Original Article

Taiwan J Ophthalmol 2023;13:219-224

Access this article online

Quick Response Code:

Website: http://journals.lww.com/TJOP

DOI: 10.4103/tjo.TJO-D-22-00135

Five-year outcome of aflibercept intravitreal injection in naïve patients with neovascular age-related macular degeneration using a modified treat-and-extend regimen: Results from a prospective observational study

Jarret Charles, TRAN Thi Ha Chau*

Abstract:

PURPOSE: The purpose is to study the 5-year results of aflibercept monotherapy using an individualized regimen in naïve patients with neovascular AMD (nAMD).

MATERIALS AND METHODS: This is a prospective observational study including naïve nAMD patients who underwent aflibercept injections with at least 5 years of follow-up. All of them received 3 monthly injections at the loading phase, followed by an observation period, then treated with an individualized treat-and-extend regimen. Visual acuity (VA) measurement and optical coherence tomography were performed at each visit.

RESULTS: Forty-eight eyes were included. Of these, 30 were followed up for 5 years. The mean follow-up was 61.7 ± 2.3 months. The mean age was 81 ± 8 years. The visual gain was 7.3 ± 12.7 letters at 1 year, 6.5 ± 12.5 letters at 2 years, 5.2 ± 17 letters at 3 years, 6.2 ± 18.6 letters at 4 years, and 5.6 ± 20 letters at 5 years. At the last observation, 53% of eyes had VA > 70 letters. A complete fluid resolution was obtained in 53% of the eyes. At the 5-year endpoint, the total number of injections was 21.6 ± 13.4. Macular atrophy was observed in 18 eyes (60%) and subretinal fibrosis in 14 eyes (46%).

CONCLUSION: Patients with exudative AMD can maintain their visual function at 5 years with aflibercept using an individualized treatment. The loss of visual gain beyond 2 years could be related to the natural progression of the disease than the direct effect of anti-vascular endothelial growth injections.

Keywords:

Aflibercept, anti-vascular endothelial growth factor, exudative age-related macular degeneration, long-term, treat and extend

Lille Catholic University, France

***Address for correspondence:**
Dr. TRAN Thi Ha Chau, Ophthalmology Department, Saint Vincent de Paul Hospital, Boulevard de Belfort – BP387. 59020 Lille Cedex. France.
E-mail: tran.hachau@ghicl.net

Submission: 29-09-2022
Accepted: 05-01-2023
Published: 17-04-2023

Introduction

Age-related macular degeneration (AMD) is the leading cause of low vision in industrialized countries among people over 50. Three anti-vascular endothelial growth (VEGF) substances are currently in use to treat neovascular AMD: ranibizumab, bevacizumab, or aflibercept by intravitreal injection (IVT). In current practice, there are different injection protocols after the loading phase, a reactive protocol (pro re nata [PRN]) and proactive protocols: A fixed interval (monthly or 2 months) and treat and extend (T and E).[1,2] The extension of

How to cite this article: Charles J, Thi Ha Chau T. Five-year outcome of aflibercept intravitreal injection in naïve patients with neovascular age-related macular degeneration using a modified treat-and-extend regimen: Results from a prospective observational study. Taiwan J Ophthalmol 2023;13:219-24.

the interval injection can be applied after the loading phase or after 6 months of observation to determine the recurrence interval according to the consensus of French experts on the practical implementation of this regimen.[3]

These different regimens have their strengths and weaknesses. With reactive treatments, there is a tendency toward undertreatment but a reduction in the risk of complications and the cost of treatment. Proactive regimens potentially have a reduced number of visits, but they may also lead to overtreatment. In a meta-analysis of more than 24,000 eyes with neovascular AMD (nAMD) treated with ranibizumab in real life, Kim in 2016 showed that the T and E regimen is associated with better visual outcomes than the PRN regimen.[4] Rainbow[5] and Perseus[6] studies demonstrated that aflibercept led to similar results to that of VIEW-1 studies at 1 year and year 2 in real life.[7] To our knowledge, little data are available on the long-term outcome of nAMD treated with aflibercept in real life.

