Title: Investigation of incidence and causes of acute vision loss during anti-vascular endothelial growth factor therapy for neovascular age-related macular degeneration during a 4-year follow-up

Abbreviated title: Acute vision loss of nAMD over 4 years

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Key Words and Summary Statement

Acute vision loss

Age-related macular degeneration (AMD)

Anti-vascular endothelial growth factor (VEGF) treatment

Intravitreal aflibercept (IVA)

Intravitreal ranibizumab (IVR)

Long-term follow-up

Macular neovascularization (MNV)

Real-world date

Treatment-naïve neovascular AMD

Treat-and-extend (TAE) regimen

About half of the patients with neovascular age-related macular degeneration treated with anti-vascular endothelial growth factor drugs experienced acute vision loss events over four years, and they had poor visual outcome. Poor baseline visual acuity and disrupted ellipsoid zone were risk factor of acute vision loss events.

Abstract

Purpose:

To investigate the incidence, risk factors, and outcomes of patients with age-related macular degeneration (AMD) who experienced acute vision loss despite periodic injections of anti-vascular endothelial growth factor (VEGF) treatment for 4 years.

Methods:

This retrospective cohort study included patients who were diagnosed with treatment-naïve neovascular AMD and completed a 4-year follow-up. The incidence and risk factors for the occurrence of three or more lines of visual loss at every check-up were investigated.

Results:

The analysis included 76 eyes of 76 patients. Acute vision loss occurred in 30 eyes (39.5%) over 4 years. Lower baseline best collected visual acuity (BCVA) and disrupted ellipsoid zone were independent predictors of vision loss occurrence. Although the causes and timing of visual acuity loss varied, retinal pigment epithelium tears were

observed only in the first year. Most (86.7%) patients who experienced vision loss recovered their vision to pre-loss levels at least once; however, the final BCVA was worse than that in the group that did not experience acute vision loss.

Conclusion:

Approximately half of the patients with AMD experienced acute vision loss during a 4-year, despite continuous anti-VEGF treatment. Most patients recovered from vision losses temporarily; however, they experienced worse visual outcomes subsequently.

Introduction

Age-related macular degeneration (AMD) is a leading cause of visual impairment, particularly in developed countries.[1-3] The visual prognosis of patients with macular neovascularization (MNV) secondary to AMD has changed considerably since the introduction of anti-vascular endothelial growth factor (VEGF) treatment. Widely used anti-VEGF agents include ranibizumab and aflibercept, which several large clinical studies have demonstrated to be efficacious. [4-7]

However, some patients still lose vision despite continuous anti-VEGF treatment.[8-11] Sub-analysis of pivotal clinical trials identified the incidence and risk of vision loss that occurs rapidly in the early phase of treatment.[12-14] This acute loss of vision, even if it improves quickly, is a predictor of poor visual outcomes in patients. [13] The causes of vision loss include the exacerbations of macular degeneration and also other ophthalmologic or systemic diseases. However, the cause is sometimes unknown. [12,13]

Although these studies provided important practical information, the observation period of the analyses was limited to one or two years. Considering that longer check-ups and treatment are required in real-world clinical practice, investigating the acute vision loss over an extended follow-up period will help improve disease management by identifying preventable causes. It will help predict which patients would experience poor visual

outcomes and enable appropriate management to optimize adherence and outcomes.

In this study, we investigated patients who lost more than three lines of vision at any visit compared to the previous visit during a four-year follow-up despite periodic injections of anti-VEGF agents and explored the incidence rates and risk factors for developing vision loss.

Methods

Study participants

This retrospective cohort study used data from all patients who were diagnosed with neovascular AMD (nAMD) and started anti-VEGF drug treatment at the Department of Ophthalmology, Nagasaki University Hospital from January 2013 to December 2016. The inclusion criteria were as follows: 1) age over 50 years, 2) presence of MNV, and 3) start of anti-VEGF therapy during the above period. Only one eye from each patient was included; if both eyes received treatment during the study period, the first eye was included in the analysis. In contrast, the exclusion criteria were as follows: 1) axial length longer than 26.5 mm, 2) occurrence of inflammatory or hereditary diseases that may cause MNV, 3) previous treatments for MNV, 4) any other retinal or optic nerve diseases, 5) a

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history of intraocular surgery except for cataract surgery, and 6) observation period less than 4 years after the start of treatment.

