

Visual Outcome and Treatment Frequency of Anti-VEGF Therapy using the Treat-and-extend and Treatment Cessation Regimen for Exudative Age-related Macular Degeneration and Pachychoroid Neovascularopathy

Takamasa Kinoshita (✉ knst129@gmail.com)

Department of Ophthalmology, Sapporo City General Hospital

Junya Mori

Department of Ophthalmology, Sapporo City General Hospital

Akira Hatanaka

Department of Ophthalmology, Sapporo City General Hospital

Kei Akaiwa

Department of Ophthalmology, Sapporo City General Hospital

Miho Shimizu

Department of Ophthalmology, Sapporo City General Hospital

Hiroko Imaizumi

Department of Ophthalmology, Sapporo City General Hospital

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Abstract

Compared with fixed dosing regimens, anti-vascular endothelial growth factor therapy using treat-and-extend (TAE) and treatment cessation regimens for exudative age-related macular degeneration (AMD) and pachychoroid neovascularopathy (PN) may reduce the treatment burden on chronic patients. To confirm this, and to determine the factors related to the successful treatment cessation, we retrospectively examined the visual outcome and treatment frequency of 101 eyes with exudative AMD and PN that underwent treatment using TAE and treatment cessation regimen. We found that visual acuity was maintained at the last visit with a mean follow-up period of four years. At the last visit, nearly half of the eyes were being treated at an interval of ≥ 12 weeks, or were under treatment cessation. Further, more than a quarter of the eyes were under successful treatment cessation with a median treatment-free period of 126 weeks. There was a significant association of successful treatment cessation at the last visit with good early treatment response and a small recurrence number. Moreover, eyes with ≥ 2 recurrences were unlikely to achieve long-term treatment cessation. This information could help physicians predict the achievement of treatment cessation for a considerable period.

Introduction

Currently, anti-vascular endothelial growth factor (anti-VEGF) therapy is the mainstream management regimen for exudative age-related macular degeneration (AMD), which is among the major causes of severe visual impairment in elderly patients worldwide^{1,2,3}. Although there have been encouraging functional and anatomical results regarding the fixed regimen of anti-VEGF injections^{4,5,6}, patients, clinicians, and health insurance providers have a large treatment burden that is unsustainable in common clinical settings. Consequently, anti-VEGF therapy, with pro re nata (PRN) or treat-and-extend (TAE) regimens, was introduced^{7,8,9}. TAE regimens, with/without modifications, have become increasingly popular in common clinical practice¹⁰.

There have been numerous reports regarding anti-VEGF therapy for exudative AMD using TAE regimens^{9,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25}. These previous studies reported outcomes as changes in best-corrected visual acuity (BCVA), central retinal thickness (CRT), and injection/visit frequency. Currently, few studies have introduced the TAE protocol with treatment cessation^{18,22}. Arendt et al. reported that patients who achieved treatment cessation using the TAE regimen with a minimum injection number (i.e., patients with good early treatment response without subsequent recurrence) did not show post-cessation recurrence²². However, the detailed relationship of early treatment responses or recurrence frequency with successful treatment cessation remains unclear.

Pachychoroid spectrum diseases, which are recently proposed clinical entities, are prevalent in Asian populations^{26,27,28}. Previously, pachychoroid neovascularopathy (PN), which involves choroidal neovascularization (CNV), was often diagnosed as AMD, especially in Asian populations²⁸. Based on the differences in clinical characteristics and genetic background between PN and drusen-driven AMD, they have been recently clearly differentiated^{21,28,29,30}.

This study aimed to report the visual outcomes and treatment frequency of anti-VEGF therapy for neovascular AMD and PN using the TAE and treatment cessation regimen in an Asian clinic. Moreover, we aimed to determine the association of early treatment response and recurrence frequency with treatment cessation under stable conditions.

Materials And Methods

This study adhered to the tenets of the Declaration of Helsinki. This study was approved by the Institutional Review Board of Sapporo City General Hospital before participant recruitment. The requirement for written informed consent was waived by the ethics committee given the retrospective nature of the study. Instead, the patients were allowed 'opt-out' consent.

This retrospective study consecutively included treatment-naïve eyes of patients aged ≥ 50 years with exudative AMD and PN involving the fovea. The eyes were diagnosed by a single physician (TK) and treated with ranibizumab or aflibercept using TAE regimen between January 2013 and December 2019 with a follow-up period of ≥ 12 months. The final data set was collected before December 25, 2020. For patients with bilateral exudative AMD or PN, we included eyes with the more recently initiated treatments.

The exclusion criteria were as follows: eyes with vitreoretinal diseases other than AMD and PN; glaucoma; high myopia; BCVA worse than 20/1000; significant cataract recommended for surgical interventions at the first anti-VEGF injection; chorioretinal scarring or atrophy involving the fovea; previous treatment using intravitreal injections of anti-VEGF agents or macular laser treatment, including photodynamic therapy (PDT); having undergone intraocular surgeries other than non-complicated cataract surgeries; and comorbid systemic diseases, including uncontrolled hypertension and renal failure. Moreover, we excluded patients who had not undergone three initial monthly injections or follow-up for ≥ 12 months after the initial injection.

Ophthalmic examinations included BCVA and intraocular pressure measurements, slit-lamp biomicroscopy, color fundus photography, fluorescein and indocyanine angiography (F-10; Nidek Co., Ltd, Gamagori, Japan), and spectral-domain optical coherence tomography (SD-OCT, Spectralis OCT instrument, Heidelberg Engineering GmbH, Heidelberg, Germany). Moreover, fundus autofluorescence and optical coherence tomography angiography were performed at the physician's discretion.

The diseases were classified as follows: typical neovascular AMD (tnAMD), polypoidal choroidal vasculopathy (PCV) without pachychoroid characteristics, retinal angiomatous proliferation (RAP), and PN with/without polypoidal lesions. Before PN introduction, numerous eyes with PN, with and without polypoidal lesions, had been diagnosed with PCV and tnAMD (occult CNV), respectively; however, they were amended before study onset. The presence of a pachychoroid was characterized as follows: obscured large choroidal vessels on color fundus photographs, thick choroid and dilated large choroidal vessels (pachyvessels) with an accompanying thin choriocapillaris layer just above the pachyvessels on SD-OCT, and choroidal vascular hyperpermeability on indocyanine angiography.