The objective of the study is to evaluate at 5-year results in naïve patients with nAMD treated with aflibercept monotherapy.

Materials and Methods

This is a longitudinal observational study including 48 naive eyes with wet AMD treated with aflibercept and followed for at least 5 years. Patients aged <50 years or history of eye surgery during the previous 3 months or choroidal neovascularization related to other etiologies were excluded. Parts of the study were reported previously.[8]

This study was carried out in accordance with the principles of the Declaration of Helsinki and with the agreement of the local ethics committee (IRB RNIPH-2022). Consent was obtained from all patients for study participation.

At baseline, all patients underwent a complete ophthalmologic clinical examination. The diagnosis of nAMD was confirmed by multimodal imaging, as described previously.[8] The type of choroidal neovascularization (CNV) was graded as type 1 (sub-RPE), type 2 (subretinal), and type 3 (retinal angiomatous proliferation or polypoidal choroidal vasculopathy) based on fluorescein angiography (FA), indocyanine green angiography, and spectral domain optical coherence tomography (SD-OCT). Patients were treated according to the induction-adaptation-individualization regimen which is a modified T and E regimen.[2,8] After three loading doses of aflibercept injection (2 mg/0.05 ml) at 4-week intervals, patients had visits and treatment as needed every 4 weeks during the adaptation and observation phase until week 32 before the T and E phase for which the initial interval was determined based on mean interval recurrence. Each visit included at least one ETDRS visual acuity (VA) measurement and SD-OCT. The maximum interval was 12 weeks until the 2nd year and then 16 weeks for the subsequent years. In the event of significant recurrence following a prolonged absence, the patient was treated with a series of three injections followed by T and E. If there was no exudation at 3 consecutive visits at an interval of 16 weeks (T and E 16), the treatment was discontinued. A series of 8-week interval visits were scheduled, and the patient was invited to return at any time in case of loss of VA.

During the follow-up, discontinuation of treatment may be decided by the physician, due to inactivity of the lesion or by the patient and/or family for nonrational reasons.

The primary endpoint was the evolution of VA during the 5-year period. The secondary endpoint was to describe changes in central macular thickness (CMT), macular volume (MV), subfoveal choroidal thickness (CT), the height of pigment epithelial detachment (PED), the mean number of injections, and rate of eyes with intra- or subretinal fluid (IRF and SRF), hyper-reflective exudation material, hyper-reflective dots, and disruption of the ellipsoid zone. The MV and the CMT were computed automatically by the software (Heidelberg Eye Explorer, Heidelberg, Germany). The CT and height of PED were measured manually by both authors. The surface of macular atrophy (MA) and the presence of subretinal fibrosis were also analyzed. MA was defined as damage to the outer layers of the retina, whether or not associated with damage to the underlying pigment epithelium, according to the Classification of Atrophy Meeting group.[9] MA was evaluated using near-infrared imaging and SD-OCT. The area of MA was measured at an initial presentation within the original CNV lesion and outside/adjacent to the CNV border and was not influenced by the presence of hemorrhage, intra- and/or subretinal fluid. The MA area was measured before aflibercept administration, at 2 years, and at 5 years. The presence of subretinal fibrosis at the last observation was defined as a well defined, whitish, or yellowish subretinal lesion on funduscopy, hypofluorescence and late staining on FA if available, and as well-defined hyper-reflective subretinal tissue on SD-OCT.

Data were collected from the medical record and entered into a computerized table monthly for up to 6 months and then 12, 24, 36, 48, and 60 months.

Paired Student's *t*-test was used to compare means. One-way ANOVA was used to study the relationship between the visual gain at 5 years and various

parameters. A level of $P \leq 0.05$ was considered statistically significant.