All procedures conformed to the tenets of the Declaration of Helsinki, and the study design was approved by the institutional review board of Nagasaki University Hospital. The ethics committee waived the requirement for written informed consent, given the study's retrospective nature; instead, patients were allowed "opt-out" consent.

Intervention and observation procedure

We employed the treat-and-extend (TAE) regimen principle. We used aflibercept in most cases of type 1 MNVs and ranibizumab for type 2 and type 3 MNV. In addition, we chose ranibizumab for patients with a high risk of stroke and cardiovascular events. The initial drug may have been switched to another when the lesion is refractory. After an initial loading phase of three doses of anti-VEGF administered 4 weeks apart, the interval for the next injection was extended by 1–2 weeks to a maximum of 16 weeks if there was no sign of exudation. The treatment interval was shortened by two or more weeks upon signs of disease recurrence, as shown by changes in anatomical parameters such as the presence of intraretinal or subretinal fluid. However, when no recurrence was observed at intervals of 12 weeks or longer, treatment cessation was discussed with

the patients. Treatment was also stopped in refractory cases, in which visual recovery

was considered unlikely even with continued injections, when the patient was referred

to another hospital for treatment, or when the patient refused further treatment. The

interval between extension and shortening, timing of treatment discontinuation, and

drug selection were at the discretion of the attending physician.

Patients underwent comprehensive examinations, including measurement of best-

corrected visual acuity (BCVA), axial length (IOLMaster 500; Carl Zeiss Meditec, Dublin,

CA), fundus photography, spectral-domain optical coherence tomography (SD-OCT,

Spectralis; Heidelberg Engineering, Heidelberg, Germany), fluorescein angiography,

indocyanine green angiography, fundus autofluorescence imaging (HRA2; Heidelberg

Engineering), and OCT-angiography (Avanti; Optovue, US) at baseline. Anticoagulant

and/or antiplatelet therapy was systematically administered during the initial check-up.

The BCVA and SD-OCT measurements were performed at each check-up. SD-OCT

images included 30° horizontal regular and enhanced depth scans through the fovea and

15 raster scans covering a 20°×15° oblong rectangle.

Subretinal hemorrhage in the fovea centralis was detected based on fundus photography

and SD-OCT. SD-OCT images were reviewed to differentiate between hemorrhagic

pigment epithelial detachment (PED). Choroidal thickness was measured using enhanced

depth imaging scans as the length between the outer border of the Bruch's membrane and the chorioscleral interface. PED height was defined as the distance between the outer border of the retinal pigment epithelium and the inner border of Bruch's membrane, and the maximum PED height on the raster scans was recorded. The presence of foveal external limiting membrane (ELM), ellipsoid zone, and vitreoretinal adhesion was evaluated on vertical and raster scans.

Disease type was determined based on angiography, SD-OCT, OCT-angiography, and fundus photography. Fundus angiography was performed before or immediately after the start of treatment unless the patient experienced an allergy to the contrast agent or other systemic risk. We assessed the presence of polypoidal lesions on indocyanine green angiography at baseline in each case. A diagnosis of aneurysmal type 1 neovascularization (also known as polypoidal choroidal vasculopathy; PCV) was made based on the finding of characteristic polypoidal lesions at the border of the branching vascular networks. Patients with retinochoroidal anastomosis were diagnosed with type 3 neovascularization (also known as retinal angiomatous proliferation [RAP]), while the other patients were diagnosed with type 1 and type 2 AMD.

Additionally, two graders (Y.H. and E.M.), blinded to the visual outcome, performed these measurements and grading. The average of the measurements was used for the

analysis, and the discrepancy in grading was arbitrated with discussion.

Main outcome measure

The main outcome measure was the incidence of more than three lines of vision loss compared with the previous examination. BCVA was measured using Landolt C and converted to the logarithm of the minimum angle of resolution (logMAR) to perform statistical analysis. A decrease of more than 0.3 units was defined as more than three lines of vision loss.

Statistical analysis

Values are presented as median and quartile ranges. All statistical analyses were performed using EZR[15], which is a modified version of R commander for statistical functions frequently used in biostatistics. Stepwise logistic regression analysis was performed using age, sex, baseline BCVA, presence of a polypoidal lesion, presence of type 3 lesion, presence of a subretinal hemorrhage, central retinal thickness (CRT), maximum PED height, choroidal thickness, ELM status, ellipsoid zone status, vitreoretinal adhesion, anticoagulant therapy as independent factors, and loss of vision

as dependent factors. A Kaplan–Meier curve was created to understand time-to-event scenarios. Statistical significance was set at $p < 0.05$.

