• Clinical Research •

Efficacy and safety of intravitreal conbercept treat-and-extend regimens in neovascular age-related macular degeneration

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Abstract

● **AIM:** To evaluate and compare the efficacy and safety of two treat-and-extend (T&E) regimens (2- and 4-week intervals, Δ2w and Δ4w) of intravitreal conbercept injections in patients with neovascular age-related macular degeneration (nAMD).

● **METHODS:** This 24-month prospective randomized controlled trial at the First Affiliated Hospital of Chongqing Medical University included patients with nAMD. Eyes were randomly assigned (1:1) to receive intravitreal conbercept (0.5 mg) with T&E regimens using 2- or 4-week interval adjustments (Δ2w and Δ4w groups). Key outcomes included best-corrected visual acuity (BCVA), central retinal thickness (CRT), subfoveal choroidal thickness (SFCT), superficial vascular density (SVD), deep vascular density (DVD), and large-medium vascular density (LMVD) within the 3 mm macular foveal region. The primary endpoint was the mean change in BCVA from baseline to the 2-year follow-up (noninferiority cutoff: 4 letters).

● **RESULTS:** Ultimately, 61 participants (68 eyes) completed the 2-year study. Baseline characteristics were similar between the two groups. At week 96, the mean number of injections was 11.17±1.13 in the Δ2w group (36 eyes, with the mean age of 70.42±9.31y) and 9.84±1.02 in the Δ4w group (32 eyes, with the mean age of 71.25±9.99y; *P*<0.001). The mean changes in BCVA were 5.19±6.58 and 5.91±5.51 letters (*P*=0.528), and Δ4w being noninferior to Δ2w (difference: 0.71 letters; 95%CI: -3.67 to 2.24). The mean changes in CRT were -118.97±106.97 and -134.98±128.77 μm (*P*=0.406), and the mean changes in SFCT were -30.03±17.48 and -32.55±22.73 μm (*P*=0.538), respectively. No significant intergroup differences in vascular densities were observed. Type 1 macular neovascularization had a higher baseline BCVA and required more injections than those with other macular neovascularization subtypes.

● **CONCLUSION:** Intravitreal conbercept injections administered *via* 2- and 4-week intervals show similar efficacy and safety. The reduced injection frequency in the Δ4w regimen may help lower the overall treatment burden, and individualized therapy based on nAMD subtypes may further optimize clinical outcomes.

● **KEYWORDS:** neovascular age-related macular degeneration; conbercept; treat-and-extend; subtype; noninferiority trial

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INTRODUCTION

Age-related macular degeneration (AMD) is a chronic progressive disease that primarily affects people over 55 years old. It seriously impairs central vision and impacts many daily functions like reading, driving, and recognizing people. It is associated with lower quality of life, reduced mobility, and depression[1]. Globally, the prevalence of vision impairment caused by AMD is projected to rise sharply, affecting approximately 21.34 million people worldwide by 2050[2]. Neovascular AMD (nAMD) represents 10% of cases but accounts for >90% of blindness. Angiogenesis plays a crucial role in nAMD progression; therefore, making anti-angiogenic

treatments essential[3]. Intravitreal injections of vascular endothelial growth factor (VEGF)-targeting drugs, such as ranibizumab, aflibercept, and conbercept, are essential for managing nAMD[4].

Conbercept® (Lumitin; Chengdu Kanghong Biotechnology Co., Ltd., Chengdu, China)[5] is an anti-VEGF drug that binds all VEGF-A subtypes, VEGF-B, VEGF-C, and placental growth factors, with high affinity[6]. It uniquely contains a domain of vascular endothelial growth factor receptor 2 (VEGFR-2) that increases its half-life[7-8]. The PHOENIX trial demonstrated its efficacy in improving visual outcomes in wet AMD[9]. However, an optimal treatment regimen is yet to be established.

The *pro re nata* regimen was the first widely used regimen for reducing the frequency of injections[10]. This strategy, which relies on monthly visits to monitor disease activity, has limitations due to challenges with long-term follow-up. Irregular follow-up can lead to treatment delays and worsen visual outcomes, highlighting the challenge of developing individualized regimens[6,11]. Treat-and-extend (T&E) is an individualized approach starting with monthly injections and adjusting intervals based on disease activity. T&E reduces recurrence risk while avoiding overtreatment or undertreatment[12], but the optimal regimen and maximum interval remain unclear.

