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Short-term effect of aflibercept on visual acuity and central macular thickness in patients not responding to ranibizumab and bevacizumab

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Summary
Purpose To analyze the clinical outcome of treatment with aflibercept in patients not responding to ranibizumab and bevacizumab.
Methods Retrospective review of 32 eyes from 30 consecutive patients with choroidal neovascularization (CNV) who showed no response to treatment with ranibizumab or bevacizumab and were switched to aflibercept. Visual acuity, central macular thickness (CMT) and presence or absence of intraretinal or subretinal fluid were analyzed before switching to aflibercept, after each of three uploading dose injections of aflibercept and 6, 8 and 10 weeks after the third aflibercept injection. All eyes had previous ranibizumab injections and the mean number of previous injections was 14.75 (± 7.38). Mean duration of previous anti-vascular endothelial growth factor (VEGF) treatment was 38 months (± 27.35 months).
Results Mean visual acuity before switching to aflibercept was 0.40 ± 0.30 logMAR. After the third injection visual acuity was 0.3 ± 0.3 logMAR and 10 weeks after the third injection it was 0.50 ± 0.20 logMAR. No significant differences were seen during treatment and follow-up. The mean CMT was 394 ± 118 µm at baseline, at follow-up (first, second and third, group week 6, group week 8 and group week 10) it was 317 ± 108 µm, 301 ± 99 µm, 292 ± 83 µm, 270 ± 78 µm, 340 ± 146 µm and 377 ± 92 µm, respectively. Significant reductions in CMT were seen between the first and third follow-up injections and at group week 8. Of the patients 59.4 % were complete non-responders to aflibercept.
Conclusion Aflibercept results in improvement in CMT in non-responders to ranibizumab and bevacizumab as long as therapy is given continuously and can therefore be an alternative therapy.

Keywords Choroidal neovascularization · Aflibercept · Non-responder · Ranibizumab · Bevacizumab

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Introduction

In industrialized countries age-related macular degeneration (AMD) is a leading cause of vision loss [1]. Severe vision loss is caused by choroidal neovascularization (CNV) and associated macular edema. Early treatment, such as laser ablation and photodynamic therapy (PDT) with verteporfin could only reduce the loss of vision but not stabilize or even improve vision [2, 3]. The suggestion of vascular endothelial growth factor (VEGF) being the driving reason in CNV and associated macular edema has led to intravitreal anti-VEGF therapy, such as ranibizumab and bevacizumab (off-label use), which showed significant visual gain in approximately one third of treated patients [4, 5]. This improvement was caused by the drug's ability to reduce intraretinal and subretinal fluid and hemorrhage; however, after several injections, some of the patients developed resistance to further treatment and recurrent exudation with vision loss probably caused by tolerance or tachyphylaxis [6, 7]. The main mechanism of this resistance to these drugs is still not known. Stewart et al. [8] evaluated whether an injection interval reduced to 2 weeks could support enduring reduction of intraretinal or subretinal fluid.

Although they achieved improved results in some of the patients, this regimen is not approved by the Food and Drug Administration (FDA) for CNV. Additionally, this regimen would lead to clearly increased costs and also patient management would be more complicated as many more visits are required. Aflibercept is a relatively new VEGF inhibitor with a high affinity to VEGF-A and VEGF-B as well as to placental growth factor in vitro and even higher than ranibizumab and bevacizumab [9]. In combination with a longer half-life (4.7 days in rabbit eyes) the efficacy of aflibercept is assumed to be elongated up to 83 days [10]. In comparison, the half-life of ranibizumab is 2.9 days and the half-life of bevacizumab 4.3 days. Bevacizumab is a humanized murine antibody against VEGF and ranibizumab is a humanized antigen-binding fragment to VEGF, whereas aflibercept is a fusion protein receptor, which leads to higher binding affinity to VEGF. This leads to the question whether eyes that have become resistant to anti-VEGF molecules show (better) response to aflibercept injections. The VIEW 1 and VIEW 2 studies already showed that treatment with 3 initial monthly injections of 2 mg aflibercept followed by injections every 8 weeks showed non-inferiority to monthly treatments with either ranibizumab or aflibercept [11, 12]. The combination of higher binding-affinity and longer half-life of aflibercept presupposes that improvement in anatomical and visual outcomes may also be achievable in eyes with treatment-resistant CNV. Some retrospective studies have already shown the efficacy of aflibercept in individualized treatment on otherwise treatment-resistant eyes. They described decreased intraretinal or subretinal fluid and stabilization or even gain in visual acuity [13–16].