To obtain SD-OCT images, we performed horizontal and vertical cross-sectional scans at 30° passing through the fovea, as well as macular volume scans covering an area of $30^\circ \times 25^\circ$ centered on the fovea. Moreover, we obtained cross-sectional enhanced depth imaging OCT images to examine the choroidal structures. The CRT was determined using the Early Treatment of Diabetic Retinopathy Study (ETDRS) center thickness map of 1 mm diameter.

Anti-VEGF therapy involved two TAE regimens; namely, prompt TAE and deferred TAE, which depended on the disease type and lesion size. The prompt TAE regimen was applied for eyes that did not meet the criteria for the deferred TAE. It involved ≥ 3 monthly injections of anti-VEGF agents until dry macula was achieved with subsequent treatment interval adjustment based on the disease activity. Dry macula is indicative of inactivated CNV lesions without retinal/subretinal hemorrhages and intraretinal/subretinal fluid (SRF), which were confirmed through biomicroscopy and SD-OCT. When confirming the dry macula, retinal pigment epithelial detachment (PED) was not considered.

The deferred TAE regimen was applied to patients with tnAMD and PN without polypoidal lesions, which both involved lesions smaller than 1 disc area approximately. Further, this regimen was applied to patients aged > 85 years or with a history of Antiplatelet Trialists' Collaboration Events³¹. Regarding the deferred TAE regimen, ≥ 3 anti-VEGF injections were administered until dry macula with subsequent observation without treatment until fluid/hemorrhage recurrence was observed on SD-OCT or biomicroscopically. In case of recurrence, the TAE regimen was started through monthly injections without a loading phase.

For both regimens, the patients were asked to make visits on the day of injections, and at one week after each injection for assessment of the BCVA, SD-OCT, and adverse events. After the loading phase, in case dry macula was observed on the injection day, the treatment interval was extended by 2 weeks. Moreover, if fluid was observed on the injection day with subsequent disappearance at one post-injection week, the treatment interval was maintained. However, if they persisted at one post-injection week, the treatment interval was shortened by two weeks. In case of intraretinal or subretinal hemorrhages, treatments were administered monthly until dry macula restoration, followed by TAE with treatment interval adjustment by 2 weeks. Treatment interval adjustment was not considered for changes in BCVA and PED.

Until 2017, the maximum treatment interval extension was 12 weeks; subsequently, in 2018, this was amended to 16 weeks. Treatment was discontinued when dry macula was confirmed at the maximum interval. After treatment cessation, the patients were asked to visit the clinic at 12 or 16 weeks after the last injection, which was equivalent to the maximum injection interval for each patient. In case of confirmation of dry macula, the patients were instructed to return after one month, followed by visit interval extension by 1 or 2 months. Successful treatment cessation was defined as dry macula retention without treatment for > 16 weeks after the last injections. In case of post-cessation recurrences, monthly treatments with TAE were started without a loading phase. The treatment intervals were adjusted for two weeks.

We defined recurrence as recurrent intraretinal and subretinal hemorrhages or fluid accumulations after obtaining the dry macula, regardless of whether the patients were under treatment cessation. For each patient, we recorded the recurrence frequency after the loading phase within the study period.

During the early and late study periods, ranibizumab (0.5 mg) and aflibercept (2 mg) were administered, respectively. In the cases with persistent CNV activity, switching of anti-VEGF drugs or concomitant PDT using verteporfin (6 mg/m²) with anti-VEGF therapy was performed.

The main outcome measures were changes in BCVA during the first year and at the last visit. Other outcome measures included changes in BCVA and CRT over time, the proportion of eyes with maintained vision (< 0.3 logarithm of minimum angle of resolution (logMAR) BCVA loss) at the last visit, proportion of eyes with good ($\geq 20/40$) and poor vision (< 20/200) at the last visit, and number of annual injections. To evaluate and compare the long-term treatment burden according to the follow-up periods, we considered the number of annual injections and the observational period without anti-VEGF injections. To this end, we defined the index (estimated annual number of injections [EANI]) as follows: EANI = total injection number during the follow-up period/follow-up period (months) \times 12.

Statistical analyses

Statistical analyses were performed using the free statistical software R (4.0.2). Data obtained on the injection days were used for analyses of individuals under continuous treatment. Data were presented as mean \pm standard deviation unless otherwise specified. We converted the BCVA from decimal visual acuity to the logMAR for statistical analyses and ETDRS letter score for among-study comparisons. The significance of changes in BCVA and CRT was determined using Friedman's test. The Bonferroni test was used for posthoc analysis. Between-group comparisons of continuous variables were determined using the Kruskal-Wallis or Mann-Whitney U tests. Between-group comparisons of categorical variables were determined using Fisher's exact test. Logistic regression analyses were used to assess the correlation of early treatment response and recurrence frequency with the successful anti-VEGF treatment cessation. Receiver operating characteristic (ROC) curve analysis was performed to determine the cut-off value of the recurrence frequency for successful treatment cessations. Statistical significance was set at a two-sided P value of < 0.05.

Results

During the study period, 140 eyes in 123 patients underwent anti-VEGF treatment by a single physician (TK) for exudative AMD and PN without other chorioretinal diseases. Subsequently, 39 eyes in 21 patients were excluded based on the exclusion criteria (Supplementary Table S1). Finally, we included 101 eyes in 101 patients.

Table 1 summarizes the baseline demographic data. All the included patients had a follow-up period of ≥ 1 year (mean follow-up period: 49.9 ± 26.9 months). Specifically, 79 (78.2%), 66 (65.3%), 54 (53.4%), and 43 (42.6%) patients were followed up for ≥ 2 , ≥ 3 , ≥ 4 , and ≥ 5 years, respectively. Additionally, 32 (31.7%) patients discontinued the hospital visits before the final data collection (Supplementary Table S1; mean follow-up period: 40.7 ± 23.4 months).

