



Intravitreal Aflibercept Therapy and Treatment Outcomes of Eyes with Neovascular Age-Related Macular Degeneration in a Real-Life Setting: A Five-Year Follow-Up Investigation

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ABSTRACT

Introduction: We aimed to evaluate visual and anatomical outcomes among eyes with neovascular age-related macular degeneration (nAMD) that were persistent to intravitreal aflibercept therapy compared to those that were nonpersistent to therapy.

Methods: We audited 648 treatment-naïve eyes of 559 patients regarding visual acuity (VA) given as the logarithm of the minimum angle of resolution (logMAR) and anatomic outcomes at baseline and at each subsequent follow-up visit for up to 5 years. Nonpersistence was defined as a visit-free interval of > 6 months.

Results: Among the enrolled eyes, 405 were persistent to the therapy and 243 (37%) were

nonpersistent, of which 161 (66%) eyes returned for further therapy after a gap of clinical care. In the nonpersistent group, we observed a decline from 0.58 ± 0.35 to 0.92 ± 0.57 logMAR ($p = 0.01$) after 60 months. Compared with the persistent group, the nonpersistent group had worse visual outcomes at their 33-month ($p = 0.03$), 42-month ($p = 0.01$), 51-month ($p = 0.001$) and 60-month ($p = 0.01$) visits. Additionally, 5/405 (1.2%) eyes in the persistent group and 8/161 (5.0%) eyes in the nonpersistent group developed an end-stage disease with a subfoveal fibrosis during the observational period ($p = 0.013$).

Conclusion: We found that eyes with nAMD that were nonpersistent to intravitreal aflibercept therapy experienced statistically significantly worse VA compared to eyes persistent to therapy within 3 years. Moreover, eyes in the nonpersistent group had a four-fold higher risk of developing a fovea-involving fibrosis. Considering the potential irreversible deterioration with respect to best-corrected VA within nAMD, strategies need to be developed for patients at risk of nonpersistence to therapy.

Keywords: Anti-VEGF; Compliance; Macular degeneration; Nonpersistence; Vision loss

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Key Summary Points

Why carry out this study?

There are currently insufficient data regarding clinical outcomes for eyes with neovascular age-related macular degeneration (nAMD) that are treated with intravitreal aflibercept therapy, especially with respect to commonly occurring gaps in ophthalmic care.

We aimed to evaluate visual and anatomical outcomes for eyes with nAMD that were persistent to intravitreal aflibercept therapy compared to those that were nonpersistent to therapy.

What was learned from the study?

Eyes with nAMD that were nonpersistent to intravitreal aflibercept therapy experienced statistically significantly worse visual acuity compared to eyes of patients persistent to therapy within 3 years and had a four-fold higher risk of developing a fovea-involving fibrosis.

Considering the potential irreversible deterioration associated with the loss of visual acuity within nAMD, strategies need to be developed for patients at risk of nonpersistence based on the results of this study.

INTRODUCTION

Since the introduction of treatment with intravitreal anti-vascular endothelial growth factor (VEGF) within pivotal randomised clinical trials (RCTs), the management of patients with neovascular age-related macular degeneration (nAMD) has been revolutionised, with disease stabilisation and visual gains achieved in the majority of cases [1, 2]. However, real-world data repeatedly prove that the visual

outcomes experienced in daily practice hardly reach the levels achieved within RCTs [3, 4].

While gold-standard RCTs (the VIEW1 and VIEW2 trials) report an increase in visual acuity (by 8.9 letters) after 12 months of treatment with intravitreal aflibercept every 8 weeks [1], a recent meta-analysis of real-life data demonstrated that visual gains in real-world settings are far behind the expectations set forth by these RCTs [3]. Previous reports have noted that the outcomes of RCTs are contingent upon a rigid treatment protocol and strict adherence and persistence to frequent therapy and follow-up examinations. In contrast, the injection rates reported in real-life studies [4, 5] were significantly lower than the rates reported in RCTs.

Previous studies have attempted to study the risk factors that lead to the inter-related phenomenon of nonadherence and nonpersistence to anti-VEGF therapy within nAMD. Increased age, fear of intravitreal injections, reduced ability to operate independently and distance from the patients' residence to ophthalmic care were among the factors that affected patients' adherence and persistence to anti-VEGF therapy [6, 7]. Given the importance of receiving frequent anti-VEGF injections, there is still a relative lack of awareness among both physicians and patients regarding the impact of nonpersistence to anti-VEGF therapy in the management of nAMD. Moreover, data reporting on the outcomes of patients with nonpersistence to intravitreal aflibercept therapy are scarce.

Thus, the present study sought to compare the visual and anatomical outcomes of eyes that were persistent to intravitreal aflibercept therapy to the eyes that were nonpersistent to therapy and returned after a gap of ophthalmological care.