The study aimed to compare the efficacy and safety of two distinct T&E regimens (2- and 4-week adjustments) for intravitreal conbercept injection in patients with nAMD, providing clinical insights for optimizing individualized treatment plans.

PARTICIPANTS AND METHODS

Ethical Approval The study adhered to the Declaration of Helsinki and was approved by the Institutional Review Board of the First Affiliated Hospital of Chongqing Medical University (approval No.20189401). Written informed consent was obtained from all participants prior to enrollment. Clinical trial registration number: NCT05539235 (retrospective registration).

Study Design This 24-month prospective study at the First Affiliated Hospital of Chongqing Medical University assessed the effects of intravitreal conbercept (0.5 mg) using T&E regimens with 2- and 4-week intervals (2- and 4-week adjustments, referred to as Δ2w and Δ4w groups, respectively). This trial was initially scheduled from November 12, 2018, to January 31, 2021, but was extended to June 30, 2024, due to the COVID-19 pandemic.

Sample Size Determination The primary endpoint of this randomized trial was the mean change in best-corrected visual acuity (BCVA). Preliminary results at 24wk showed mean changes in BCVA of 7.28±7.75 and 2.15±3.83 letters for Δ2w and Δ4w groups, respectively. With α=0.05 and 90% power, the sample size was calculated using the following formula:

$$n = \frac{2\left(z_\alpha + z_\beta\right)^2 \times \sigma^2}{\delta^2}$$

After accounting for a 15% dropout rate, a minimum sample size of 27 patients per group at baseline was inflated to 32 eyes per group, yielding a required total sample size of at least 64 eyes.

Examination and Enrollment This prospective study enrolled patients aged ≥50y with nAMD. Eligible eyes had a BCVA of 20–70 Early Treatment Diabetic Retinopathy Study (ETDRS) letters and confirmed subretinal neovascularization verified by fundus fluorescein angiography (FFA) and indocyanine green angiography (ICGA). Eligible participants were randomly assigned to either the Δ2w or Δ4w treatment group. No participants received prior anti-VEGF or ocular treatment.

Exclusion criteria included subretinal scarring, hypersensitivity to mydriatic agents, prior intraocular surgery, concomitant retinal diseases (*e.g.*, diabetic retinopathy), significant media opacity, systemic conditions (*e.g.*, renal and cardiovascular disorders), glaucoma, pregnancy, and poor treatment compliance.

The BCVA was recorded using the ETDRS chart. Optical coherence tomography (OCT) and optical coherence tomography angiography (OCTA) were performed using the CIRRUS HD-OCT 5000 with the pupil dilated to approximately 7 mm. FFA and ICGA examinations were acquired using the Heidelberg Spectralis Retina Angiograph (HRA) system.

BCVA, central retinal thickness (CRT), subfoveal choroidal thickness (SFCT), superficial retinal vascular density (SVD), deep retinal vascular density (DVD), and large-medium vascular density (LMVD) within 3 mm of the macular fovea were measured in all eligible patients before and at 12, 24, 48, 72, and 96wk after treatment. Although multifocal electroretinogram was originally planned according to the study protocol as an additional functional outcome measure, it was not included in the final analysis due to pandemic-related logistical limitations and incomplete follow-up data collection. According to the default segmentation algorithm of the OCTA system, SVD was defined as the region from the internal limiting membrane to the inner plexiform layer, whereas DVD covered the area from the inner plexiform layer to the outer plexiform layer. All measurements were analyzed using the built-in OCTA software. Automated segmentation results were reviewed and manually corrected by a senior ophthalmologist when necessary.

Treatment Both groups received standardized intravitreal conbercept injections (0.5 mg) at 2- and 4-week intervals, respectively. Initially, both groups received monthly injections

Table 1 Criteria for shortening, maintaining, or extending the IVT-conbercept injection interval

Criteria for shortening the treatment interval (Each eye included in the study only needs to meet one of the following conditions)
1. Loss of ≥ 5 ETDRS letters from the previous visit
2. New fluid intra- or subretinal fluid on OCT
3. New macular hemorrhage
4. New-onset neovascularization
Criteria for maintaining the treatment interval (Each eye included in the study needs to meet all of the following conditions)
1. Loss of ≤5 ETDRS letters from the previous visit
2. No new macular hemorrhage or neovascularization was observed
3. Persistent fluid with unchanged from the previous visit
Criteria for extending the treatment interval (Each eye included in the study needs to meet all of the following conditions)
1. Loss of ≤5 ETDRS letters from the previous visit
2. The lesion exhibited no signs of exudative activity such as re-bleeding and edema[13]

IVT: Intravitreal; OCT: Optical coherence tomography; ETDRS: Early Treatment Diabetic Retinopathy Study.

for 3mo. Subsequent to the third injection, treatment intervals were adjusted based on BCVA, funduscopic examination, and OCT results. The criteria for shortening, maintaining, or extending the injection interval are shown in Table 1[13]. The allowable minimum and maximum injection intervals were 4 and 16wk, respectively.