Results

Description of the cohort

Forty-eight eyes (38 patients) were treated with intravitreal aflibercept as first-line therapy for nAMD from November 2013 to May 2015. The sex ratio was 26 women (68%)/12 men (32%). Of the 38 patients, 10 presented with bilateral involvement. Forty-one eyes were followed for at least 12 months, 35 eyes for 24 months, 31 eyes for 48 months, and finally, 30 eyes achieved the 60-month endpoint. The rate of dropped out patients at 5 years was 37.5%. Our reminder system by staff members indicated that reasons of drop out were fall, comorbidity, or relative constraints, resulting in mis appointment and treatment interruption. The mean follow-up duration was 61.7 ± 2.3 months.

Functional results

The best corrected VA was 56.1 ± 16.3 letters at baseline. At 6, 12, and 24 months, the visual gain was + 5.0 ± 11 letters (61.1 ± 17.2 letters, $P = 0.017$), +7.3 ± 12.7 letters (63.4 ± 14.8 letters, $P = 0.015$), and + 6.5 ± 12.5 letters (62.5 ± 19.3 letters, $P = 0.018$), respectively. At 36 and 48 months, visual gain lost its statistical significance compared to baseline, although we observed a gain of + 5.2 ± 16.9 letters (61.3 ± 21 letters, $P = 0.224$) and + 6.2 ± 18.6 letters (62.3 ± 24.5 letters, $P = 0.162$), respectively. At the last observation, the best-corrected VA (BCVA) was 61.7 ± 23.2 ($P = 0.282$) letters with a nonsignificant visual gain of + 5.6 ± 20 [Figure 1].

The number of eyes with BCVA ≥70 letters was 14/48 (29%) at baseline and 16/30 (53%) at 60 months. Overall, after 5 years of follow-up, 7 eyes (23%) gained ≥15 ETDRS letters, 3 eyes (10%) gained 10–14 letters, 4 eyes (13%) gained between 5 and 9 letters, 5 eyes (17%) gained between 0 and 4 letters, 7 eyes (23%) lost <15 letters, and 4 eyes (13%) lost ≥15 letters.

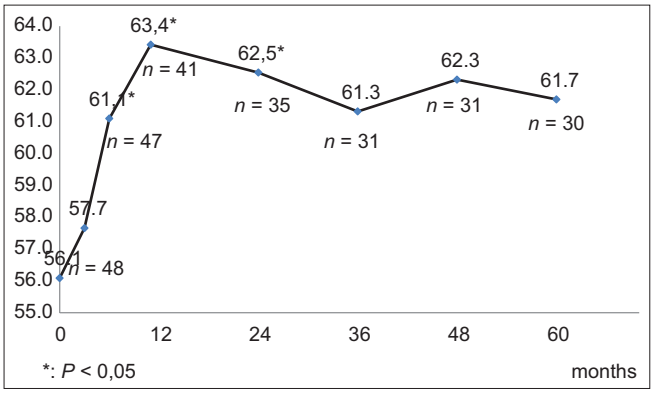

Figure 1: Evolution of visual acuity over 5 years

One-way ANOVA showed that visual gain obtained at 5 years was not related to the initial VA ($P = 0.7$), nor to the number of injections received ($P = 0.7$), but was correlated to the visual gain obtained after the loading phase at 4 months (degree of freedom = 27, $P = 0.046$).

Anatomical responses

Quantitative results

OCT parameters are summarized in Table 1. A significant decrease in CMT, MV, and PED height was observed after the loading phase; then, these values remained stable. The anatomical gain obtained after the initiation of treatment was maintained for up to 5 years.

Qualitative results

The results of qualitative OCT parameters are summarized in Table 2.

IRF or SRF was observed in 94% of eyes at baseline. After the loading phase, the proportion of eyes with intra- or subretinal fluid decreased to 16%. At 5 years, the fluid was still present in 43% of the eyes.

Subretinal hyper-reflective exudation was present in 91% of the eyes at baseline and in 80% of the eyes after the loading phase, and this rate dropped to 27% of eyes at 60 months.

Ellipsoid line (EZ) disruption was present in 94% of the eyes at baseline and was found to be frequent and stable during follow-up.