METHODS

Study Design and Population

We conducted a retrospective comparative cohort study among eyes receiving intravitreal aflibercept therapy for nAMD. All enrolled eyes that were treatment-naïve to anti-VEGF therapy at baseline received a loading dose of monthly

intravitreal injections of aflibercept for 3 consecutive months. After treatment initiation, all eyes were routinely retreated according to a treat-and-extend regimen.

Data were gathered from an electronic database of patients receiving anti-VEGF therapy at the Medical University of Innsbruck (Innsbruck, Austria). Consecutively presenting treatment-naïve eyes that received intravitreal aflibercept between September 2015 and December 2019 were included in this retrospective audit.

The exclusion criteria were as follows: (1) a history of diabetic retinopathy, (2) a history of retinal vein occlusion, (3) subretinal haemorrhage at baseline, (4) posterior uveitis and (5) other retinal abnormalities or diseases potentially impairing visual acuity.

The functional and anatomical outcomes of eyes that were persistent to intravitreal aflibercept therapy (persistent group) were compared to the outcomes of eyes that were nonpersistent to therapy for at least 6 months during their individual observation period (the nonpersistent group). As suggested by Okada et al., we defined nonpersistence as not attending any scheduled treatment or monitoring visit for any reasons for at least 6 months within the observational period [8]. Patients who were scheduled beyond 6 months for the follow-up were not considered as nonpersistent.

Ethics approval for this study was granted by the Institutional Review Board of the Medical University of Innsbruck (Innsbruck, Austria, protocol no. 1261/2020). All data were anonymised prior to the analysis. The research adhered to the principles of the Declaration of Helsinki and its later amendments.

Clinical Assessment and Study Dataset

For each case, nAMD was diagnosed by a retinal specialist using either fundoscopic examination and fluorescence angiography or optical coherence tomography angiography (OCT-A; Heidelberg Spectralis® OCT, Heidelberg Engineering, Heidelberg, Germany).

The following data were audited: visual acuity expressed as the logarithm of the minimum angle of resolution (logMAR), type of macular

neovascularisation as well as central macular thickness (CMT) at baseline, at each follow-up visit in all eyes, at the visit before being non-persistent to therapy for 6 months as well as at the 3-month, 6-month and 12-month follow-up visits after an episode of nonpersistence. We likewise evaluated the number of nonpersistence, duration of nonpersistence, number of follow-up visits, number of intravitreal injections of aflibercept per year and patient demographic data, including age, sex and the distance between patients' residences and the clinic.

Statistical Analysis

Eyes were gathered into persistent and nonpersistent groups. Normal distribution was verified using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Normally distributed data are presented as means and standard deviations; inter-group comparisons were conducted using unpaired sample *t*-tests. Non-normally distributed data are presented as medians and interquartile ranges (IQR) and inter-group comparisons were conducted using the Mann-Whitney *U* test. Categorical data are presented as counts and percentages and inter-group comparisons were conducted using the chi-square test and Fisher's exact test. Student's *t*-tests were conducted to compare normally distributed data concerning best-corrected visual acuity (BCVA) and CMT for within-group analyses. Binary logistic regression was conducted to assess the odds ratios for specific anatomic outcomes and to compare BCVA and CMT at the given time points. Baseline characteristics that showed *p*-values < 0.1 in univariate analyses were used as covariates in the binary regression analysis. Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS, Inc., version 26; IBM, Armonk, NY, USA). Two-sided *p*-values < 0.05 were interpreted as statistically significant.

RESULTS

This retrospective study enrolled 648 treatment-naïve eyes of 559 patients with nAMD (average

age: 79 ± 7 years, 67% female). Among these eyes, 405 (63%) were persistent to intravitreal aflibercept therapy during the observation period (persistent group) and 243 (37%) had an unintended pause of therapy or monitoring visits for at least 6 months. Among the latter group, 161 (66%) eyes returned to our department for further follow-up examinations and therapy (nonpersistent group). There were no

differences regarding BCVA (0.54 ± 0.34 vs. 0.58 ± 0.36 logMAR, respectively; $p = 0.258$) and CMT ($422 \pm 163 \mu\text{m}$ vs. $434 \pm 170 \mu\text{m}$, respectively; $p = 0.451$) between these two groups at baseline. In the persistent group, 98 (24%) eyes of 78 patients and in the nonpersistent group 38 (24%) eyes ($p = 0.731$) of 31 patients received a cataract surgery during the observation period. Baseline demographic and

Table 1 Demographic and clinical baseline characteristics of eyes persistent to anti-VEGF therapy and eyes nonpersistent for therapy after loss to follow-up