In this retrospective study we focused on short-term visual and anatomical outcomes including persistent intraretinal or subretinal fluid in patients with CNV that have developed resistance to treatment with ranibizumab and/or bevacizumab and were switched to injections with 2 mg aflibercept. Special focus is on the period after the third aflibercept injection (following the common treatment scheme) and if an extension to injection intervals every 2 months seems reasonable.

Material and methods

This study was a retrospective observational case series of patients with CNV resistant to treatment of monthly injections of either ranibizumab or bevacizumab or both. Included in the study were all eyes with persistent subfoveal fluid that were switched to 3 monthly injections of aflibercept between 31 July 2013 and 31 January 2014 as we started using aflibercept in our clinic at this point of time. Treatment-resistant eyes were defined by a reaction of central macular thickness (CMT) by less than 50 µm and no change or even worsening in visual acuity since beginning therapy. Exclusion criteria were visual acuity >1.0 logMAR due to macular fibrosis and scarring, concomitant ocular pathology with significant visual impairment (such as vitreous hemorrhage), less than three previous anti-VEGF injections and lack of follow-up after conversion to aflibercept. The study protocol was approved by the ethics committee of the city of Vienna (Ethikkommission der Stadt Wien, EK-13-036) and adhered to the Declaration of Helsinki. This protocol allowed retrospective data collection of patients with CNV who were treated with intravitreal aflibercept injections. Treatment indications and retreatment indications were at the discretion of individual retina specialists of our clinic due to criteria for non-responders. Written consent was obtained from patients prior to each injection treatment. Visual acuity was measured using Snellen charts and was afterwards converted to logMAR.

Spectral domain optical coherence tomography (SD-OCT) was performed using the Spectralis SD-OCT system (Heidelberg Engineering, Germany). The CMT values were obtained using the integrated software. Baseline values were defined as those measured at the last visit before conversion to aflibercept. Injection interval was 4 week and best corrected visual acuity (BCVA) and CMT were measured 4 weeks after each injection (first, second and third follow-up) by performing Snellen Visus and Spectralis OCT. Additionally, the anatomical structure was analyzed with a focus on persistent intraretinal or subretinal fluid. Patients who still showed intraretinal or subretinal fluid at the third follow-up were retreated with ranibizumab or bevacizumab and excluded from the study. In the case of no subfoveal fluid after three injections, patients were observed until recurrence of intraretinal or subretinal fluid. Retrospective analysis then revealed three different follow-up groups: 6, 8 and 10 weeks after the third aflibercept injection (i.e. group week 6, group week 8 and group week 10); therefore, data from eyes in those 2-week blocks after the third injection were used to evaluate at what point after three consecutive aflibercept injections patients show intraretinal or subretinal fluid and need to be re-treated.

The primary objective of our study was evaluation of the efficacy of aflibercept in eyes resistant to treatment with ranibizumab and bevacizumab regarding visual acuity and persistent intraretinal or subretinal fluid. The secondary objective was whether stabilization of CMT also leads to stabilization of visual acuity in short-term follow-up. Statistical analysis was performed using commercially available software SPSS Version 19.0 (IBM, Armonk, NY) for Windows.

Table 1 Patient characteristics

Demographics	
Patients, *n* (eyes)	30 (32)
Mean age (years, range, SD)	78 (65–89, ± 7)
Women, *n* (%)	13 (43 %)
Men, *n* (%)	17 (57 %)
Previous ranibizumab injections, mean (SD)	8.25 (± 5.21)
Previous bevacizumab injections, mean (SD)	6.50 (± 5.69)
All previous injections, mean (SD)	14.75 (± 7.83)
Previous PDT, *n* (%)	10 (31 %)
Previous laser therapy, *n* (%)	1 (3 %)
Months of previous anti-VEGF treatment, mean (SD)	38 (± 27.35)
Months from last injection until conversion, mean (SD)	2.13 (± 1.16)

SD standard deviation, *PDT* photodynamic therapy, *VEGF* vascular endothelial growth factor

Results

Patient characteristics

A total of 32 eyes from 30 patients with neovascular AMD who were converted from ranibizumab and/or bevacizumab to aflibercept were identified. Patient characteristics at the time of conversion are summarized in Table 1.