Results

Overall, 155 eyes from 155 patients were diagnosed with nAMD, and anti-VEGF induction started between 2013 and 2016. According to the criteria, 1, 9, 11, and 58 eyes were excluded because of age, previous treatment, other diseases or surgery, and terminated observation within 4 years, respectively. Of the 58 eyes that terminated observation, 28 stopped treatment without recurrence, 4 stopped treatment due to lack of or insufficient effect, 7 were transferred to another hospital for therapy, and 19 dropped out for unknown reasons. Finally, 76 eyes were included in the analysis. Fifty-nine of the 76 eyes continued anti-VEGF treatments for 4 years, and 17 eyes stopped treatment and continued coming for check-ups (Figure 1). Among the 17 eyes, 12 eyes stopped treatment without recurrence, 4 eyes stopped treatment due to insufficient effect, and 1 eye refused to continue treatment.

Table 1 shows the demographic characteristics of the study population. This study included 52 men and 24 women. Fifty-five eyes had type 1 MNV (42 of 55 had aneurysmal type 1 MNV), 16 eyes had type 2 MNV, and 5 eyes had type 3 MNV. The

median age was 71.0 (quartile range: 65.0–79.3), and the median number of injections was 20.0 (13.0–28.3).

Acute vision loss occurred in 30 eyes (39.5%) at a median follow-up period of 11.5 months (4.0–22.6) after the initial treatment. The median period from the last injection to the occurrence of vision loss was 52 days (31-66), with no difference between aflibercept and ranibizumab ($P = 0.838$). The eyes with vision loss included 20 eyes with type 1 MNV (36.4% of eyes with type 1 MNV), 6 eyes with type 2 MNV (37.5% of eyes with type 2 MNV), and 4 eyes with type 3 MNV (80.0% of eyes with type 3 MNV). Although there were 22 eyes with multiple vision loss events during the 4-year observation period, only the first event was analyzed in this study. The presumed cause for visual decline was an increase/development of subretinal fluid (SRF; 4 eyes, 13.3%), increase/development of subretinal hemorrhage (4 eyes, 13.3%), an increase in macular edema (3 eyes, 10.0%), development of macular atrophy (3 eyes, 10.0%), formation of a fibrotic scar (3 eyes, 10.0%), formation of retinal pigment epithelium (RPE) tears (3 eyes, 10.0%), and an increase/development of subretinal hyperreflective materials (SHRM; 2 eyes, 6.7%). Furthermore, 4 eyes (13.3%) developed cataracts, underwent cataract surgery, and experienced an improved vision. The progression of cataracts was determined to be the cause of vision loss in 4 eyes, and vision was improved by cataract

surgery. One eye (3.3%) developed severe retinal schisis due to progressive traction,

and no treatment was administered. No apparent cause was identified in 3 eyes (10.0%).

Of the 30 eyes with vision loss, only 1 eye developed vision loss after cessation of

treatment, which was unrelated to AMD exacerbation. Figure 2 shows the representative

cases.

No baseline characteristics were associated with a specific cause of vision loss, and

anticoagulant use was not associated with the risk of SRH-related vision loss. Vision

loss due to any reason may occur at any time; however, RPE tear tends to occur in the

early phase; in this study, all RPE tear-associated vision loss occurred in the first year.

Table 2 shows the comparisons of eyes with and without vision loss. Patients

with vision loss had lower baseline BCVA, larger CRT, more frequent disruption of the

ELM, and an ellipsoid zone. Logistic regression analysis identified lower baseline

BCVA and disrupted ellipsoid zone as factors contributing to the incidence of vision

loss. Odds ratios were 1.24 (95% confidence interval (CI) 1.06–1.46, $P = 0.007$) for a

0.1 logMAR unit increase in BCVA, and 6.28 (95% CI 1.25–31.5, $P = 0.025$) for a

disrupted ellipsoid zone.