Table 1
Baseline demographic data of the 101 studied patients

	All participants (n = 101)	tnAMD (n = 28)	PCV without pachychoroid (n = 36)	RAP (n = 9)	PN (n = 28)	P value
Age, year	74.4 (10.0)	74.8 (10.2)	74.6 (9.5)	82.9 (6.9)	71.0 (10.2)	0.018*
Sex, No. (%) Men	67 (66.3)	21 (75.0)	24 (66.7)	4 (44.4)	18 (64.3)	0.403†
BCVA, logMAR	0.42 (0.41)	0.70 (0.35)	0.44 (0.48)	0.66 (0.45)	0.32 (0.34)	0.215*
Eyes with BCVA \geq 20/40	58 (57.4)	16 (57.1)	20 (55.6)	2 (22.2)	20 (71.4)	0.078†
Eyes with BCVA \leq 20/200	15 (14.9)	3 (10.7)	6 (16.7)	3 (33.3)	3 (10.7)	0.337†
Lesion size, mm ²	6.5 (6.23)	4.3 (3.22)	8.6 (8.48)	8.3 (5.38)	5.5 (4.47)	0.070*
Lens status, No. (%), pseudophakia	27 (26.7)	6 (21.4)	7 (19.4)	6 (66.7)	8 (28.6)	0.049†
Central retinal thickness, μ m	390.6 (188.1)	365.1 (121.9)	392.6 (210.3)	485.1 (145.7)	382.9 (207.7)	0.178*
subfoveal choroidal thickness, μ m	206.1 (100.8)	160.8 (74.6)	191.3 (80.4)	118.4 (42.4)	306.4 (94.5)	< 0.001*
IRF, No. (%)	25 (24.8)	7 (25.0)	5 (13.9)	9 (100)	4 (24.8)	< 0.001†
SRF, No. (%)	79 (78.2)	24 (85.7)	28 (77.8)	6 (66.7)	21 (75.0)	0.585†
PED, No. (%)	38 (37.6)	5 (17.9)	21 (58.3)	4 (44.4)	8 (28.6)	0.005†
Vitreoretinal adhesion, No. (%)	20 (19.8)	5 (17.9)	6 (16.7)	0 (0.0)	9 (32.1)	0.189†
Data are presented as mean (SD) unless otherwise specified. tnAMD, typical neovascular age-related macular degeneration; PCV, polypoidal choroidal vasculopathy; RAP, retinal angiomatous proliferation; PN, pachychoroid neovascularopathy; BCVA, best-corrected visual acuity; logMAR, logarithm of the minimum angle of resolution; IRF, intraretinal fluid; SRF, subretinal fluid; PED, pigment epithelial detachment.						
* Kruskal-Wallis analysis						
†Fisher's exact test						

Prompt and deferred TAE were applied to 62 and 39 eyes, respectively. Among the 39 eyes treated with deferred TAE, 33 (84.6%) and 6 (15.4%) eyes were treated according to the treatment criteria and patients' preferences, respectively.

Further, 56 (55.4%), 15 (14.9%), and 30 (29.7%) eyes were treated using aflibercept only, ranibizumab only, and both agents, respectively. PDT and cataract surgeries were performed in 13 (12.8%) and 27 (26.7%) eyes, respectively.

Figure 1 and Table 2 present the temporal changes in BCVA. Compared with the baseline BCVA (0.42 ± 0.41 logMAR), there was a significant improvement in the BCVA at 12 weeks (0.34 ± 0.36 logMAR, $p = 0.004$), but not at the first year (0.37 ± 0.43 logMAR, $p = 0.067$) and last visit (0.43 ± 0.45 logMAR, $p = 1.000$). Eighty-three (82.2%) eyes maintained vision at the last visit. The BCVA was 20/40 or better in 58 (57.4%) and 54 (53.5%) eyes at baseline and last visit, respectively. Moreover, the BCVA was 20/200 or worse in 15 (14.9%) and 14 (13.9%) eyes at baseline and last visit, respectively.

Table 2
Visual outcome, central retinal thickness, and treatment frequency in different disease types

	All participants (n = 101)	tnAMD (n = 28)	PCV without pachychoroid (n = 36)	RAP (n = 9)	PN (n = 28)	P value
Follow-up period, months	49.9 (26.9)	52.2 (25.5)	50.9 (24.7)	41.4 (31.9)	49.0 (30.4)	0.740*
TAE regimen, No. (%), prompt TAE	62 (60.4)	9 (32.1)	29 (80.6)	7 (77.8)	17 (60.7)	0.002†
Change in BCVA at year 1, logMAR	-0.048 (0.331)	-0.076 (0.266)	-0.016 (0.418)	-0.091 (0.253)	-0.048 (0.282)	0.349*
Change in BCVA at the last visit, logMAR	0.010 (0.364)	0.030 (0.343)	0.020 (0.447)	-0.014 (0.391)	-0.018 (0.255)	0.947*
Change in CRT at year 1, μm	-125.6 (164.1)	-108.4 (107.3)	-108.3 (147.1)	-200.4 (129.9)	-139.6 (226.5)	0.107*
Change in CRT at the last visit, μm	-122.8 (180.9)	-121.0 (138.2)	-97.2 (194.7)	-189.4 (150.8)	-136.1 (209.3)	0.253*
Maintained vision at the last visit‡, n (%)	83 (82.2)	23 (82.1)	29 (80.6)	6 (66.7)	25 (89.3)	0.484†
Improved vision at the last visits**, n (%)	13 (12.9)	3 (10.7)	4 (11.1)	3 (33.3)	3 (10.7)	0.297†
BCVA \geq 20/40 at the last visit, n (%)	54 (53.5)	17 (60.7)	18 (50.0)	1 (11.1)	18 (64.3)	0.034†
BCVA \leq 20/200 at the last visits, n (%)	14 (13.9)	4 (14.3)	6 (16.7)	3 (33.3)	1 (3.6)	0.116†
Total injection number	21.1 (16.4)	20.0 (16.9)	21.4 (16.1)	19.2 (17.3)	22.4 (16.9)	0.883*
Injection number in the first year	6.8 (2.33)	5.8 (2.43)	7.1 (2.32)	7.8 (2.49)	6.9 (1.95)	0.038*
Estimated annual injection number	5.5 (2.86)	4.8 (2.78)	5.7 (3.16)	6.4 (3.38)	5.7 (2.29)	0.324*
Eyes treated frequently at the last visits††	29 (28.7)	6 (21.4)	13 (36.1)	1 (11.1)	9 (32.1)	0.390†
Data are presented as mean (SD) unless otherwise specified. Changes in BCVA or CRT at year 1 and at last visit were determined as BCVA or CRT at year 1 and last visit subtracted from those at baseline.						
tnAMD, typical neovascular age-related macular degeneration; PCV, polypoidal choroidal vasculopathy; RAP, retinal angiomatous proliferation; PN, pachychoroid neovascularization; TAE, treat-and-extend; BCVA, best-corrected visual acuity; logMAR, logarithm of the minimum angle of resolution; CRT, central retinal thickness.						
*Kruskal-Wallis analysis						
†Fisher's exact test						
‡Loss of BCVA < 0.3 logMAR						
**Gain of BCVA > 0.3 logMAR						
††eyes treated with a treatment interval of < 8 weeks						
‡‡eyes treated with a treatment interval of \geq 12 weeks or under treatment cessation						