	Persistent group (<i>n</i> = 405)	Nonpersistent group (<i>n</i> = 161)	<i>p</i> -value
Age (SD)	78 (7)	80 (7)	0.002*
Sex			0.921
Male (%)	272 (67)	133 (33)	–
Female (%)	109 (68)	52 (32)	–
Right eyes (%)	200 (49)	86 (53)	0.403
Pseudophakic at baseline (%)	194 (48)	83 (52)	0.457
Cataract surgery during observation (%)	98 (24)	38 (24)	0.731
Distance to clinic, km (IQR)	15.1 (2.7–38.8)	11.5 (2.7–32.2)	0.162
BCVA of study eye at baseline, logMAR (SD)	0.54 (0.34)	0.58 (0.36)	0.258
MNV types			
Type 1 (%)	219 (54)	78 (48)	0.248
Type 2 (%)	61 (15)	29 (18)	0.386
Type 3 (%)	51 (13)	19 (12)	0.445
Mixed type (%)	55 (13)	26 (16)	0.271
Other ^a (%)	19 (5)	9 (6)	0.395
CMT at baseline, μm (SD)	422 (163)	434 (170)	0.451
SRF at baseline (%)	173 (43)	62 (38.5)	0.700
IRF at baseline (%)	99 (24)	37 (23)	0.999
SRF + IRF at baseline (%)	133 (33)	62 (38.5)	0.106
Injections in 1st year, <i>n</i> (SD)	5.5 (1.8)	4.8 (1.9)	< 0.001*

BCVA best-corrected visual acuity, CMT central macular thickness, IRF intraretinal fluid, logMAR logarithm of minimum angle of resolution, IQR interquartile range, km kilometres, SD standard deviation, SRF subretinal fluid, VEGF vascular endothelial growth factor

*Indicates statistical significance ($p < 0.05$)

^aNot classified

medical characteristics for the persistent and nonpersistent groups are presented in Table 1. Prior to a gap of clinical care, the nonpersistent group adhered to therapy and follow-up examinations for a median (IQR) of 20 (11–36) months. This cohort returned for further therapy after a median (IQR) of 7 (7–9) months and remained adherent for a median (IQR) of 7 (6–9) months.

Changes in Visual Acuity by Persistence Group

We observed an initial increase in BCVA from baseline (0.54 ± 0.34 logMAR) to the 3-month visits in the persistent group (0.47 ± 0.33 logMAR; $p < 0.001$; 95% CI 0.032–0.093). Compared to baseline, the visual outcomes of eyes in the persistent group decreased at the 24-month (0.59 ± 0.38 logMAR; $p = 0.031$) and 33-month (0.59 ± 0.40 logMAR; $p = 0.020$) visits. They remained consistently below baseline after 3 years, showing a statistically significant

decrease at the 39-month (0.61 ± 0.41 logMAR; $p = 0.003$), 42-month (0.56 ± 0.39 logMAR; $p = 0.017$), 45-month (0.60 ± 0.42 logMAR; $p = 0.003$), 51-month (0.58 ± 0.42 logMAR; $p < 0.001$) and 60-month (0.62 ± 0.43 logMAR; $p = 0.003$) visits (see Fig. 1).

In the nonpersistent group, visual outcomes of eyes declined at the 18-month (0.61 ± 0.43 logMAR; $p = 0.042$), 21-month (0.70 ± 0.48 logMAR; $p = 0.014$) and 33-month (0.74 ± 0.44 logMAR; $p = 0.017$) visits compared to baseline (0.58 ± 0.35 logMAR). They remained at a lower level at the 39-month (0.78 ± 0.47 logMAR; $p = 0.019$), 42-month (0.75 ± 0.49 logMAR; $p = 0.003$), 51-month (0.70 ± 0.47 logMAR; $p = 0.002$) and 60-month (0.92 ± 0.57 logMAR; $p = 0.004$) visits. The mean BCVA in the nonpersistent group decreased from baseline (0.58 ± 0.35 logMAR) to the last visit prior to nonpersistence (0.65 ± 0.45 logMAR; $p = 0.018$) and further decreased from the last visit prior to nonpersistence to the return visit (0.75 ± 0.45 ; $p < 0.001$; 95% CI -0.154 to -0.060). In total, 71 (44%) eyes required