Treatment characteristics

Of the eyes 32 had therapy-refractory neovascular AMD, 2 were previously treated with ranibizumab alone, none with bevacizumab alone and 30 with both ranibizumab and bevacizumab. The mean duration of previous anti-VEGF treatment was 38 ± 27.35 months. Patients received on average 14.75 ± 7.83 intravitreal injections before switching to aflibercept. In addition, 10 eyes also had a history of being treated with PDT and one eye had previous had laser treatment. All patients were previously treated using a pro re nata (PRN) scheme. There was only one patient who received only 2 ranibizumab and 2 bevacizumab injections before switching to aflibercept. Only 2 patients had just 3 ranibizumab injections before switching therapy and 1 patient had 4 ranibizumab injections but no bevacizumab injections. Those four were switched quite rapidly as they showed no response at all in the CMT and visual acuity to previous injections. All other patients had at least 4 up to 24 previous ranibizumab injections and 1 up to 19 bevacizumab injections. All eyes were incomplete responders to ranibizumab and/or bevacizumab. Fig. 1 and 2 show the OCT pictures of two non-responding patients to previous ranibizumab and/or bevacizumab therapy or reactivation of CNV. The point of switching therapy and the follow-up are also shown.

Conversion to aflibercept took place on average 2.13 (± 1.16) months after the last injection with

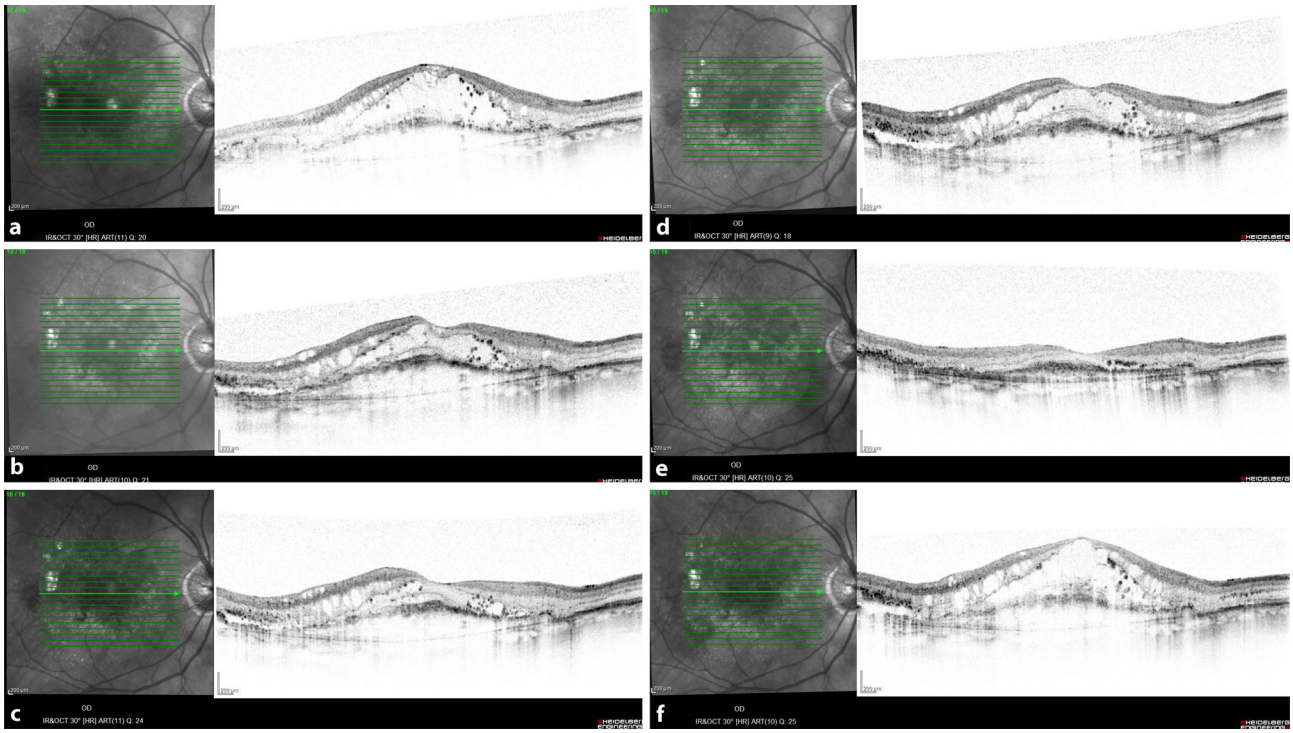

Fig. 1 Patient 1: **a** 1 year before switching to aflibercept, **b** 5 months before switching to aflibercept, **c** 3 months before switching to aflibercept, **d** day of switch, **e** after 3 aflibercept injections and **f** 2 months after the third aflibercept injection