	All participants (n = 101)	tnAMD (n = 28)	PCV without pachychoroid (n = 36)	RAP (n = 9)	PN (n = 28)	P value
Eyes treated less frequently at the last visits ^{‡‡}	48 (47.5)	16 (57.1)	18 (50.0)	3 (33.3)	11 (39.3)	0.478 [†]
Eyes under treatment cessation at the last visits, n (%)	27 (26.7)	9 (32.1)	10 (27.8)	3 (33.3)	5 (17.9)	0.617 [†]
Successful treatment cessation during the study period	56 (55.4)	18 (64.3)	17 (47.2)	4 (44.4)	17 (60.7)	0.453 [†]
Number of recurrences	3.0 (3.7)	3.1 (4.4)	3.3 (3.7)	0.8 (1.0)	3.2 (3.4)	0.070 [*]
Data are presented as mean (SD) unless otherwise specified. Changes in BCVA or CRT at year 1 and at last visit were determined as BCVA or CRT at year 1 and last visit subtracted from those at baseline.						
tnAMD, typical neovascular age-related macular degeneration; PCV, polypoidal choroidal vasculopathy; RAP, retinal angiomatous proliferation; PN, pachychoroid neovasculopathy; TAE, treat-and-extend; BCVA, best-corrected visual acuity; logMAR, logarithm of the minimum angle of resolution; CRT, central retinal thickness.						
*Kruskal-Wallis analysis						
†Fisher's exact test						
‡Loss of BCVA < 0.3 logMAR						
**Gain of BCVA > 0.3 logMAR						
††eyes treated with a treatment interval of < 8 weeks						
‡‡eyes treated with a treatment interval of ≥ 12 weeks or under treatment cessation						

There were no significant between-disease differences in changes in BCVA at year 1 and last visit ($p = 0.349$ and $p = 0.947$, respectively; Table 2), eyes treated with prompt and deferred TAE ($p = 0.085$ and $p = 0.936$, respectively), eyes treated and not treated with additional PDT ($p = 0.444$ and $p = 0.331$, respectively), and eyes of patients who completed and did not complete hospital visits until final data collection ($p = 0.929$ and $p = 0.156$, respectively). There were no significant differences in the baseline ($p = 0.247$) and final BCVA ($p = 0.349$) between eyes treated and not treated with cataract surgery; however, the BCVA at the first year was significantly worse in eyes treated with cataract surgery ($p = 0.018$).

The injection numbers from the first to fifth year were 6.8 ± 2.31 , 4.6 ± 3.24 , 4.7 ± 3.51 , 4.5 ± 3.53 , and 3.7 ± 3.64 , respectively. The EANI for included eyes was 5.5 injections/year. There were no significant between-disease differences in EANI ($p = 0.324$). The injection number in the first year and EANI were significantly smaller in the deferred TAE group (4.8 ± 1.8 and 3.9 ± 2.5 , respectively) than in the prompt TAE group (8.0 ± 1.7 and 6.5 ± 2.6 , respectively; $p < 0.001$ for both). Multivariate regression analysis revealed an association of eyes without SRF at baseline ($p = 0.045$) and eyes treated with deferred TAE ($p < 0.001$) with smaller EANI (Table 3). At the last visit, 48 (47.5%) and 29 (28.7%) eyes were treated with a treatment interval of ≥ 12 and < 8 weeks, respectively. There were no between-disease differences in the distributions ($p = 0.478$, $p = 0.390$, respectively, Table 2).

Table 3
Multivariate regression analysis for determinants that could affect the EANI

	B	SE	Lower bound of 95% CI	Upper bound of 95% CI	P value
Constant	4.870	0.816	3.249	6.490	
Disease type	-0.034	0.697	-1.418	1.350	0.961
tnAMD					
PCV without pachychoroid	-0.464	0.661	-1.776	0.848	0.484
RAP	0.694	0.974	-1.241	2.629	0.478
PN	0				
SRF at baseline	1.251	0.614	0.031	2.471	0.045
PED at baseline	-0.260	0.548	-1.348	0.827	0.636
Vitreomacular adhesion at baseline	1.124	0.644	-0.155	2.403	0.084
Use of aflibercept in the loading phase	1.017	0.536	-0.048	2.082	0.061
Deferred TAE	-2.535	0.567	-3.661	-1.408	< 0.001
Six possible clinically relevant variables were selected as independent variables, considering the results of previous studies to prevent overfitting in the regression model.					
EANI, estimated annual number of injections; B, unstandardized coefficients; SE, standard error; CI, confidence interval; tnAMD, typical neovascular age-related macular degeneration; PCV, polypoidal choroidal vasculopathy; RAP, retinal angiomatous proliferation; PN, pachychoroid neovascuopathy; SRF, subretinal fluid; PED, pigment epithelial detachment; TAE, treat-and-extend.					

Figure 2 summarizes the treatment course. During the study period, 56 (55.4%) eyes achieved ≥ 1 successful treatment cessation, with a median treatment-free period of 66 weeks. Additionally, 27 (26.7%) eyes were under successful treatment cessation at the last visit, with a median treatment-free period of 126 weeks. There were no between-disease differences in the distributions ($p = 0.453$ and $p = 0.617$, respectively; Table 2). Among the 27 eyes under successful treatment cessation at the last visit, 17 (63.0%), 4 (14.8%), 3 (11.1%), 2 (7.4%), and 1 (3.7%) eyes had 0, 1, 2, 3, and 5 recurrences, respectively, before successful treatment cessation.