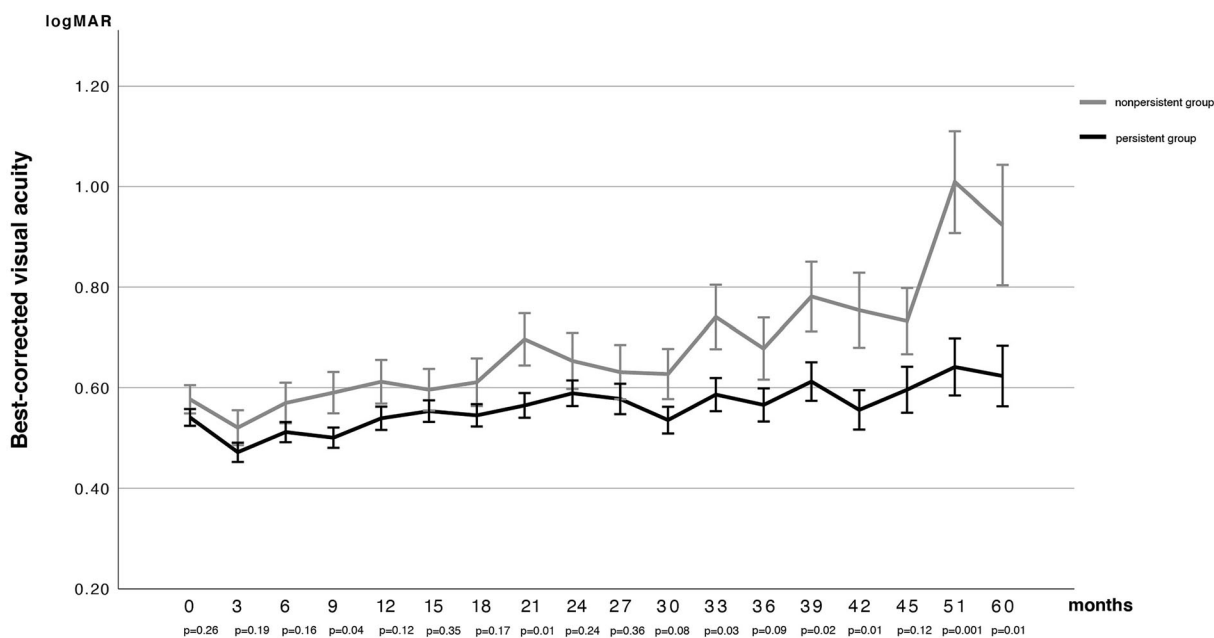


Fig. 1 Graph presenting changes in the best-corrected visual acuity (BCVA) among eyes persistent and eyes nonpersistent to therapy returning after an episode of loss to follow-up. *P*-values below the designated time points correspond to statistical comparisons of BCVA between

the two groups and error bars correspond to standard errors of the mean. *logMAR* logarithm of the minimum angle of resolution

further aflibercept therapy at their return visit. Among recipients, we noticed a statistically significant increase in BCVA at visits occurring 6 months after returning to therapy (0.62 ± 0.47 ; $p = 0.010$), though BCVA levels had worsened to the level of the first return visit after 12 months (0.71 ± 0.47 ; $p = 0.696$).

Mean Visual Acuity by Persistence Group

The persistent group had better visual outcomes at their 21-month (0.70 ± 0.48 vs. 0.56 ± 0.38 log MAR; $p = 0.01$), 33-month (0.74 ± 0.44 vs. 0.59 ± 0.40 logMAR; $p = 0.03$), 39-month (0.78 ± 0.47 vs. 0.61 ± 0.41 logMAR; $p = 0.02$), 42-month (0.75 ± 0.49 vs. 0.56 ± 0.39 logMAR; $p = 0.01$), 51-month (0.70 ± 0.40 vs. 0.58 ± 0.42 logMAR; $p = 0.001$) and 60-month (0.92 ± 0.57 vs. 0.60 ± 0.43 logMAR; $p = 0.01$) visits compared to the nonpersistent group. Additionally, the persistent group demonstrated better BCVA at each eye's end of follow-up (0.74 ± 0.49 vs. 0.61 ± 0.40 logMAR; $p = 0.008$).

Anatomic Outcomes

The persistent group showed a statistically significant initial decrease in CMT at its 3-month follow-up visit compared to baseline (318 ± 141 vs. 422 ± 163 μm ; $p < 0.001$; 95% CI 96.4–130.0); CMT values remained below baseline at each subsequent follow-up until the end of the observational period (385 ± 196 μm ; $p = 0.037$).

Similarly, the nonpersistent group presented with an initial CMT decrease from baseline (434 ± 170 μm) to the 3-month follow-up visit (305 ± 94 μm ; $p < 0.001$; 95% CI 93.5–156.0); compared to baseline, CMT values were statistically significantly lower at each follow-up visit ($p < 0.05$) including the 60-month visit (322 ± 131 μm ; $p = 0.018$). There were no differences in CMT between the groups at any follow-up visit during the observation period (see Fig. 2). We observed a statistically significant reduction in CMT from baseline (434 ± 174 μm) to the last visit before experiencing nonpersistence (305 ± 93 ; $p < 0.001$).