Figure 3A shows the Kaplan–Meier survival curve. The survival rate (not losing three

lines of vision) at 4 years was 60.5%. Fifteen of the 30 patients with vision loss

experienced an event during the first year. For additional analysis, the Kaplan–Meier

survival curves for eyes with and without BCVA > 0.5 logMAR (the value was

arbitrarily determined from the median BCVA of 0.52) are shown in Figure 3B, and

with and without CRT > 400 μ m (the value was arbitrarily determined from the median

CRT of 368 μ m) are shown in Figure 3C, with and without disruption in the ELM and

ellipsoid zone, are shown in Figure 3D, E. Eyes with lower baseline BCVA ($P < 0.001$,

log-rank test), eyes with higher CRT ($P = 0.004$), eyes with disrupted ELM ($P = 0.008$),

and eyes with disrupted ellipsoid zones ($P < 0.001$) had lower survival.

Subsequently, we investigated the clinical course of vision loss. Permanent vision loss

(i.e., no return to the level before the vision loss event) was noted in 4 eyes among the

30 eyes that experienced vision loss. Table 3 presents a comparison of eyes

with temporary and permanent vision loss. The eyes with permanent vision loss were in

older patients ($P = 0.030$). The time to permanent vision loss was evenly distributed

over the observation period, and no characteristic cause could be found. All vision loss

unrelated to MNV or of unknown cause were temporary and recovered to a pre-vision

loss event.

Discussion

Incidence of vision loss in one and four years

This study focused on the incidence of three or more lines of acute vision loss during long-term anti-VEGF drug treatment. During the 4-year follow-up, 39.5% of patients with AMD experienced one or more episodes of acute vision loss. Particularly, 60.5% of the patients did not experience acute vision loss. Notably, half of the vision loss (19.7% of all patients) occurred in the first year, indicating the importance of the initial treatment. The 19.7% incidence of vision loss in the first year was slightly higher than the 13.9% reported in the MARINA and ANCHOR studies [12] and 8.2% in a previous report using aflibercept.[14] This may be due to inclusion bias; patients who were good responders may have stopped coming for check-ups within those 4 years and were excluded from the analysis. Patients who experienced acute vision loss had lower BCVA at baseline, maximum BCVA during 4-year, and visual acuity at 4 years than the group that did not experience vision loss, which is generally consistent with previous reports.[13]

Causes of acute vision loss

This study showed various causes of vision loss at different time intervals. However, a correlation between specific causes, early or late events, and patient background was not

found. The exception was an RPE tear, which developed only in the first year after the initial treatment, as previously reported. [16-18] Similar to previous reports, anticoagulant use was not associated with SRH-related vision loss. [19,20]

We considered that we could find preventable vision loss, such as exacerbation of CME, SRF, and hemorrhage due to insufficient injections. However, in this study, not many vision loss events were associated with active exacerbation of MNV (13 cases, 43.3% of all vision loss), and all occurred during the TAE regimen rather than after treatment discontinuation. The number of injections was not associated with loss of vision. It is debatable whether more intensive drug administration would have effectively prevented the event; however, it would be difficult to apply more intensive treatment for these cases selectively in advance, given the absence of any predictive factors.

This study also identified a certain number of cases of unexplained vision loss and AMD-unrelated vision loss. Considering that studies of MNV essentially include elderly cohorts, cataract progression should be considered when interpreting long-term results. Unexplained vision loss may also be caused by fluctuations in examination results due to the patient's age. Additionally, all unexplained vision loss was temporary.

Risk of acute vision loss

Patients with poor baseline BCVA may be expected to have fewer vision loss events due to floor effects; however, this study associated poor baseline BCVA with a risk of acute vision loss. Poor baseline BCVA indicates higher disease activity, which may lead to a higher incidence of vision loss.

Morphological analysis revealed an association between baseline disease activity and a higher incidence of vision loss. Patients with increased CRT, disrupted ELM, and ellipsoid zone were at a high risk of vision loss. A recent study showed that variability in CRT is a predictor of visual outcomes.[21] Eyes with higher CRT at baseline may have a higher magnitude of CRT variability, which may be the cause of the association between increased CRT and a higher incidence of vision loss.

The status of the ELM [22,23] and ellipsoid zone [24,25] has been suggested as a valid indicator of photoreceptor integrity in AMD. In this study, the integrity of the ellipsoid zone was found to be a more important predictor, probably because the baseline visual acuity was relatively good. ELM may be a better indicator in a cohort with poor baseline vision. Evaluating both the ELM and ellipsoid zones is generally recommended in clinical practice.