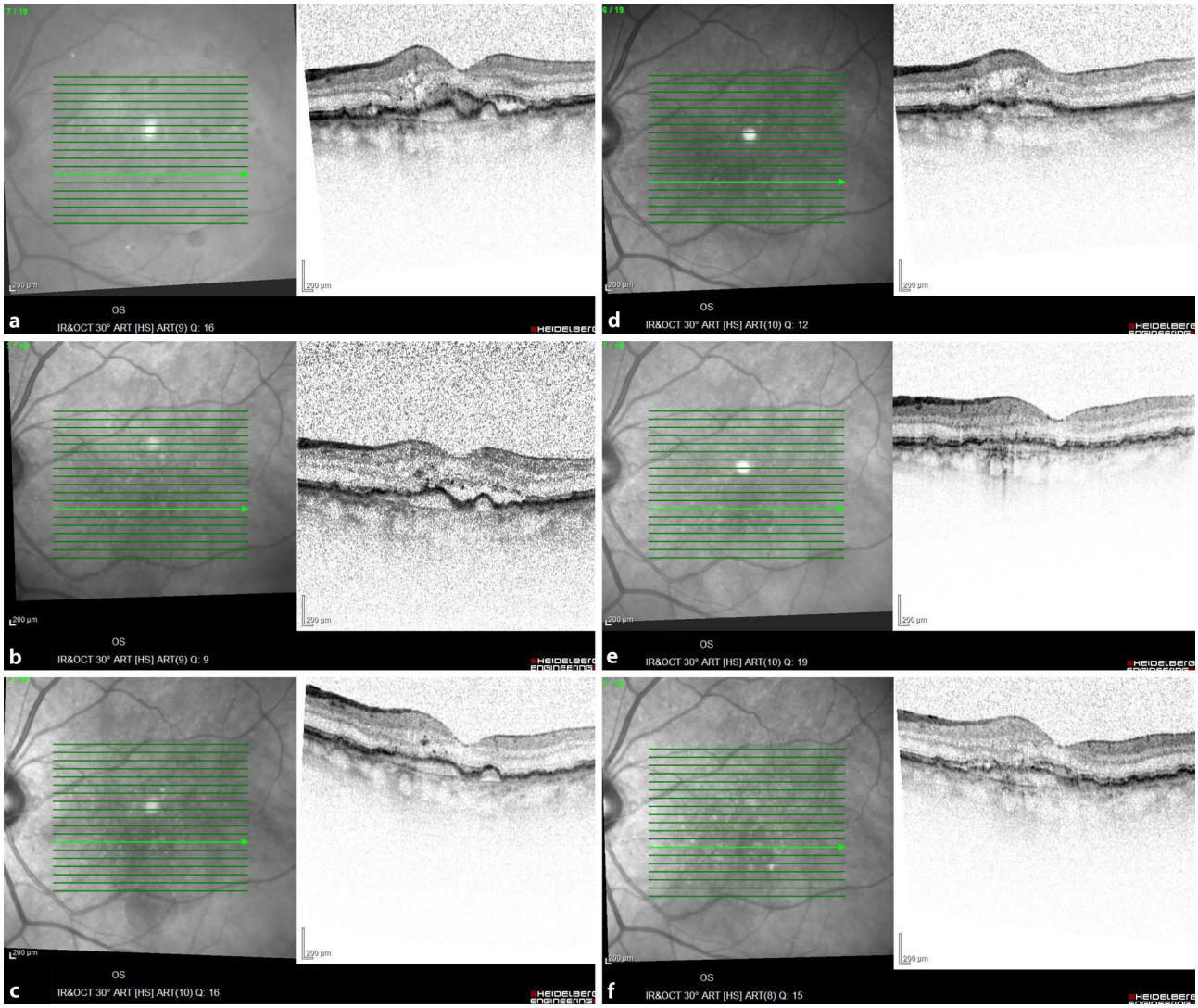

Fig. 2 Patient 2: **a** 1 year before switching, **b** 6 months before switching, **c** 3 months before switching, **d** day of switch, **e** 4 weeks after third aflibercept injection and **f** 6 weeks after third aflibercept injection

ranibizumab or bevacizumab. The injection interval was 4 weeks and all patients received 3 injections.