Compared to the last visit prior to nonpersistence, we measured statistically significant increases in CMT at the return visit (339 ± 113 ; $p < 0.001$) followed by another decline at the 6-month visit (280 ± 79 ; $p = 0.002$) and the 12-month visit (264 ± 64 ; $p = 0.002$) after returning for therapy.

In the nonpersistent group, the proportion of eyes with remaining subretinal fluid (SRF) of any kind, meaning SRF alone or combined with intraretinal fluid (IRF), decreased from baseline to the last visit prior to nonpersistence, from baseline to the return visit and from baseline to the last visit (Table 2). However, the number of eyes with IRF alone ($n = 37$; 23%) did not decline significantly from baseline to the visit prior to experiencing nonpersistence ($n = 41$, 26%; $p = 0.433$), but instead increased from baseline to the return visit ($n = 55$, 34%; $p = 0.037$) and from baseline to the last visit ($n = 54$, 34%; $p = 0.045$).

A statistically significant higher proportion of eyes developed a foveal fibrosis during the observation period in the nonpersistent group ($n = 8$; 5.0%) compared to the persistent group ($n = 5$; 1.2%; $p = 0.013$). Binary logistic regression adjusting for age revealed a four-fold higher risk of developing a fovea-involving fibrosis in the nonpersistent group.

DISCUSSION

In the past 2 decades, intravitreal injections of anti-VEGF have become the mainstay in the management of patients with nAMD [9]. Numerous RCTs have proven the efficiency and efficacy of intravitreal anti-VEGF therapy, thereby raising patients' and physicians' expectations regarding functional outcomes [1, 2]. However, these expectations have not been entirely met in real-life settings. Specifically, despite initial visual improvement and stabilisation, a considerable proportion of patients eventually experiences vision loss [3, 4]. This discrepancy in outcomes may be explained by the fact that RCTs are conducted under idealised circumstances based on a rigid treatment protocol that requires complete adherence and persistence to therapy.

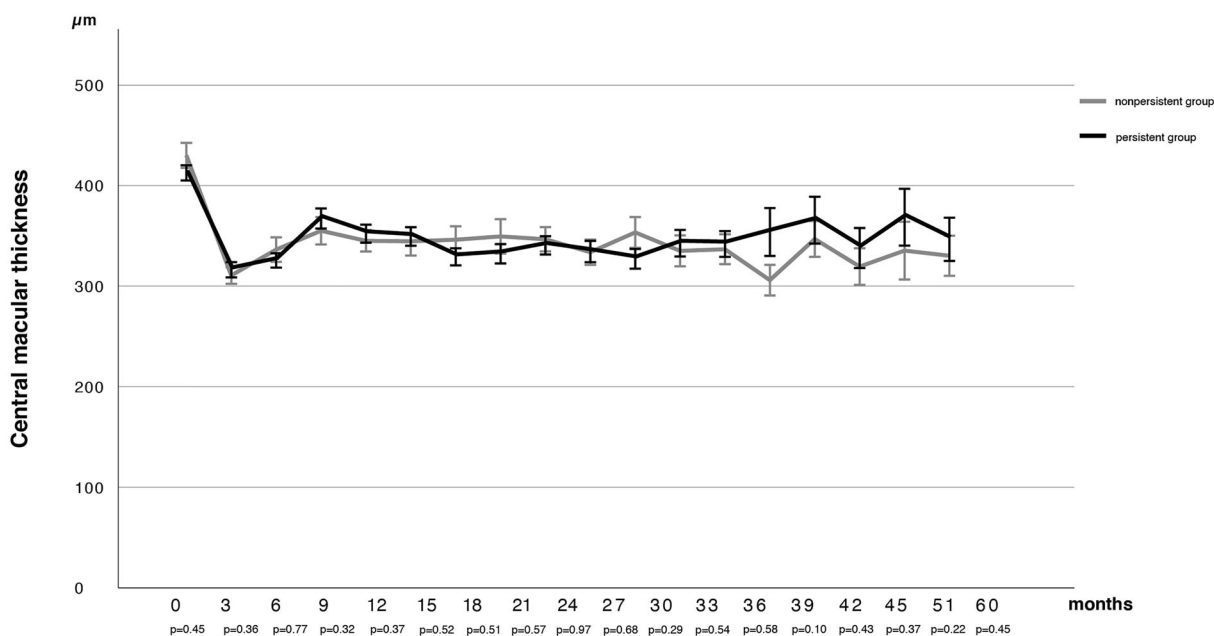


Fig. 2 Graph presenting changes in central macular thickness (CMT) among eyes persistent and eyes nonpersistent to therapy returning after an episode of loss to follow-up. *P*-values below the designated time points

correspond to statistical comparisons of CMT between the two groups and error bars correspond to standard errors of the mean