Compared with eyes under continuous treatment, eyes under treatment cessation at the last visit had infrequent SRF at baseline ($p = 0.032$), infrequent disease activity at 12 weeks ($p = 0.002$), and a smaller recurrence number ($p = 0.003$, Table 4). Multivariate logistic regression analysis revealed an association of the absence of disease activity at 12 weeks and the recurrence number during the follow-up period with successful treatment cessation at the last visit (Table 5). Moreover, there was a significant association of successful treatment cessation during the follow-up period with a small recurrence number ($p = 0.002$), use of aflibercept during the loading phase ($p = 0.011$), and absence of PED at baseline ($p = 0.017$).

Table 4
Comparison of variables between eyes under continuous treatment and treatment cessation

	At the last visit		<i>P</i> value	During the study period		
	Eyes under continuous treatment (n = 74)	Eyes under treatment cessation (n = 27)		Not achieved the successful cessation (n = 45)	Achieved the successful cessation (n = 56)	<i>P</i> value
Age, year	75.0 (9.1)	72.7 (12.3)	0.620*	75.6 (8.8)	73.4 (10.9)	0.436*
Sex, No. (%) Men	51 (68.9)	16 (59.3)	0.476†	13 (28.9)	21 (37.5)	0.403†
Baseline BCVA, logMAR	0.35 (0.34)	0.59 (0.55)	0.067*	0.30 (0.31)	0.51 (0.46)	0.026*
Lesion size, mm ²	6.4 (5.9)	6.8 (7.1)	0.820*	7.0 (6.7)	6.1 (5.9)	0.341*
Lens status at baseline, No.(%), pseudophakia	21 (28.4)	6 (22.2)	0.618†	15 (33.3)	12 (21.4)	0.263
Central retinal thickness at baseline, μm	395.7 (192.8)	376.4 (159.8)	0.939*	438.5 (219.2)	352.0 (140.3)	0.070*
Subfoveal choroidal thickness at baseline, μm	212.6 (101.1)	189.8 (101.9)	0.380*	202.2 (80.0)	209.7 (112.9)	0.809*
IRF at baseline, No. (%)	17 (23.0)	8 (29.6)	0.329†	10 (22.2)	15 (26.8)	0.649†
SRF at baseline, No. (%)	62 (83.8)	17 (63.0)	0.032†	37 (82.2)	42 (75.0)	0.470†
PED at baseline, No. (%)	26 (35.1)	12 (44.4)	0.265†	22 (48.9)	16 (8.6)	0.041†
Vitreoretinal adhesion at baseline, No. (%)	16 (21.6)	4 (14.8)	0.325†	12 (26.7)	8 (14.3)	0.138†
Anti-VEGF agent used for loading phase, No. (%) aflibercept	49 (66.2)	14 (51.9)	0.139†	11 (24.4)	27 (48.2)	0.022†
Disease activity at 12 weeks, No. (%), absent	39 (52.7)	23 (85.2)	0.002†	20 (44.4)	42 (75.0)	0.002†
Number of recurrences during the study period	3.9 (4.0)	0.8 (1.3)	< 0.001"	4.5 (4.9)	1.9 (1.9)	0.002*
Follow-up period, months	48.8 (27.2)	53.0 (26.8)	0.468*	44.0 (26.8)	54.4 (26.4)	0.053*
Data were presented as mean (SD) unless otherwise specified.						
BCVA, best corrected visual acuity; logMAR, logarithm of the minimum angle of resolution; IRF, intraretinal fluid; SRF, subretinal fluid; PED, pigment epithelial detachment; VEGF, vascular endothelial growth factor.						
* Mann-Whitney U test						
†Fisher's exact test						

Table 5

Multivariate logistic regression analysis of factors associated with successful treatment cessation at the last visits and successful treatment cessation during the study period

Dependent variable; successful cessation at the last visits (27 eyes)				
Independent variable	Odds ratio	Lower 95% confident interval	Upper 95% confident interval	<i>P</i> value
Disease activity at 12 weeks, absent	6.650	1.750	25.300	0.005
Number of recurrences	0.377	0.235	0.607	< 0.001
Dependent variable; successful treatment cessation during the study period (56 eyes)				
Independent variable	Odds ratio	Lower 95% confident interval	Upper 95% confident interval	<i>P</i> value
Disease activity at 12 weeks, absent	2.530	0.936	6.860	0.067
Number of recurrences	0.688	0.545	0.868	0.002
Using aflibercept in the loading phase	3.970	1.380	11.400	0.011
PED at baseline, present	0.291	0.106	0.803	0.017
In the upper model, absence of disease activity at 12 weeks and the recurrence number during the follow-up period were entered as independent variables to fulfill the study objectives and prevent overfitting in the regression model. The results were similar even with the inclusion of SRF presence at baseline in the regression model using the stepwise method (data not shown). Similarly, four independent variables were selected in the lower model.				
PED, pigment epithelial detachment.				

ROC analysis with successful treatment cessation at the last visit, and recurrence number set as the objective and explanatory variables, respectively revealed an area under the curve of 0.841 (95% CI: -0.775-0.927, $p < 0.001$ against diagonal). The curve was closest to the upper-left corner with a sensitivity and specificity of 0.718 and 0.778, respectively, with a cut-off value for the recurrence number of ≤ 1 (Fig. 3).

The central retinal thickness was $390 \pm 188.1 \mu\text{m}$ at baseline, which significantly decreased to $269.5 \pm 135.2 \mu\text{m}$ at 12 weeks ($p < 0.001$). This significant decrease was maintained at year 1 and the last visit ($p < 0.01$ for both, Table 2).

Serious ocular adverse events included cataract progression, intraocular pressure elevation $> 30 \text{ mmHg}$, and retinal pigment epithelial tear in 27 (26.7%), 2 (2.0 %), and 1 (1.0%) eye, respectively. Serious systemic adverse events included death, out-of-hospital cardiac arrest, arteriothrombotic events, and progressive dementia in 1 (1.0 %), 1 (1.0 %), 2 (2.0 %), and 4 (4.0 %) patients, respectively.