Hyper-reflective dots and subretinal hyper-reflective exudation regression were observed during the first 2 years of treatment. These lesions dramatically decreased at 5 years, indicating a tendency for the lesions to be inactive.

The proportion of eyes with intra- or subretinal fluid decreased after the loading phase and remained stable from 1 year to the 5-year endpoint. Complete resolution of the fluid was obtained in 57% of the eyes. Fluid persistence was observed in 43% of eyes, distributed in the intraretinal compartment in 20% of the eyes and in the subretinal space in 23% of the eyes.

Table 1: Anatomical outcome over 5 years of the whole cohort

	Baseline	M6	M12	M24	M36	M48	M60
n	48	44	41	35	31	31	30
CMT (µm)	410	288*	294*	288*	289*	292*	263*
MV (mm²)	8.97	8.04*	8.03*	7.97*	8.07*	8.20*	7.91*
PED height (µm)	165	129*	122*	141*	140*	147*	132*
Subfoveal CT (µm)	192	185	185	185	189	184	192
Atrophy area (mm²)	1.81			3.02*			6.05*

*P<0.05. CMT=Central macular thickness, MV=Macular volume, PED=Pigment epithelium detachment, CT=Choroidal thickness

Table 2: Qualitative optical coherence tomography parameters over 5 years

	M0, *n* (%)	M6, *n* (%)	M12, *n* (%)	M24, *n* (%)	M36, *n* (%)	M48, *n* (%)	M60, *n* (%)
Number of eyes (*n*)	48	44	41	35	31	31	30
SRF	29 (62)	8 (18)	5 (12)	7 (20)	5 (16)	6 (19)	7 (23)
IRF	29 (62)	10 (23)	7 (17)	7 (20)	6 (19)	9 (29)	6 (20)
Fluid persistence	45 (94)	23 (52)	16 (39)	12 (34)	10 (32)	13 (42)	13 (43)
HRD	43 (91)	28 (64)	26 (63)	15 (43)	22 (71)	23 (74)	8 (27)
SHE	27 (57)	14 (32)	8 (20)	7 (20)	11 (35)	10 (32)	2 (7)
EZ disruption	44 (94)	30 (68)	34 (83)	31 (89)	27 (87)	29 (94)	26 (7)

SRF=Subretinal fluid, IRF=Intraretinal fluid, HRD=Hyper-reflective dots, SHE=Subretinal hyper-reflective exudation

Macular atrophy development

Geographic atrophy was present in 12/48 eyes (25%) at presentation, 18/34 eyes (53%) at 24 months, and 18/30 eyes, i.e., 60% of the eyes at 5 years. The progression of the atrophy surface was statistically significant from baseline to 2 years (1.8 ± 4.6 mm^2 vs. 3 ± 4.6 mm^2, $P = 0.01$) and to 5 years (1.8 ± 4.6 mm^2–6 ± 4.5 mm^2, $P < 0.001$). The progression of atrophy was more important and significant from 2 and 5 years than during the first 2 years (3 ± 2.3 mm^2 vs. 1.2 ± 1.8 mm^2, $P < 0.001$). Among the 18 eyes that developed MA, most eyes (9/18) had type 3 CNV, followed by type 1 CNV (6/18) and then type 2 CNV (3/18). The progression of the atrophy area was 8.2 ± 6.2 mm^2 for type 1 CNV, 4.78 ± 3.8 mm^2 for type 2 CNV, and 5 ± 3.4 mm^2 for type 3 CNV. There was no difference in progression of atrophy among the subtypes. Of the 18 eyes with MA, 11 had VA <70 letters. We find a significant negative correlation between the final visual gain and the area of the atrophy at 2 years ($r = -0.4$, $P = 0.024$) and at 5 years ($r = -0.5$, $P = 0.006$).

At 5 years, subretinal fibrosis was observed in 14 out of 30 eyes (46%), although it was not present at the initial examination. From these, 12/14 had subretinal hyper-reflective exudation at presentation.