Temporary vision loss and final visual outcome

Four of the 30 patients with acute vision loss experienced permanent vision loss. Specifically, 90% of vision loss improved to the pre-vision-loss level with continuous injection and other treatments such as cataract surgery at least during one check-up. Particularly, all the vision loss unrelated to MNV and of unknown cause improved. Previous studies reported that acute vision loss increases the frequency of patient dropouts and cessation. [26,27] However, our data suggest that visual acuity is likely to improve with continued long-term treatment in most cases. Therefore, encouraging patients to continue treatment would help their recovery.

Meanwhile, it should be noted that the occurrence of vision loss is a risk factor for a worse long-term visual outcome. Even when vision loss is temporary, these patients are at a high risk of gradual loss of vision in the long term. The question of whether we should apply more intensive treatment for these patients needs to be investigated in the future.

Strength and Limitation

The strengths of this study were that the patients were treated with an identical protocol, examined systematically, and observed over a long period. The most significant limitation is the retrospective design and associated selection bias. Larger prospective studies would provide more detailed information about the causes and risks of acute vision loss. Most

patients who stopped treatment for whatever reason did not continue follow-up for 4 years

and were excluded from the study. In addition, the final treatment decision was at the

physician's discretion. Nevertheless, we believe that the results represent a typical

outcome in a clinical setting and can be generalized to various populations.

In conclusion, this study showed that about half of patiensts with AMD experience three

lines of acute vision loss within years, despite treatment with continuous anti-VEGF

medications. Poor baseline visual acuity and disrupted ellipsoid zones are risk factors for

vision loss. Most patients' vision loss was recovered temporarily; however, they

experienced a poor visual outcome after 4 years. These results suggest the importance of

appropriate TAE to avoid acute vision loss and the importance of continuing treatment

and observation, even in the presence of acute vision loss.

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Figure legends

Figure 1. Flowchart of screening process in the present study. We screened 155 patients with neovascular age-related macular degeneration, and 79 eyes were excluded according to the criteria. Finally, 76 eyes were used for analysis.

Abbreviations: VEGF, vascular endothelial growth factor; AMD, age-related macular degeneration.

Figure 2. Color fundus photography and optical coherence tomography images of representative cases with vision loss during the treatment of age-related macular degeneration. (A) a case with best-corrected visual acuity (BCVA) loss from 20/50 to 20/100 due to subretinal fluid. (B) a case with BCVA loss from 20/15 to 20/40 due to macular edema. (C) a case with BCVA loss from 20/20 to 20/40 due to subretinal hemorrhage. D) a case with BCVA loss from 20/20 to 20/40 due to subretinal hyperreflective materials. (E) a case with BCVA loss from 20/50 to 20/100 due to macular atrophy. (F) a case with BCVA loss from 20/100 to 20/200 due to fibrotic scar.

Figure 3. Kaplan–Meyer survival curves (i.e., free of vision loss) for patients with age-

related macular degeneration treated with anti-VEGF drugs. Vision loss was defined as more than three lines of vision loss compared to the previous examination. Panel (A) shows that the overall survival rate was 60.5% of 76 patients in 4 years. Patients with poor visual acuity (worse than 0.5 logMAR) showed a lower rate of survival ($P < 0.001$), panel (B). Greater central retinal thickness (CRT) was also associated with a higher incidence of vision loss ($P = 0.004$), panel (C). Panels (D) and (E) show that eyes without an intact external limiting membrane ($P = 0.008$) and ellipsoid zone ($P < 0.001$) are associated with a higher incidence of vision loss.

List of Supplemental Digital Content:

Table 1: Baseline characteristics and changes in best-corrected visual acuity of patients with age-related macular degeneration treated with anti-VEGF drugs