Discussion

We retrospectively examined the visual outcome in patients with exudative AMD and PN who were treated with anti-VEGF agents using the TAE regimen with a mean follow-up period of 4 years. There have been numerous reports regarding the outcomes of anti-VEGF therapy using the TAE regimen; however, the long-term outcomes remain unclear^{19,23}. The mean BCVA at year 1 was 0.37 logMAR (66.5 letters) with a mean gain of 2.7 letters. Although the visual gain was smaller than previously reported values^{11,14,15,16,19,20,23}, the absolute BCVA was comparable. Change in the BCVA at the last visit was -0.7 letters, which was worse than that reported by Train et al. and Berg et al. (+ 3.6 letters and + 7.4 letters,

respectively)^{19,23}. However, the absolute BCVA in our study was 0.43 logMAR (62.3 letters), which was comparable to those at year 4 in the previous reports (63.4 letters and 63.5 letters, respectively). Contrastingly, in our study, 53.5% of the eyes had good ($\geq 20/40$) final BCVA at the last visit, which was slightly better than that in the previous study (45.2%)²³.

Given that this was a retrospective study conducted at a common clinical practice, there were some minor protocol deviations, including one-week injection delays from the planned days. This could cause multiple recurrences, which leads to a less favorable visual outcome. Another reason for the lower improvement in our study may be our inclusion of eyes with better baseline BCVA than those in previous studies. In our study, 58 (57.4%) and 29 (28.7%) eyes had good ($\geq 20/40$) and excellent ($\geq 20/25$) baseline BCVA, respectively, with a mean BCVA of 63 letters. This could impede visual improvement due to the ceiling effect; moreover, as previously reported, these eyes could be vulnerable to vision loss^{13,32}. Furthermore, previous studies excluded eyes requiring additional treatment other than anti-VEGF treatment^{19,23}; however, we included these cases to represent real-world treatment outcomes of exudative AMD in common clinical practice. These may have contributed to the inconsistencies in the visual outcome.

There were no between-disease differences in visual outcomes. Matsumoto et al. evaluated the efficacy of intravitreal aflibercept using the TAE regimen in Japanese patients with type 1 neovascular AMD and PN and reported similar treatment effectiveness in both diseases²¹, which is consistent with our results. A randomized study on monthly or PRN regimens reported that patients with RAP lesions showed favorable visual outcome in the first year³³. Conversely, another study using the TAE regimen reported that RAP lesion was a predictive factor of poor visual outcome at year 2¹⁷. The present study could not clarify this issue since we only included 9 eyes with RAP lesions. There is a need for future studies with larger sample sizes and longer follow-up periods.

The number of treatments over time in our study was similar to that in a previous report²³. Compared with the monthly injection regimen, the TAE regimen reduces the injection number with comparable visual improvement^{15,20}. However, the TAE regimen may involve overtreatment for a certain proportion of eyes. Previous studies have shown that 20–34% of patients needed no additional injections after the loading phase during the first year^{34,35,36}. Similarly, in our study, 10 (25.6%) eyes treated with deferred TAE did not require additional injections after the three loading injections until the last visit, with a median follow-up period of 165 weeks. Recent studies have introduced more individually customized regimens with favorable visual outcomes and reduced injection numbers^{36,37}. These regimens involved initial monthly treatment until CNV stabilization with subsequent observation without treatment. Treatment was initiated after recurrence with the treatment interval being determined based on the disease recurrence interval. These regimens may allow overtreatment prevention, as well as reduction of the treatment burden, and possible adverse events.

Another effective measure for reducing the patients' burden may be treatment cessation after stabilization following continuous treatment. Recent studies have reported successful treatment cessation in 14.8%–26.0% of patients after continuous treatment^{23,38,39}. Similarly, in our study, approximately a quarter of all eyes were treatment-free at the last visit, with a median treatment-free period of 126 weeks.

Factors associated with frequent injections include PED and vitreomacular adhesion^{40,41,42,43} at baseline, as well as the use of ranibizumab rather than aflibercept²⁴. The correlation between SRF at baseline and treatment frequency remains unclear^{20,40,41,43,44}. In our study, the presence of SRF at baseline was associated with frequent injections. Moreover, the absence of PED at baseline and treatment initiation with aflibercept rather than ranibizumab were associated with successful treatment cessation for > 16 weeks. This is consistent with previous findings. However, successful treatment cessation at the last visit was not associated with the aforementioned characteristics; rather, it was associated with the absence of disease activity at 12 weeks and fewer recurrences. Intraocular VEGF levels can vary among patients with phenotypically similar disease states⁴⁵. Therefore, based on only baseline phenotypical characteristics, it is difficult to

predict successful treatment cessation with VEGF suppression. Instead, clinicians can predict the long-term treatment cessation based on the early treatment response and the recurrence number.

In our study, ROC analysis revealed that the optimal cut-off value of the recurrence number for predicting successful treatment cessation at the last visits was 1. This suggests that eyes with ≥ 2 recurrences are unlikely to show long-term successful treatment cessation. Almost all eyes that achieved successful treatment cessation at the last visit had ≤ 3 recurrences during the follow-up period. This information may help physicians answer common questions from patients regarding whether they could achieve successful treatment cessation.

Limitations

This study has several limitations. First, this was a retrospective study with a relatively small sample size. Other limitations include the use of two different anti-VEGF agents, maximum treatment intervals, and treatment regimens. This could limit the robustness of our findings. However, such heterogeneity is common in clinical practice for updating and providing better medical care, especially for relatively long-term follow-up periods. Moreover, we believe that it reflects actual conditions in common clinical practice.

Conclusions

In conclusion, we reported the outcomes of anti-VEGF treatment for exudative AMD and PN using the TAE regimen. Visual acuity was maintained during the mean follow-up period of 4 years. Clinicians may expect treatment cessation in patients with good early response to treatment and fewer recurrences. This information may help clinicians provide more individualized anti-VEGF treatment and reduce the patients' burden.

Declarations

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Author Contributions

T.K. designed the study; T.K., J.M., and A.H. collected the data; T.K. and K.A. analyzed the data; T.K., J.M., A.H., K.A., M.S., and H.I. interpreted the data; T.K. wrote the original manuscript; and T.K., J.M., A.H., K.A., M.S., and H.I. revised the manuscript. All authors approved the final version of the manuscript.

Competing interests:

The authors declare no competing interests.