Number of intravitreal injections of aflibercept

The mean number of aflibercept injections was 5.7 ± 2 IVT at 1 year, 2.9 ± 2.9 at 2 years, 3.5 ± 3.3 at 3 years, 4.0 ± 3.4 at 4 years, and 4.2 ± 3.3 at 5 years. The mean number of aflibercept injections was 21.6 ± 13.4 over 5 years. At the end of the study, 20% of the eyes did not require any injection due to inactivity for at least 12 months. The percentage of eyes with treatment interval ≥12 weeks was 56.7% at 5 years, 74% at 4 years, 58% at 3 years, and 39% at 2 years.

During follow-up, one patient was switched to ranibizumab at 12 months and then switched back to aflibercept at 18 months.

Discussion

The study provides data on the 5-year outcome of aflibercept therapy for nAMD. To the best of our knowledge, there are little data on the long-term outcome of aflibercept in the literature. In France, treatment costs are covered by national health insurance. Therefore, the outcome was not influenced by reimbursement.

Our study showed that 37.5% of patients dropped out from follow-up at 5 years despite the reminder system put in place to promote therapeutic compliance. Boulanger-Scemama *et al*. found a rate of missed appointments at 5 years in 57% of patients in a French study with ranibizumab.[10] The three main causes of discontinuation of follow-up were a significant distance from the hospital, the impression of the ineffectiveness of treatment, and the excessive burden of visits and injections.

On average, 77% of patients with naïve nAMD of our cohort who underwent aflibercept injections gained VA or lost <15 letters from baseline over 5 years. These results suggest that good VA is likely maintained in these patients who were continuously monitored and treated with T and E protocol.[11,12]

We found that the visual gain was + 5.6 letters at 5 years, although the difference was not statistically significant. The visual gain obtained after the initiation of treatment was maintained for up to 2 years and then was no longer significant after year 3.[12] Chandra *et al*.[13] reported that VA gain in the first year of + 6.3 letters dropped to + 3.9 in the second and + 1.7 in the third year despite a recommended aflibercept T and E protocol. We have summarized in Table 3 the studies which evaluated the results of anti-VEGF in nAMD at 5 years according to the drug, treatment protocol, and initial VA. Most studies reported that the visual gain obtained during the first 2 years is no longer observed after the 3rd year. However, our study showed that the percentage of eyes with VA ≥5/10 allowing driving was 53%, whereas it was only 29% at the initial examination, which was encouraging. This rate varied from 27.4% to 50%,[14-23] proving that anti-VEGF constitutes a major long-term therapeutic advance in exudative AMD. Visual gain at 5 years was found to be correlated with that at 4 months after the loading phase, suggesting the importance of early treatment and respect for the

Table 3: Results of 5-year studies on anti-vascular endothelial growth factor therapy in neovascular age-related macular degeneration

Author	Number of patients	FU duration (years)	Anti-VEGF	Protocol	Baseline VA	VA at 5 years	VA gain from baseline	IVT (*n*)	Atrophy rate (%)	Rate of eyes with >70 letters	Dropout (%)
Khanani[14]	26	5	A, B, R	T and E	72	NA	NA	31	NA	34	72
Berg *et al*.[15]	62	5*	A, B, R	T and E	56.1	55 to 60	3.4	35	95	NA	60
Jaki Mekjavic[16]	101	5	B, R	T and E	60.5	58.6	–1.9	30.5	30	38.6	VA
Gillies *et al*.[17]	549	5**	A, B, R	T and E in most cases, PRN	55.1	59.4	+0.7	25	37	43	55
Invernizzi *et al*.[18]	811	5	R	T and E in most cases, PRN	56.9	56.7	–0.24	30	NA	35.2	58
					52.9	53.2	+0.01	29		31.8	
					49.2	50.4	+1.19	29		27.4	
Maguire *et al*.[19]	647	5.5	A, B, R	PRN	62.2	58.9	–3	15.4	41	50	70.8
Horner *et al*.[20]	95	5*	A, B, R	PRN	61.1	61.1	–1.9	25	NA	41	45.7
Wecker *et al*.[21]	121	5	A, B, R	PRN	60	51	–9	24	NA	NA	87
Jacob *et al*.[22]	52	5***	R	PRN	58.9	54.9	–1.1	20.3	NA	22.8	24.6
Boulanger-Scemama *et al*.[10]	201	5	R	PRN	52.3	49.5	–2.8	15	NA	NA	NA
Wada *et al*.[23]	177	5	R	PRN	65	52	NA	11.4	43	NA	40
Wolff *et al*.[24]	116	5****	R	PRN	57.5	49	–10	15.5	NA	NA	NA
Peden *et al*.[25]	89	5	R	Fix regimen	45.6	59.2	+14	52.5	NA	46.8	89.9
Current study	30	5	A	T and E	56.1	61.7	5.6	21.6	60	53	37.5