Follow-up All participants completed a 96-week outpatient follow-up. Key observational indicators, including BCVA, CRT, SFCT, SVD, DVD, LMVD, and intraocular pressure, as well as the total number of anti-VEGF injections, were recorded at baseline and at 12, 24, 48, 72, and 96wk post-treatment. Fundus lesions were evaluated at baseline and all follow-up time points. Macular neovascularization (MNV) was classified based on baseline OCTA, and neovascular regression was evaluated at each visit. Ocular and systemic complications, including subconjunctival hemorrhage, endophthalmitis, vitreous hemorrhage, and retinal detachment, were closely monitored throughout the study period.

Masking Randomization was performed at the eye level. Researcher Ding XH allocated eligible eyes to the Δ2w and Δ4w groups using a lottery-based randomization strategy, achieving a nearly balanced group distribution. All clinical and imaging assessments were performed by independent masked investigators. Specifically, an experienced ophthalmologist (Ju H) recorded BCVA, CRT, SFCT, SVD, DVD, and LMVD. Another independent ophthalmologist (Wang X) evaluated and classified OCT, OCTA, FFA, and ICGA images. Ju H and Wang X were masked to treatment allocation throughout the study to minimize assessment bias.

Statistical Analysis The clinical noninferiority margin was set at four ETDRS letters[14]. The primary endpoint was the mean change in BCVA from baseline to 2y. All statistical analyses were performed using SPSS version 22.0. Considering the non-independence of bilateral ocular data from the same participant, linear mixed models were used for continuous variables and generalized estimating equations for categorical variables to adjust for inter-eye correlation. Continuous variables were presented as mean±standard deviation, and categorical variables were described as frequencies and percentages. *P* value <0.05 was considered statistically significant.

RESULTS

Comparison of General Characteristics A total of 76 patients (89 eyes) were enrolled in this study. Of these, 10 patients (13 eyes) were excluded due to protocol non-compliance, and 5 patients (8 eyes) were excluded owing to incomplete follow-up. Ultimately, 61 participants (68 eyes) completed the 2-year study. Baseline characteristics were comparable between the two groups (Table 2).

Changes in the Observational Indicators Before and After Treatment

BCVA At the 96-week follow-up, both groups demonstrated significant improvements in BCVA (Δ2w group: 5.19±6.58 letters; Δ4w group: 5.91±5.51 letters). However, the between-group difference [0.71 letters; 95% confidence interval (CI): -3.67 to 2.24] was not statistically significant (*P*=0.528; Table 3, Figure 1A). The lower limit of the two-sided 95%CI fell within the 4-letter noninferiority margin, indicating that the Δ4w group was noninferior to the Δ2w group (Figure 2). The mean baseline BCVA for type 1 MNV (58.12±17.05 letters) was significantly higher than other types (*P*<0.001; Figure 3A). At week 96, no significant differences in BCVA changes were noted across MNV types (*P*=0.345; Table 4).

CRT In both groups, CRT decreased significantly from baseline to week 96 (Δ2w group: -118.97±106.97 μm, Δ4w group: -134.98±128.77 μm), with no significant difference between the two groups (*P*=0.406; Table 3, Figure 1B). The mean baseline CRT for type 1 MNV (329.55±114.80 μm) was significantly lower than the other types (*P*<0.001; Figure 3B). At week 96, CRT changes in type 1 were lower than those in type 3 (*P*=0.013; Table 4).