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Figures

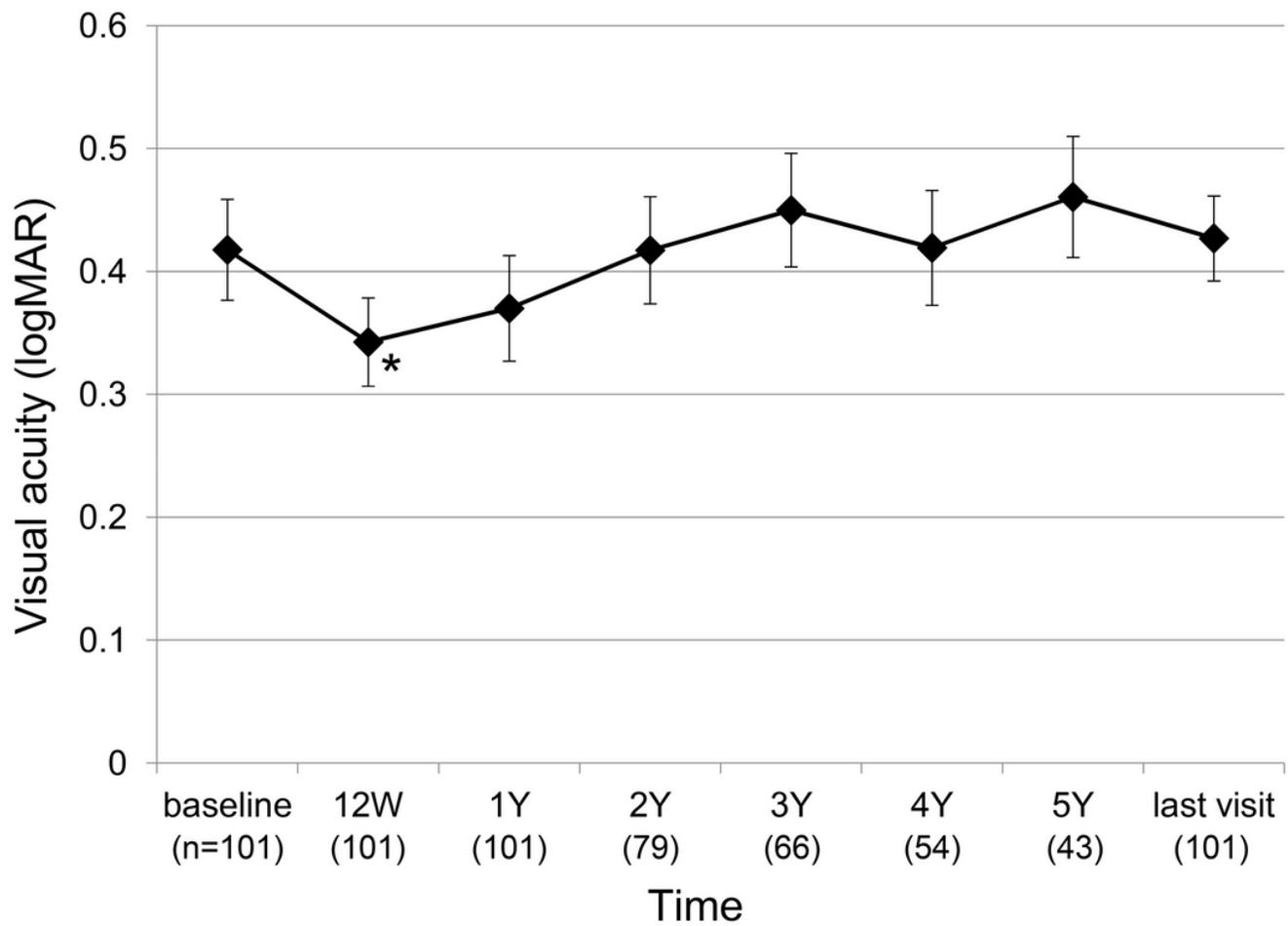


Figure 1

Temporal changes in the best-corrected visual acuity. Compared with the baseline BCVA, the BCVA significantly improved at 12 weeks ($p=0.004$), but not at year 1 ($p = 0.067$) and the last visit ($p = 1.000$). Error bars indicate standard errors.