*Data extracted at 5 years from an 8-year study, **Data extracted at 5 years from a 7-year study, ***Data extracted at 5 years from a 6- year study, ****Data extracted at 5 years from a 10-year study, A=Aflibercept, B=Bevacizumab, R=Ranibizumab, T and E=Treat and extend, PRN=Pro re nata, NA=Not available data, FU=Follow-up, VEGF=Vascular endothelial growth, IVT=Intravitreal injection, VA=Visual acuity

loading dose to maximize the final long-term functional gain. Indeed, the long-term visual function depends on the initial response to treatment in neovascular AMD.[26] Patients of our cohort received a minimum of 6 injections and gained + 6 letters during the 1st year, which was similar to the real-life evidence provided by the RAINBOW study.[5] In our study, the number of injections was 21.6 over 5 years. This number is higher than that of the studies using the PRN protocol (from 11.4 to 15) and lower than the T and E studies reported in the literature (from 25 to 35). Chandra *et al*. reported that over 5 years, their cohort received a mean of 24 injections of aflibercept. The lower number of injections in our cohort can be explained by the modified T and E protocol, going through an observation phase to separate "happy few" eyes, which remained inactive for years after the loading phase. The rate of the "happy few eyes" was 14.6% in our study, which was reported as 13%–20% in the literature.[27] During the study period, 56.7% of patients had an interval of ≥12 weeks. Twenty percent of the eyes were followed only with regular visits without IVT because they did not longer show exudation. This longer interval could be explained by the longer durability of aflibercept. Although getting patients' compliance to T and E protocol over 5 years is challenging, our study shows that we do need to continue visits and treatment in most eyes to maintain VA.

The prevalence of MA with central involvement was found in 60% of our patients at 5 years. The evolution of atrophy was significantly faster between the 2nd and 5th years compared to the first 2 years. Grunwald *et al*.[27] report a cumulative incidence of MA of 12% in the first year, 17% in the second year, and 38% after 5 years, and the growth of atrophy to be 0.33 mm^2/year. Previous studies have reported that atrophy affects almost all eyes, more precisely 93% at 10 years.[15] We also found that subretinal fibrosis developed in 46% of our patients at 5 years. Although we did not use polarization-sensitive optical coherence tomography to classify subretinal fibrosis, we also found that most patients (12/14) who developed subretinal fibrosis at 5 years had subretinal hyper-reflective exudation at presentation, which might be a baseline factor predictor as reported Roberts *et al*.[28] The percentage of eyes with subretinal fibrosis can reach up to 71% at 10 years in a single-center study using other anti-VEGF therapy.[24] The development of fibrosis as well as atrophy may hence contribute to the visual decline in the natural history of AMD. Although disease progression is inevitable, the frequency of injection needs to be sustained on a strict protocol to obtain maximal visual potential for our patients in long-term studies on anti-VEGF in nAMD.

This study has the strength of a prospective design, the use of a modified T and E aflibercept protocol for all patients to avoid under- or overtreatment, and the evolution of anatomical outcome.[2,11] The patients were followed up and treated by the same physician, ensuring a standardized personalized regimen. The weaknesses of our study were its single-center nature, the size of the sample, and the number of losses of follow-ups, which could lead to analysis bias.