In retrospective evaluation the eyes were divided into four groups

All eyes completed the first, second and third follow-up (32 eyes), 4 eyes were in group week 6, 12 eyes were in group week 8 and 12 eyes were in group week 10. The mean follow-up was 16 weeks after the first injection of aflibercept and all eyes received 3 aflibercept injections. At the third follow-up 4 eyes still showed intraretinal or subretinal fluid, therefore needed retreatment and were excluded from further follow-up, as they were given ranibizumab or bevacizumab for cost reasons and so development of macular edema was influenced by other drugs.

Visual outcome

For visual outcomes see Table 2. During follow-up, no significant improvements or decrease in visual acuity were found.

Anatomical outcome

After the first, second and third injections of aflibercept there was a significant improvement in CMT. In group week 6 there were no more significant reductions in CMT; however, it must be taken into consideration that at this follow-up point only 4 eyes were included whereas 12 eyes were present in both group week 8 and group week 10. At group week 8 the reduction in CMT was statistically significant but was no longer significant at group week 10 (Table 2). Table 3 shows the number of patients with persistent intraretinal or subretinal fluid over the whole treatment period. The lowest number of eyes with intraretinal

Table 2 Treatment response after converting to aflibercept

	All	*p*
Mean visual acuity (logMAR)	Mean (SD)	–
Baseline	0.4 (± 0.3)	–
After 1 injection (first follow-up)	0.4 (± 0.3)	0.855
After 2 injections (second follow-up)	0.4 (± 0.3)	0.914
After 3 injections (third follow-up)	0.3 (± 0.3)	0.481
Group week 6 (4 eyes)	0.6 (± 0.5)	0.315
Group week 8 (12 eyes)	0.5 (± 0.4)	0.726
Group week 10 (12 eyes)	0.5 (± 0.2)	0.630
Mean CMT (µm)	–	–
Baseline	394 (± 118)	–
After 1 injection (first follow-up)	317 (± 108)	0.002
After 2 injections (second follow-up)	301 (± 99)	0.000
After 3 injections (third follow-up)	292 (± 83)	0.000
Group week 6 (4 eyes)	270 (± 78)	0.057
Group week 8 (12 eyes)	340 (± 146)	0.035
Group week 10 (12 eyes)	377 (± 92)	0.668

CMT central macular thickness, *SD* standard deviation
p-values describe significance in changes between measurement points and baseline

Table 3 Number of eyes with persistent or recurrent intraretinal or subretinal fluid

Intraretinal or subretinal fluid	Eyes	%
Baseline	32	100
After 1 injection (first follow-up)	22	68.8
After 2 injections (second follow-up)	22	68.8
After 3 injections (third follow-up)	19	59.4
Group week 6 (4 eyes = 100 %)	3	75.0
Group week 8 (12 eyes = 100 %)	9	75.0
Group week 10 (12 eyes = 100 %)	11	91.7

or subretinal fluid was measured at the third follow-up, after three consecutive aflibercept injections. It is important to mention that 14 patients showed intraretinal or subretinal fluid at all visits during therapy with aflibercept and fluid recurred 4 weeks after the third aflibercept injection in 5 patients. At group weeks 6–10 there was a high number of eyes with intraretinal or subretinal fluid.

Patients who showed intraretinal or subretinal fluid at group week 6, group week 8 or group week 10 were re-treated with bevacizumab following the standard procedures in our clinic and therefore measurement results after re-treatment were not included in this study as it would not be possible to differentiate from which drug effectiveness these results come.