Table 2 Baseline characteristics

Variables	Δ2w (*n*=36 eyes)	Δ4w (*n*=32 eyes)	*P*
Sex, *n* (%)			0.774
Eyes from male patients	19 (52.8)	18 (56.3)	
Eyes from female patients	17 (47.2)	14 (43.7)	
Age (y)			
Mean±SD	70.42±9.31	71.25±9.99	0.723
Median (range)	71 (51–88)	70.5 (53–91)	
BCVA baseline (letters)			
Mean±SD	49.31±17.17	47.06±17.80	0.599
Median (range)	49 (19–83)	47 (18–80)	
CRT baseline (μm)			
Mean±SD	419.77±176.06	440.68±170.54	0.507
Median (range)	375.49 (200.59–830.51)	410.99 (218.71–826.09)	
SFCT (μm)			
Mean±SD	253.70±47.33	248.24±45.82	0.487
Median (range)	249.36 (139.25–334.53)	239.14 (155.36–346.78.43)	
SVD (%)			
Mean±SD	39.23±4.62	40.39±4.01	0.422
Median (range)	39.25 (30.66-49.66)	40.23 (31.73–47.08)	
DVD (%)			
Mean±SD	44.51±3.97	45.62±4.12	0.408
Median (range)	45.00 (36.48–52.20)	44.93 (37.40–54.00)	
LMVD (%)			
Mean±SD	60.52±6.08	61.48±5.34	0.542
Median (range)	61.55 (49.18–69.3)	61.55 (51.49–71.11)	
MNV classification, *n* (%)			0.313
1	15 (41.67)	10 (31.25)	
2	16 (44.44)	16 (50.00)	
3	3 (8.30)	3 (9.38)	
Mixed	2 (5.56)	3 (9.38)	
Frequency of injections			
Mean±SD	11.17±1.13	9.84±1.02	<0.001
Median (range)	11 (10–14)	9.5 (9–12)	

SD: Standard deviation; BCVA: Best-corrected visual acuity; CRT: Central retinal thickness; SFCT: Subfoveal choroidal thickness; SVD: Superficial vessel density; DVD: Deep vessel density; LMVD: Large-medium vascular density; MNV: Macular neovascularization.

SFCT After 96wk, the SFCT significantly decreased in both groups (Δ2w group: -30.03±17.48 μm, Δ4w group: -32.55±22.73 μm), with no significant difference between the two groups (*P*=0.538; Table 3, Figure 1C). The mean baseline SFCT for type 1 MNV (275.36±36.99 μm) was significantly higher than that of the other MNV types (*P*=0.013; Figure 3C). At week 96, changes in SFCT among the four MNV types showed no significant differences (*P*=0.336; Table 4).

SVD According to the 96-week follow-up results, SVD showed no significant change from baseline in both groups but displayed a decreasing trend (Δ2w group: -1.45%±0.89%, Δ4w group: -1.87%±1.44%), with no statistically significant difference between the two groups (*P*=0.149; Table 3, Figure 1D). The mean baseline SVD for type 1 MNV (37.80%±3.34%) was significantly lower than that of the other MNV types (*P*=0.015; Figure 3D). At week 96, no significant differences in SVD changes were noted across MNV types (*P*=0.853; Table 4).

DVD The DVD data up to the 96-week follow-up demonstrated a general decline from baseline in both groups (Δ2w group: -1.65%±0.93%, Δ4w group: -1.87%±1.68%), with no significant difference between the two groups (*P*=0.487; Table 3, Figure 1E). The mean baseline DVD for type 1 MNV (42.51±2.56%) was significantly lower than that of the other MNV types (*P*<0.001, Figure 3E). At week 96, no significant difference in DVD change from baseline was