Conclusion

The results of this study show that naïve nAMD patients treated with individualized T and E aflibercept regimen can maintain their visual function at 5 years. Half of them had a driving VA in the long term, which is a therapeutic advance of the disease. Aggressive, early, proactive, and persistent treatment in most eyes is necessary to achieve and maintain good VA over 5 years.

Financial support and sponsorship

Nil.

Conflicts of interest

The authors declare that there are no conflicts of interests of this paper.

References

1. Kodjikian L, Fourmaux E, Coscas F, Dumas S, Français C, Morel C, *et al.* Treatment of age-related macular degeneration: Expert opinion and therapeutic algorithm. J Fr Ophtalmol 2015;38:639-45.
2. Semoun O, Cohen SY, Srour M, Creuzot-Garchet C, Oubraham-Mebroukine H, Kodjikian L, *et al.* Individualized management of patients with exudative AMD, IOI protocol: Injection-observational-individualization. J Fr Ophtalmol 2017;40:169-76.
3. Abri Aghdam K, Pielen A, Framme C, Junker B. Correlation between hyperreflective foci and clinical outcomes in neovascular age-related macular degeneration after switching to aflibercept. Invest Ophthalmol Vis Sci 2015;56:6448-55.
4. Kim JH. Short-term changes in choroidal thickness after aflibercept therapy for neovascular age-related macular degeneration. Am J Ophthalmol 2015;160:207.
5. Weber M, Kodjikian L, Coscas F, Faure C, Aubry I, Dufour I, *et al.* Impact of intravitreal aflibercept dosing regimens in treatment-naïve patients with neovascular age-related macular degeneration in routine clinical practice in France: Results from the RAINBOW study. BMJ Open Ophthalmol 2020;5:e000377.
6. Framme C, Eter N, Hamacher T, Hasanbasic Z, Jochmann C, Johnson KT, *et al.* Aflibercept for patients with neovascular age-related macular degeneration in routine clinical practice in Germany: Twelve-month outcomes of PERSEUS. Ophthalmol Retina 2018;2:539-49.
7. Heier JS, Brown DM, Chong V, Korobelnik JF, Kaiser PK, Nguyen QD, *et al.* Intravitreal aflibercept (VEGF trap-eye) in wet age-related macular degeneration. Ophthalmology 2012;119:2537-48.
8. Tran TH, Dumas S, Coscas F. Two-year outcome of aflibercept in patients with pigment epithelial detachment due to neovascular age-related macular degeneration (nAMD) refractory to ranibizumab. J Ophthalmol 2017;2017:8984313.
9. Sadda SR, Guymer R, Holz FG, Schmitz-Valckenberg S, Curcio CA, Bird AC, *et al.* Consensus definition for atrophy associated with age-related macular degeneration on OCT: Classification of atrophy report 3. Ophthalmology 2018;125:537-48.
10. Boulanger-Scemama E, Querques G, About F, Puche N, Srour M, Mane V, *et al.* Ranibizumab for exudative age-related macular degeneration: A five year study of adherence to follow-up in a real-life setting. J Fr Ophtalmol 2015;38:620-7.
11. Eleftheriadou M, Gemenetzi M, Lukic M, Sivaprasad S, Hykin PG, Hamilton RD, *et al.* Three-year outcomes of aflibercept treatment for neovascular age-related macular degeneration: Evidence from a clinical setting. Ophthalmol Ther 2018;7:361-8.
12. Gayadine-Harricham Y, Rufin V, Law-Koune S, Tran THC. Four-year outcome of aflibercept treatment-naïve patients for neovascular age-related macular degeneration: Evidence from a clinical setting. J Ophthalmol 2020;2020:7465270.
13. Chandra S, Rasheed R, Menon D, Patrao N, Lamin A, Gurudas S, *et al.* Impact of injection frequency on 5-year real-world visual acuity outcomes of aflibercept therapy for neovascular age-related macular degeneration. Eye (Lond) 2021;35:409-17.