Discussion

Aflibercept is a new VEGF inhibitor that shows good results in treatment of naïve eyes with neovascular AMD as shown in the VIEW trials [17]. In this retrospective case series we evaluated the short-term effect of aflibercept on patients who showed recurrence of macular fluid or were refractive to therapy with ranibizumab and/or bevacizumab. In detail we evaluated concomitance between anatomical and visual outcome after each of the first three intravitreal aflibercept injections (first, second and third follow-up) and if there was still persistent fluid or recurrence of fluid after 6, 8 or 10 weeks after the third aflibercept injection (group week 6, group week 8 and group week 10, respectively). Our results were similar to those of Yonekawa et al. [18] and Cho et al. [19] showing that aflibercept results in significant reduction of subretinal or intraretinal fluid as well as stabilization of visual acuity; however, in our study this effect was only observed as long as the intravitreal injections were continuously given. At group week 8 and group week 10 the CMT was relatively stable compared to baseline but did not significantly decreased. Furthermore, we found that as early as 4 weeks after 3 initial monthly injections (third follow-up), 4 patients still showed subretinal fluid and already needed treatment to be continued and therefore were excluded from further follow-up. There were only 10 eyes that showed increased visual acuity; however, this increase was not statistically significant. Visual acuity showed no significant improvement over the whole study period. Regarding the correlation between visual acuity and central retinal thickness 4 weeks after each injection, we observed that aflibercept resulted in a good response in CMT at the beginning of treatment but no gain in visual acuity. This good response of the CMT to aflibercept was soon lost and in our follow-up visits there was no more significant reduction in CMT compared to baseline. To our knowledge no other study has yet evaluated the presence or absence of intraretinal or subretinal fluid. Development or change of CMT is an important factor in therapy of CNV but a decrease in CMT does not automatically mean absence of intraretinal or subretinal fluid. In this study we found that over the whole treatment and follow-up period at least 59.4 % of patients showed intraretinal or subretinal fluid. At group week 10, 11 out of 12 patients showed macular edema. This leads to the question whether an upload with 3 monthly injections and then extension to every 8 weeks is a good treatment regimen. Nevertheless, this regimen has already shown non-inferiority to monthly treatment with ranibizumab or bevacizumab in treatment-naïve eyes, is more cost-effective and reduces patient appointments [20]. The outcome supports the theory that only stabilization but no improvement can be achieved as long as therapy is given continuously and not extended to more than 4 weeks. As our study group was very heterogeneous and the follow-up groups were not comparable, further studies focusing on this aspect with a higher number of patients and a clear prospective study design should be initiated to analyze whether common treatment regimens should be re-evaluated. There is controversy about the gain in visual acuity and reduction of CMT after aflibercept

treatment in non-responders. Some studies showed significant improvement in visual acuity as well as in anatomical structure [21–24]. Compared to this a 12-month follow-up study from Hall et al. using aflibercept in previously treated eyes (bevacizumab mean number of 12.4 injections and ranibizumab mean 19 injections) showed reduction in CMT but no statistically significant improvement in visual acuity. The CMT at the initial visit was 261 ± 10.9 and at 12 months 237 ± 10.2 (p = 0.012) [24]. Similar results were also found in other studies [25–28].

The reasons for differences in these results may be different follow-up durations, non-standardized measurement protocols and differing treatment washout periods. Our results raise the question whether eyes that are treated for years rapidly develop tolerance for a new drug and therefore show decreased response. Otherwise it is known that eyes that were already treated for a long time also develop changes in molecular structure, atrophy and scarring and therefore the reaction to a new drug is generally reduced in treatment-resistant eyes [29]. At least, stabilization compared to baseline was achieved which may be a good result for individuals as the disease could be handled with continuous aflibercept injections. In our study we did not evaluate long-term follow-up, therefore further examinations are required to show if stabilization can be achieved over more than this short follow-up time. This study provides evidence that aflibercept can stabilize visual and anatomical outcomes in pretreated eyes as long as treatment with intravitreal injection is continued in regular time frames. Limitations of our study were the small group of patients, a short time of follow-up and a heterogeneous patient group due to the retrospective review but our data analysis during the treatment period showed the change of CMT and visual acuity after each injection of aflibercept, which cannot be found in the current literature.

In summary, injection of 2.0 mg aflibercept seems to be a treatment option in eyes resistant to treatment with ranibizumab and/or bevacizumab. Although our study showed no significant improvement in visual acuity aflibercept still can lead to stabilization, which is an important factor in each individual suffering from CNV.

Conflict of interest S. Maksys, S. Richter-Müksch, B. Weingessel, and P.V. Vécsei-Marlovits declare that they have no competing interests.

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