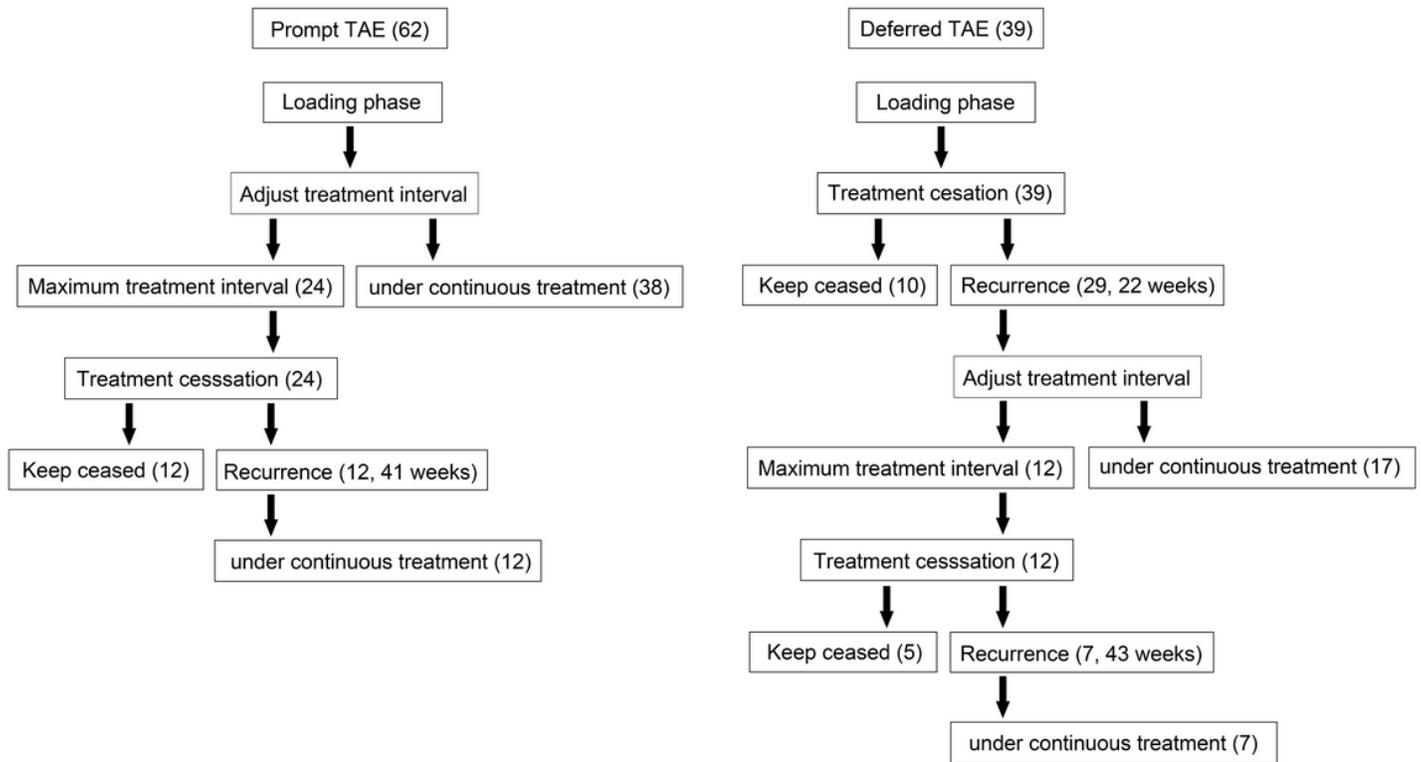


Figure 2

Summary of the treatment course using two TAE regimens. The numbers of eyes are shown in parentheses. Regarding eyes with post-cessation recurrences, the median treatment-free periods between treatment cessation and recurrences are shown in parentheses next to the number of eyes. Among 62 eyes treated with the prompt TAE regimen, 24 (39.3%) eyes achieved treatment cessation. Among them, 12 (50.0%) eyes were treatment-free at the last visit, with a median treatment-free period of 53 weeks. Twelve (50.0%) eyes had recurrences after a median treatment-free period of 41 weeks. Among the 39 eyes treated with the deferred TAE regimen, 10 (25.6%) eyes lacked additional injections after the three loading injections until the last visit, with a median treatment-free period of 165 weeks. Twelve (30.7%) eyes reached treatment cessation after TAE followed by recurrence. Among them, 5 eyes were under treatment cessation at the last visit, with a median treatment-free period of 166 weeks. TAE, treat-and-extend

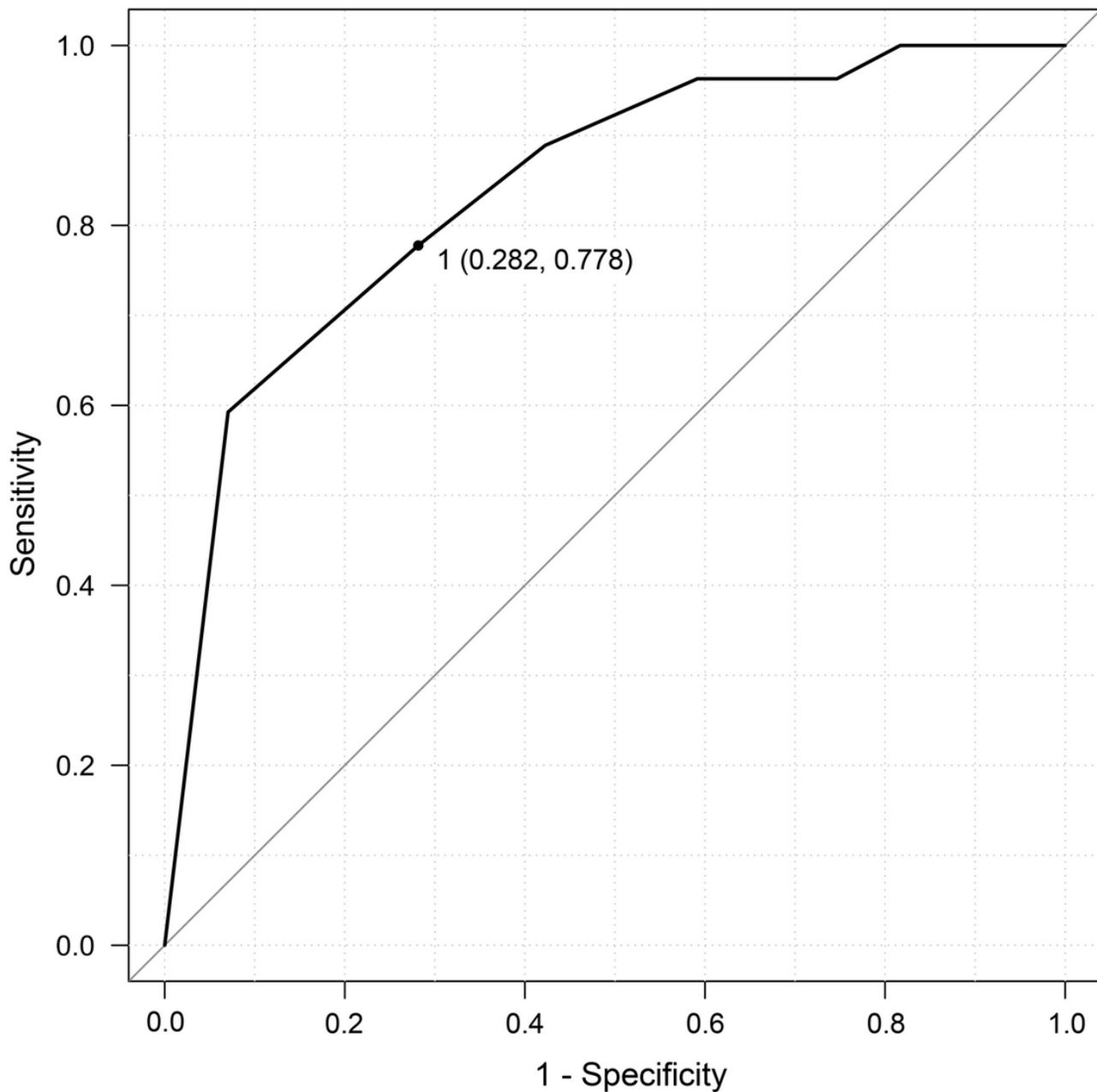


Figure 3

ROC curve for predicting successful treatment cessation at the last visits. ROC analysis showed that the area under the curve was 0.841. The curve was closest to the upper-left corner with a sensitivity and specificity of 0.718 and 0.778, respectively, when the cut-off value for the recurrence number was set to ≤ 1 .

Supplementary Files

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