14. Khanani AM. Clinical experience with fixed bimonthly aflibercept dosing in treatment-experienced patients with neovascular age-related macular degeneration. Clin Ophthalmol 2015;9:1315-20.
15. Berg K, Roald AB, Navaratnam J, Bragadóttir R. An 8-year follow-up of anti-vascular endothelial growth factor treatment with a treat-and-extend modality for neovascular age-related macular degeneration. Acta Ophthalmol 2017;95:796-802.
16. Jaki Mekjavic P, Zaletel Benda P. Outcome of 5-year treatment of neovascular age-related macular degeneration with intravitreal anti-VEGF using "Treat and Extend" regimen. Front Med (Lausanne) 2018;5:125.
17. Gillies MC, Campain A, Barthelmes D, Simpson JM, Arnold JJ, Guymer RH, *et al.* Long-term outcomes of treatment of neovascular age-related macular degeneration: Data from an observational study. Ophthalmology 2015;122:1837-45.
18. Invernizzi A, Nguyen V, Teo K, Barthelmes D, Fung A, Vincent A, *et al.* Five-year real-world outcomes of occult and classic choroidal neovascularization: Data from the fight retinal blindness! Project. Am J Ophthalmol 2019;204:105-12.
19. Comparison of Age-related Macular Degeneration Treatments Trials (CATT) Research Group, Maguire MG, Martin DF, Ying GS, Jaffe GJ, Daniel E, *et al.* Five-year outcomes with anti-vascular endothelial growth factor treatment of neovascular age-related macular degeneration: The comparison of age-related macular degeneration treatments trials. Ophthalmology 2016;123:1751-61.
20. Horner F, Lip PL, Clark H, Chavan R, Sarmad A, Mushtaq B. Real-world visual and clinical outcomes for patients with neovascular age-related macular degeneration treated with intravitreal ranibizumab: An 8-year observational cohort (AMD8). Clin Ophthalmol 2019;13:2461-7.
21. Wecker T, Ehlken C, Bühler A, Lange C, Agostini H, Böhringer D, *et al.* Five-year visual acuity outcomes and injection patterns in patients with pro-re-nata treatments for AMD, DME, RVO and myopic CNV. Br J Ophthalmol 2017;101:353-9.
22. Jacob J, Brié H, Leys A, Levecq L, Mergaerts F, Denhaerynck K, *et al.* Six-year outcomes in neovascular age-related macular degeneration with ranibizumab. Int J Ophthalmol 2017;10:81-90.
23. Wada I, Oshima Y, Shiose S, Kano K, Nakao S, Kaizu Y, *et al.* Five-year treatment outcomes following intravitreal ranibizumab injections for neovascular age-related macular degeneration in Japanese patients. Graefes Arch Clin Exp Ophthalmol 2019;257:1411-8.
24. Wolff B, Macioce V, Vasseur V, Castelnovo L, Michel G, Nguyen V, *et al.* Ten-year outcomes of anti-vascular endothelial growth factor treatment for neovascular age-related macular disease: A single-centre French study. Clin Exp Ophthalmol 2020;48:636-43.
25. Peden MC, Suñer IJ, Hammer ME, Grizzard WS. Long-term outcomes in eyes receiving fixed-interval dosing of anti-vascular endothelial growth factor agents for wet age-related macular degeneration. Ophthalmology 2015;122:803-8.
26. Nguyen V, Daien V, Guymer R, Young S, Hunyor A, Fraser-Bell S, *et al.* Projection of long-term visual acuity outcomes based on initial treatment response in neovascular age-related macular degeneration. Ophthalmology 2019;126:64-74.
27. Grunwald JE, Pistilli M, Daniel E, Ying GS, Pan W, Jaffe GJ, *et al.* Incidence and growth of geographic atrophy during 5 years of comparison of age-related macular degeneration treatments trials. Ophthalmology 2017;124:97-104.
28. Roberts PK, Schranz M, Motschi A, Desissaire S, Hacker V, Pircher M , *et al.* Sci Rep 2022;12:88.