	Total	Type 1		Type 2	Type 3 (RAP)
		without polyp	with polyp (PCV)		
Number of eyes	76	13	42	16	5
Age, years	71.0 (65.0-79.3)	72.0 (68.0-81.0)	68.0 (64.0-77.0)	74.5 (67.8-80.3)	77.0 (70.0-79.0)
Sex (male/ female)	52 / 24	7 / 6	32 / 10	10 / 6	3 / 2
BCVA first, logMAR	0.52 (0.22-0.73)	0.52 (0.30-0.70)	0.46 (0.22-0.82)	0.52 (0.40-0.77)	0.52 (0.52-0.70)
BCVA max, logMAR	0.05 (-0.02-0.24)	0.15 (0.05-0.22)	0.00 (-0.08-0.25)	0.12 (0.00-0.15)	0.40 (0.10-0.40)
BCVA 4Y, logMAR	0.22 (0.05-0.40)	0.30 (0.30-0.40)	0.12 (0.00-0.40)	0.30 (0.20-0.30)	0.52 (0.40-0.52)
CRT, μm	378.5 (261.8-471.3)	354.0 (258.0-443.0)	312.5 (231.0-435.0)	427.0 (315.8-496.5)	512.0 (455.0-640.0)
Maximum PED, μm	230.5 (159.0-420.3)	236.0 (165.0-321.0)	362.0 (191.8-494.3)	150.5 (118.8-187.8)	221.0 (156.0-424.0)
Choroidal thickness, μm	231.0 (191.0-285.3)	223.0 (201.0-277.0)	238.0 (208.0-308.8)	238.5 (178.0-287.3)	208.0 (121.0-220.0)
Number of injections	20.0 (13.0–28.3)	20.0 (19.0-30.0)	20.5 (12.0-29.8)	20.0 (16.8-26.3)	13.0 (13.0-27.0)
Initial drug (aflibercept/ ranibizumab)	54 / 22	10 / 3	36 / 6	8 / 8	0 / 5
Switch to another drug	6 / 11	2 / 3	4 / 3	0 / 4	0 / 1

Continuous values are shown as median and quartile ranges.

CRT, central retinal thickness; logMAR, logarithm of the minimum angle of resolution; PCV, polypoidal choroidal vasculopathy; PED, pigment epithelium detachment; RAP, retinal angiomatous proliferation; BCVA first, best–corrected visual acuity at baseline; BCVA 4Y, bestcorrected visual acuity at 4 years; BCVA max, maximum best–corrected visual acuity over 4 years.

Table 2. Baseline characteristics and changes in best-corrected visual acuity of patients with age-related macular degeneration who experienced acute vision loss and did not undergo treatment with anti-VEGF drugs.

	No Vision Loss (N = 46)	With Vision Loss (N = 30)	*P*
Age, years	68.0 (64.3–77.8)	76.0 (66.5–81.8)	0.063
Sex (male / female)	31 / 15	21 / 9	1.000
Subtype (type1 / 2 / 3)	35 / 10 / 1	20 / 6 / 4	0.216
BCVA first, logMAR	0.40 (0.15–0.70)	0.70 (0.52–1.05)	<0.001
BCVA max, logMAR	0.00 (-0.08–0.05)	0.30 (0.15–0.40)	<0.001
BCVA 4Y, logMAR	0.10 (0.00–0.30)	0.46 (0.30–0.82)	<0.001
Central retinal thickness, µm	341.0 (256.5–411.5)	441.0 (276.8–513.5)	0.031
Maximum PED, µm	223.0 (136.0–377.0)	241.5 (184.8–462.8)	0.088
Choroidal thickness, µm	241.0 (211.5–286.0)	215.5 (138.5–282.3)	0.101
Subretinal hemorrhage	22 (47.8%)	16 (53.3%)	0.815
Disrupted foveal ELM	17 (37.0%)	20 (66.7%)	0.018
Disrupted foveal Ellipsoid zone	26 (56.5%)	28 (93.3%)	0.001
Vitreoretinal detachment	40 (87.0%)	26 (86.7%)	1.000
Use of anti-coagulant	6 (13.0%)	6 (20.0%)	0.524
Number of injections	21.0 (15.5–29.8)	18.5 (10.3–26.8)	0.159

Continuous values are shown as median and quartile ranges.

ELM, external limiting membrane; logMAR, logarithm of the minimum angle of resolution; PED, pigment epithelium detachment; BCVA first, best-corrected visual acuity at baseline; BCVA 4Y, best-corrected visual acuity at four years; BCVA max, maximum best-corrected visual acuity during four years.

Table 3: Baseline characteristics and changes in best-corrected visual acuity of patients with age-related macular degeneration who experienced temporary or permanent acute vision loss and did not undergo treatment with anti-VEGF drugs.