Table 2 OCT characteristics of eyes that were not persistent to anti-VEGF therapy at baseline, their last visit prior to loss to follow-up, their return visit and their last study visit

	Baseline	Last visit before nonpersistence ^a	Return visit ^b	Last visit ^b
CMT, µm ± SD (<i>p</i> -value)	434 ± 170	305 ± 93 (<i>p</i> < 0.001*)	346 ± 119 (<i>p</i> < 0.001*)	264 ± 64 (<i>p</i> = 0.002*)
Presence of retinal fluid, <i>n</i> (%)	161 (100)	88 (55; <i>p</i> < 0.001*)	118 (73; <i>p</i> < 0.001*)	94 (58 <i>p</i> = 0.502)
SRF, <i>n</i> (%; <i>p</i> -value)	62 (38.5)	23 (14.3; <i>p</i> < 0.001*)	24 (14.9; <i>p</i> = 0.500)	15 (9.3; <i>p</i> = 0.113*)
IRF, <i>n</i> (%; <i>p</i> -value)	37 (23.0)	41 (25.5; <i>p</i> = 0.433)	55 (34.2; <i>p</i> = 0.037*)	54 (33.5; <i>p</i> = 0.045*)
SRF + IRF, <i>n</i> (%; <i>p</i> -value)	62 (38.5)	24 (14.9; <i>p</i> < 0.001*)	39 (24.2; <i>p</i> = 0.024*)	25 (15.5; <i>p</i> = 0.500)

CMT central macular thickness, IRF intraretinal fluid, OCT optical coherence tomography, SRF subretinal fluid, VEGF vascular endothelial growth factor

*Indicates statistical significance (*p* < 0.05)

^aCompared to baseline

^bCompared to the last visit prior to nonpersistence

Therefore, the outcomes of patients with reduced adherence were not reflected in previous RCT reports. Observational studies have reported a gap in clinical care lasting for at least 6 months in 20–40% of nAMD cases [6, 10, 11]. This group of patients appears to be at a high risk for irreversible deterioration of visual acuity.

In the present study, we demonstrated that eyes with a nonpersistence to intravitreal aflibercept therapy for > 6 months during the observation period had statistically significantly worse visual and anatomic outcomes than eyes that were persistent to therapy. Most eyes in the nonpersistent group were treated and followed for approximately 20 months before discontinuation and then returned for therapy after a median of 7 months. Consecutive to this gap of clinical care, the nonpersistent group showed worse visual outcomes within 3 years, which constantly decreased thereafter. Thus, we found that eyes examined consecutive to a gap of clinical care experienced an irreversible decrease in VA despite normalisation of CMT within 12 months after reinitiating therapy.

