5 mg monthly) showed a rapid decrease in central foveal thickness at day 7 that continued through month 3 and was sustained from month 3 to month 12. At 12 months it demonstrated a decrease from baseline in total area of CNV and total area of CNV flattening [12]. Clemens described a complete lesion flattening in the serous vascularized PED group in 30% of patients and a complete absorption of SRF after three injections observed in approximately 70% under a 0.5 mg monthly Ranibizumab treatment dose [13]. This is in accordance with previously published Schmidt-Erfurth data [3]. Němčanský states that after one-year long Aflibercept therapy, residual macular fluid was present in 27.8% of all patients, without specifying whether it was subretinal or intra-retinal fluid [14].

Some studies also correlate the baseline morphological finding in the macula at the beginning of nvAMD treatment and the functional outcome of the therapy. Ashraf states that patients with PED, IRF and vitreomacular adhesion achieved less visual gains [15]. A post hoc analysis of the VIEW 1 / VIEW 2 results looked at the association between various morphological features and functional outcomes. The study found that regardless of the medication used, the presence of IRF and PED at baseline was associated with less BCVA change from baseline at week 52 (2.11 less letters for IRF and 1.88 less letters for RPE detachment) compared to SRF, which was associated with 2.11 letters gain BCVA from baseline at week 52 [16,17].

There are also initial studies comparing the develop-

Table 4. Measured values of parameters of interest before and after treatment

	N		"95% CI (upper/lower limit)"		Median	25th	75th	p[1]
BASELINE: RPE ABLATION								
Ranibizumab	74	189.9	54.5	662	179.5	137	297.7	0.054
Aflibercept	63	155.9	52.7	461.1	149	105.5	217.6	
BASELINE: SUBRETINAL FLUID								
Ranibizumab	64	142.3	60	337.6	148.5	104.2	183	0.661
Aflibercept	59	149.2	37.6	590.9	159	98.5	229	
BASELINE: INTRARETINAL FLUID								
Ranibizumab	39	146.2	36.9	578.6	157	91.5	217	0.001
Aflibercept	45	248.5	71.4	865.5	275	163	381	
AFTER TREATMENT: RPE ABLATION								
Ranibizumab	71	139.2	33.9	570.7	141	95	227.5	0.126
Aflibercept	59	114	26.2	496	105	73	215	
AFTER TREATMENT: SUBRETINAL FLUID								
Ranibizumab	42	100.5	33.4	302.6	84.4	70.5	140.7	0.36
Aflibercept	34	88.8	27.4	287.5	82.5	60.2	123.2	
AFTER TREATMENT: INTRARETINAL FLUID								
Ranibizumab	20	119.7	27.7	516.7	147.8	75.7	183	0.433
Aflibercept	22	146.2	25.7	830.2	166.8	86.5	259.7	

p[1]-value of t-test
RPE – Retinal pigment epithelium

ment of morphological findings in the macula in the treatment with Ranibizumab and aflibercept. In the Heier study, Aflibercept tended to show increased efficacy for fluid absorption; 27.6% of patients treated with Aflibercept had persistent fluid for 1 year in comparison with 38% of patients treated with Ranibizumab [7].

The VIEW 1 and VIEW 2 studies compared the efficacy and safety of intravitreal Aflibercept injections (IAI) and Ranibizumab injections in treatment-naive eyes with nvAMD. 0.5 mg intravitreal Ranibizumab every 4 weeks (Rq4), 2 mg IAI every 4 weeks (2q4) and 2 mg IAI every 8 weeks (2q8) after 3 initial monthly injections. In both the 2q4 and 2q8 groups, more than 50% of the study eyes had the first episode of retinal fluid absence by week 4. At week 12, more than 75% of the eyes treated with 2q4 or 2q8 were dry on at least 1 visit. The 75% cumulative incidence of a dry retina on at least 1 visit for eyes treated with Rq4 was reached at week 20. On the basis of the relative hazard ratio for sustained dryness, eyes treated with 2q4 were approximately 1.5 times more likely than those treated Rq4 and 2q8 to achieve sustained dryness. When early persistent intra-retinal or subretinal fluid was present after the initial 3 injections (a finding present in approximately 20% of eyes initially treated with IAI and in 30% of eyes with Rq4), there may be a benefit to monthly IAI compared with the other regimens as demonstrated by a higher proportion of dry retinas, greater visual acuity improvement, and a smaller proportion with visual acuity loss in eyes treated with 2q4 compared with eyes treated with Rq4 or 2q8 at week 52. The reason for better visual acuity outcomes in the IAI 2q4 treatment group among eyes with persistent fluid is unknown. The authors hypothesize that treatment-naive eyes, in which the fluid persists after initial treatment, may be less sensitive to the anti-VEGF anti-permeability effects of anti-VEGF and require continuous anti-VEGF treatment to avoid the adverse effects of fluid on photoreceptors and other neurosensory retinal structures. They were unable to assess the effect of early persistent fluid on retinal microanatomy because lower-resolution time-domain OCT was used in this study [16,17]. Dirani published a study which investigated factors influencing the visual acuity and PED response in nvAMD after 3 months of anti-VEGF treatment, including the comparison between Ranibizumab and aflibercept. Dirani observed a reduction of the maximum PED height 66 mm greater in patients treated with Aflibercept than in Ranibizumab-treated eyes (p = 0.22) [18]. Massougnes performed a retrospective comparison of the effect of 12-month-long treatment of Ranibizumab and Aflibercept on PED in patients with the wet form of AMD. Patients treated with Aflibercept displayed a 90.66 µm greater reduction of the maximum PED height than Ranibizumab-treated eyes (p = 0.008) [19]. Cho additionally observed that Aflibercept showed a greater probability of RPE flattening than Ranibizumab (p = 0.039) after 12 months of treatment, although the complete resolution of PED was limited to only 19.5% of subjects [20].

The large multicentric studies in neovascular AMD showed that the biggest change in retinal thickness occurs after the first treatment, which suggests that the first anti-VEGF injection has the largest morphological impact on the retina and greatest stress on the RPE [21,22]. The functional effect of anti-VEGF medication is most pronounced during the loading phase of therapy [10,11]. Therefore, we focused on morphological changes of macula during the loading phase of therapy. In contrast to Dirani and Massougnes, there was no statistically significant difference in the efficacy of Aflibercept versus Ranibizumab on PED. Our study not only directly compares the effects of Aflibercept and Ranibizumab on PED, but also on SRF and IRF, again during the loading phase of therapy. Neither SRF nor IRF showed statistically significant differences in efficacy between the two preparations.

In the available literature, we found no other studies that would prospectively assess the effect of Ranibizumab and Aflibercept on the all three typical morphological changes in treatment-naive eyes with nvAMD with a comparable number of injections during the same time interval. The results of this study may be used as the grounds for future prospective studies of the effects of Ranibizumab, Aflibercept and the newly emerging Brolucizumab on morphological changes in the macula of patients with naive nvAMD.

CONCLUSION

Anti-VEGF treatment significantly reduces serous PED, SRF and IRF in patients with nvAMD. The weakest effect of the treatment was observed in serous PED, where the success rate of treatment was on the border of statistical significance. We found no statistically significant differences in the effect of Ranibizumab and Aflibercept on morphological changes in patients with nvAMD. Our results show that the effect of Ranibizumab and Aflibercept on serous PED, SRF and IRF in the macula of patients with nvAMD is comparable during the initial loading phase.

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