	Temporary Vision Loss (N = 26)	Permanent Vision Loss (N = 4)	P
Age, years	74.5 (65.3–79.8)	86.0 (80.5–89.0)	0.030
Sex (male / female)	19 / 7	2 / 2	0.563
BCVA first, logMAR	0.61 (0.52–1.04)	1.02 (0.88–1.14)	0.241
BCVA max, logMAR	0.26 (0.11–0.40)	0.46 (0.38–0.52)	0.090
BCVA 4Y, logMAR	0.40 (0.24–0.65)	1.50 (0.92–2.00)	0.010
Central retinal thickness, μm	441.0 (276.8–511.8)	497.5 (372.0–591.5)	0.855
Maximum PED, μm	241.5 (186.5–480.8)	274.0 (180.5–384.8)	0.583
Choroidal thickness, μm	207.5 (123.5–282.3)	229.5 (207.5–251.5)	0.692
Subretinal hemorrhage	14 (53.8%)	2 (50.0%)	0.563
Disrupted foveal ELM	18 (69.2%)	2 (50.0%)	0.584
Disrupted foveal Ellipsoid zone	25 (96.2%)	3 (75%)	0.253
Vitreoretinal detachment	22 (84.6%)	4 (100%)	1.000
Use of anti-coagulant	4 (15.4%)	2 (50.0%)	0.169
Number of injections	18.5 (11.3–27.8)	13.0 (7.0–20.3)	0.210

Continuous values are shown as median and quartile ranges.