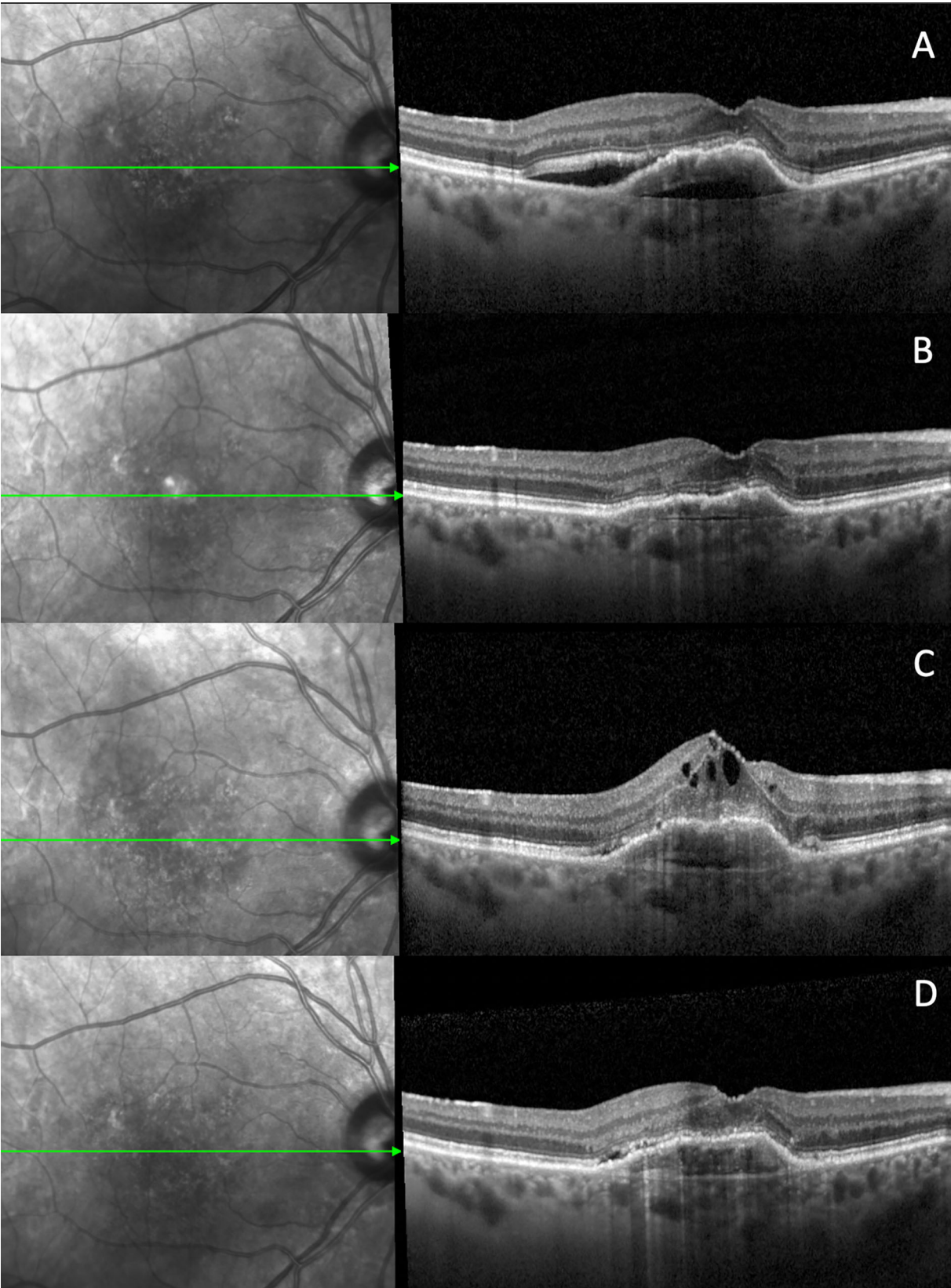
Considering the missing differences in CMT between both groups at the end of the observation period, we anticipate that eyes with nonpersistence to ophthalmological care experience greater distortion and photoreceptor degeneration secondary to persistent disease activity (see Fig. 3). Intriguingly, the proportion of eyes with IRF increased from baseline to the first return visit and remained increased until the last visit. This may have contributed to the worse visual outcomes observed in this group [12, 13]. Notably, we observed a four-fold higher risk of developing a subfoveal fibrosis as an end-stage manifestation of disease in the nonpersistent group. However, considering the rare appearance of this anatomic outcome in the current study, it is difficult to draw definitive conclusions and our results need to be confirmed within future investigations.

In the present study, we observed an alarming rate of 37% eyes being nonpersistent to monitoring visits and therapy. However, we should not overlook the role of comorbidities in patients with nAMD. Recent reports on the preferences of nAMD patients have postulated

Fig. 3 A representative example of a spectral-domain optical coherence tomography (SD-OCT) image series of a patient who was nonpersistent to therapy and monitoring visits and returned after a gap of clinical care for further intravitreal aflibercept therapy. The patient initially presented with a type 1 macular neovascularisation and subretinal fluid in his right eye (A). At the last visit before nonpersistence there were no signs of retinal fluids (B). Upon a gap of clinical care of 7 months the patient presented with a thickened central macula and intraretinal fluid (C). After reinitiating intravitreal aflibercept therapy, the SD-OCT revealed a macula without signs of retinal fluid that showed an incomplete outer retinal atrophy (D). The visual acuity decreased from 0.3 to 1.0 logMAR corresponding with the images (B,D) respectively

that the presence of comorbidities is the most serious risk factor for reduced adherence or nonpersistence to therapy [14]. Specifically, comorbidities as well as increased age may result in a reduced ability to operate independently in daily living, and some patients may thus require increasing assistance to attend appointments and adhere to treatment schedules [15]. Given the frequent need for injections and follow-up examinations in the rigid therapy regimens prescribed for patients with nAMD, such dependency can be devastating. Prior reports within our study group demonstrated a strong association between reduced adherence in older patients and dependence on an ambulance or caretaker for transfer to the clinic [16, 17]. Consistent with these conclusions, the study populations enrolled in RCTs are commonly younger and more homogeneous than the portion of the population represented in real-life observational studies [18].