ELM, external limiting membrane; logMAR, logarithm of the minimum angle of resolution; PED, pigment epithelium detachment; BCVA first, best-corrected visual acuity at baseline; BCVA 4Y, best-corrected visual acuity at four years; BCVA max, maximum best-corrected visual acuity during four years.
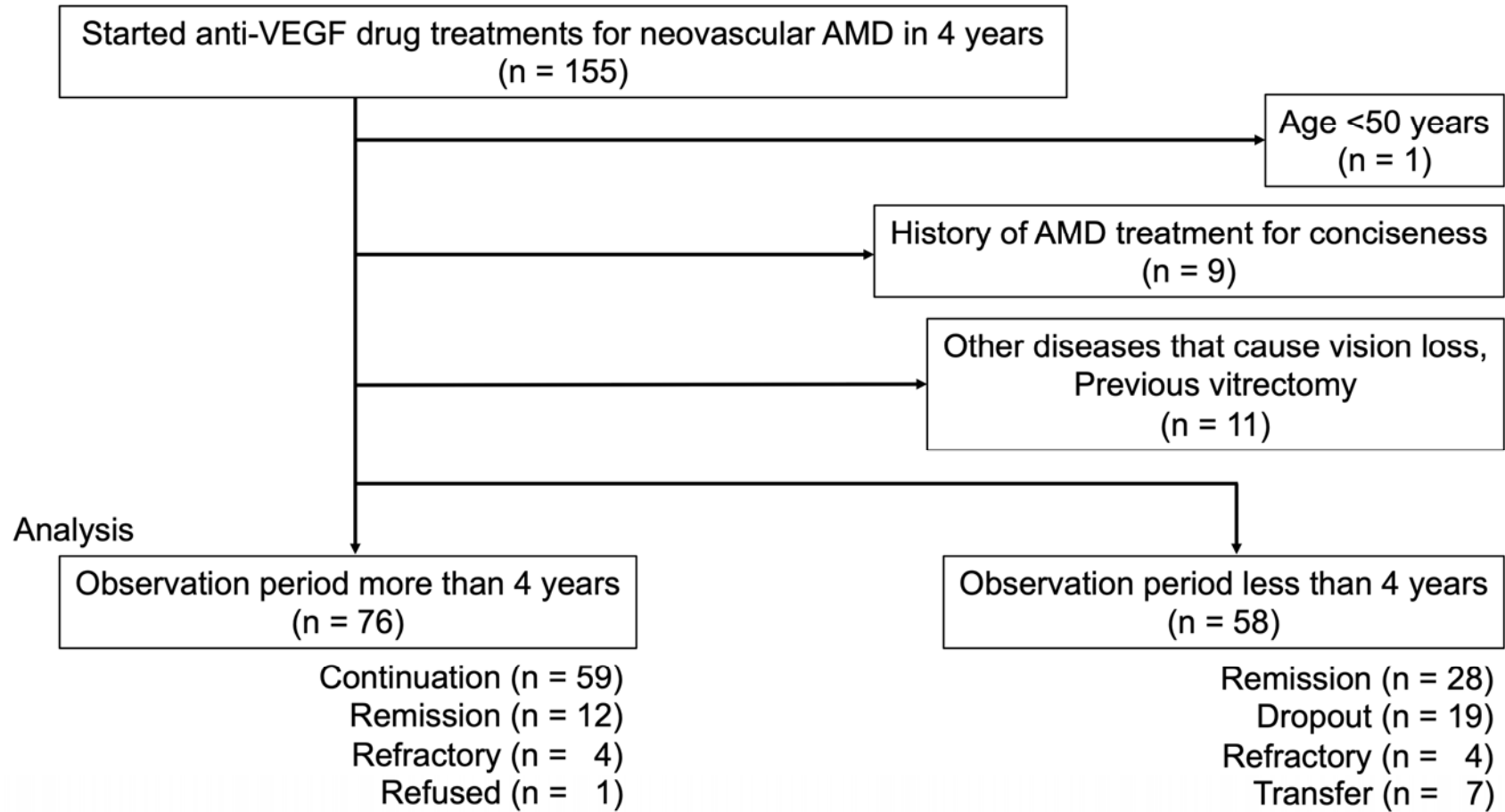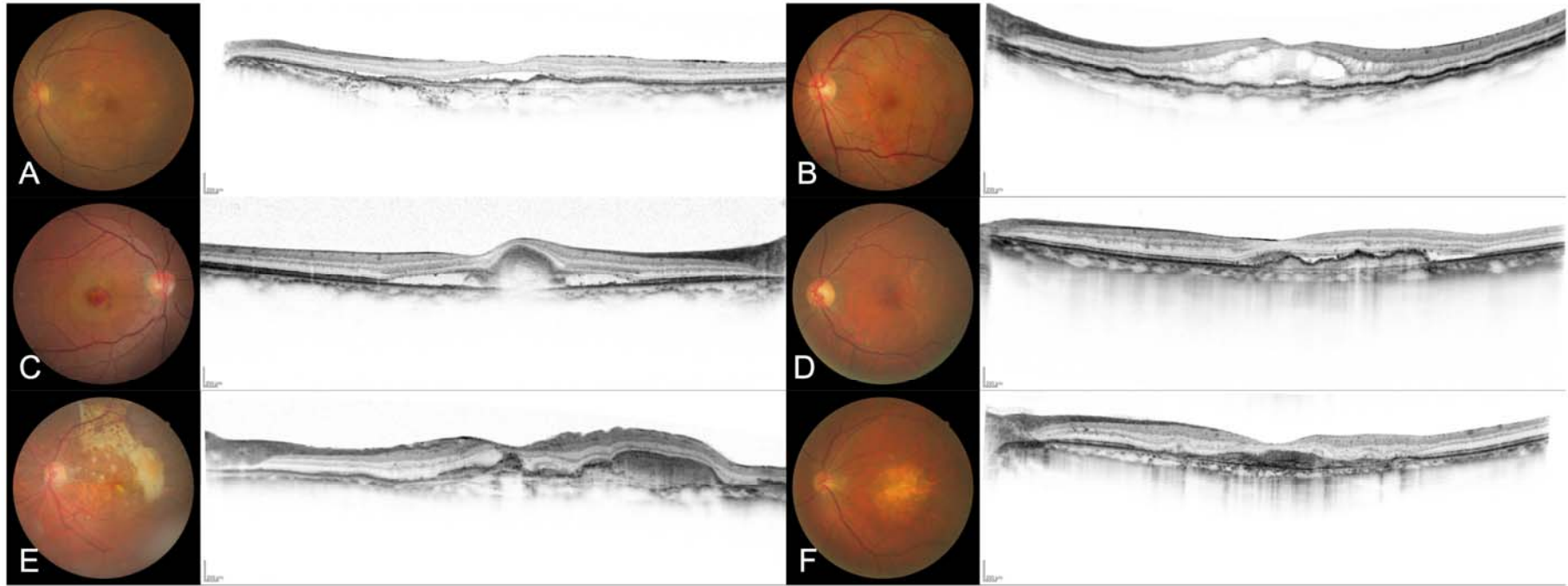
Fig. 1

Fig. 2

Fig. 3