The multifactorial reasons leading to a reduced persistence to therapy contribute to a small proportion of patients returning for further therapy following a gap in ophthalmological care. Consequently, to the best of our knowledge, there have only been a few reports regarding the effects of nonpersistence to anti-VEGF therapy in patients with nAMD. Recently, there has been great interest in studying the potential adverse effects of treatment discontinuation that may be caused by the coronavirus disease 2019 (COVID-19) pandemic. For



example, retrospective studies analysing the potential effects of pandemic-associated gaps in ophthalmological care have reported permanent vision loss occurring 3–12 months after reinitiating intravitreal anti-VEGF therapy [19–23]. In addition, a recent report by Soares et al. [24] investigated patients who were treated with bevacizumab, ranibizumab or aflibercept prior to experiencing a gap of clinical care > 6 months. While the aflibercept group did not experience a visual decline after returning for therapy, the ranibizumab and bevacizumab groups presented with worse VA at their return visit that persisted until their final study visit. However, the researchers acknowledged the small sample size within the aflibercept group ($n = 22$) as a limitation of their study. Furthermore, the use of billing codes to retrospectively retrieve the data of patients with nAMD may have impeded the researchers' ability to include treatment-naïve patients in their investigation.

Taken together, our findings contribute to a better understanding of the consequences of nonpersistence to intravitreal anti-VEGF therapy among eyes with nAMD. Although there are new sustained delivery systems and anti-VEGF agents that may potentially reduce the burden of this disease, there is still a great demand for further solutions that would allow for increasing persistence to anti-VEGF therapy in patients with nAMD. For example, although these measures may be difficult to apply within an older population, the implementation of reminder software and teaching programs might promote improved long-term adherence and persistence [25]. Furthermore, the broader use of the growing field of telemedicine and artificial intelligence may prove to be viable tools for identifying patients at risk of vision loss and improving the management of patients at risk for nonadherence or nonpersistence to therapy [26, 27]. Further studies and strategies are urgently needed to increase patients' persistence to currently implemented rigid anti-VEGF treatment protocols.

The difference in age between the two study groups is a limitation of the current study. Although increased age appears to be a common risk factor for reduced adherence [6, 7], we conducted a multivariate analysis adjusting for

age to avoid potential bias in the assessment of clinical differences between persistent and nonpersistent groups. Furthermore, despite the availability of other anti-VEGF agents licensed by the European Medicines Agency, we hereby report the impact of nonpersistence to treatment with only one anti-VEGF agent (aflibercept). The presented results might therefore not be applicable to other treatment regimens that use other anti-VEGF agents and/or switch between anti-VEGF medications.

Another limitation was the definition of nonpersistence as nonattendance to any treatment or monitoring visit for 6 months. This was partly owed to long treatment intervals of up to 16 weeks; thus, a cut-off after 4 months would be too short [8]. To address all these challenges, future investigations could determine their nonattendance cut-off depending on the treatment protocol and/or the patients' individual treatment interval. However, this would require a long-term observational study with a substantially higher number of patients to be able to categorize different levels of persistence and analyse their impact on visual outcomes.

A substantial strength of the current investigation is that all study participants were treatment-naïve to anti-VEGF and were exclusively treated with intravitreal aflibercept in a healthcare system with universal health coverage. Moreover, Austria's universal insurance only covers intravitreal injections in hospitals with an ophthalmological department. These unique guidelines have allowed us to ensure long-term follow-up at one clinic and to comprehensively analyse the impact of nonpersistence to anti-VEGF therapy on visual outcomes and disease progression in eyes with nAMD.

CONCLUSIONS

The present study revealed a significant decline in visual acuity over the course of long-term follow-up among eyes with nAMD that were nonpersistent to intravitreal aflibercept therapy. Moreover, eyes in the nonpersistent group had a four-fold higher risk of developing a subfoveal fibrosis. Given the potentially irreversible deterioration of macular function among eyes with

nAMD being nonpersistent to treatment and monitoring visits, there is a great demand for further studies assessing risk factors and solutions to ameliorate nonpersistence.

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Author Contributions. Reinhard Angermann is the lead author and guarantor: conception, design, data acquisition, writing, statistical analysis, interpretation of data, original draft preparation; Alexander Franchi, Victoria Stöckl, Julia Rettenwander, Tanja Rettenwander, David Goldin: data acquisition, formal analysis and interpretation of data, draft of the article; Martin Stättin: statistical analysis and interpretation of data, draft of the article; Martina T. Kralinger: resources, thorough revision of the article; Claus Zehetner: conception, final draft preparation, critical revision. All authors read and approved the final version of the manuscript.

Disclosures. Reinhard Angermann, Alexander Franchi, Victoria Stöckl, Julia Rettenwander, Tanja Rettenwander, David Goldin, Martin Stättin, Martina T. Kralinger and Claus Zehetner declare that they have no actual or potential conflicts of interest related to this submission.

Compliance with Ethics Guidelines. Ethics approval for this study was granted by the Institutional Review Board of the Medical University of Innsbruck (Innsbruck, Austria,

protocol no. 1261/2020). All data were anonymised prior to the analysis. The research adhered to the principles of the Declaration of Helsinki and its later amendments.

Data Availability. Reinhard Angermann and Claus Zehetner had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. The data used for this study, though not available in a public repository, will be made available to other researchers upon reasonable request.

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