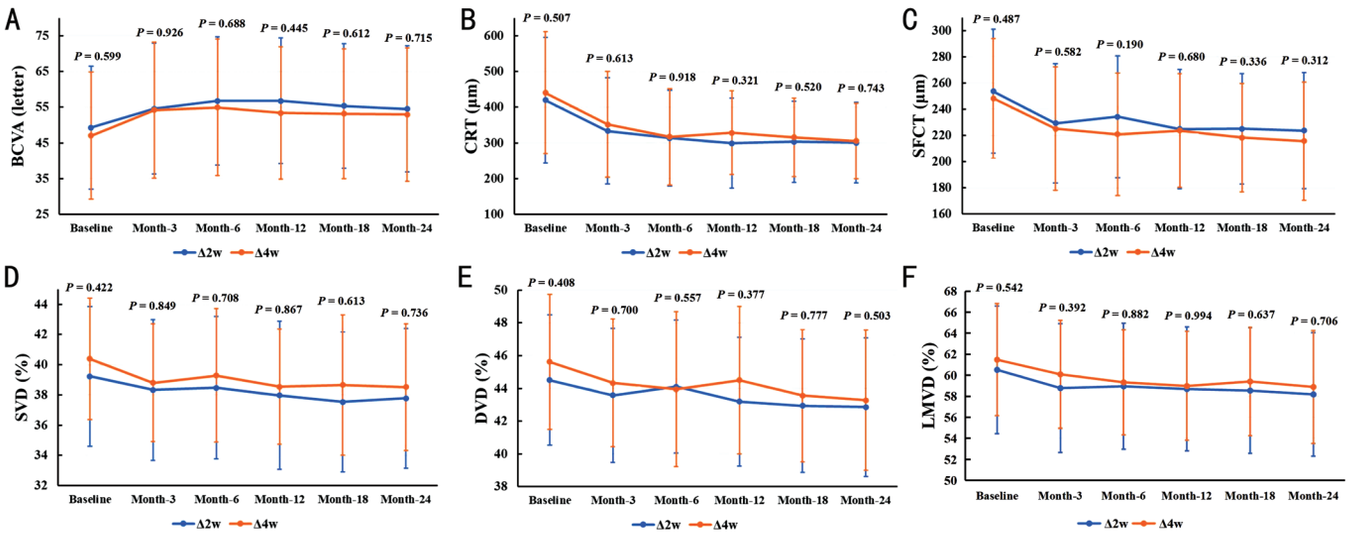


Figure 1 Changes in key ocular parameters from baseline to 24-month follow-up in the two groups A: Mean BCVA (letter); B: Mean CRT (μm); C: Mean SFCT (μm); D: Mean SVD (%); E: Mean DVD (%); F: Mean LMVD (%). BCVA: Best-corrected visual acuity; CRT: Central retinal thickness; SFCT: Subfoveal choroidal thickness; SVD: Superficial vascular density; DVD: Deep vascular density; LMVD: Large-medium vascular density.

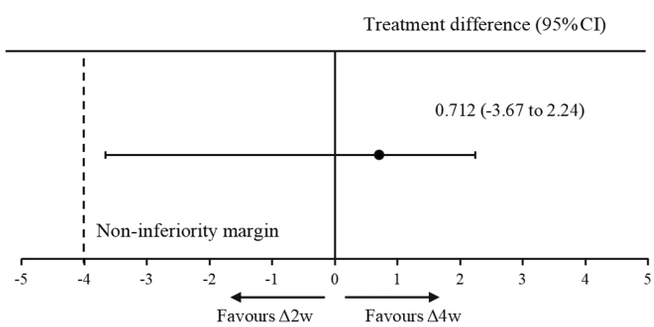


Figure 2 Absolute between-group difference in BCVA improvement at 96wk (95%CI) BCVA: Best-corrected visual acuity; CI: Confidence interval.

observed between the four MNV types (P=0.463; Table 4).

LMVD The LMVD data at 96wk showed no significant changes from baseline in either group, despite a general decline (Δ2w group: -2.34%±0.76%, Δ4w group: -2.59%±1.96%). There was no statistically significant difference between the two groups (P=0.198; Table 3, Figure 1F). The mean baseline LMVD for type 1 MNV (58.36%±5.23%) was significantly lower than that of the other MNV types (P=0.017; Figure 3F). At week 96, no significant differences in LMVD changes from baseline were found among the four MNV types (P=0.346; Table 4).

Number of Injections During the 96-week follow-up, the Δ2w group required more injections (mean: 11.17±1.13) than the Δ4w group (mean: 9.84±1.02, P<0.001; Table 2, Figure 4A). Overall, 78% of eyes in the Δ2w group achieved intervals of ≥16wk, whereas all eyes in the Δ4w group reached treatment intervals of ≥16wk (Figure 4C and 4D). Type 1 MNV required significantly more injections (11.16±1.43) than type 2 MNV (9.93±0.90; P=0.001, Figure 4B).

Correlation of BCVA with the Observed Indicators The changes in CRT, SFCT, SVD, DVD, and LMVD at the last follow-up compared with the baseline data were correlated with changes in BCVA. This revealed that CRT, SFCT, DVD, and LMVD had a significant negative correlation with BCVA (P<0.05; Table 5).

Postoperative Complications This study found four cases of subconjunctival hemorrhage: one in the Δ2w group and three in the Δ4w group, all resolving spontaneously without specific treatment. No postoperative complications, such as glaucoma, endophthalmitis, or retinal detachment, occurred.

DISCUSSION

The T&E regimen, a personalized approach for nAMD patients with variable retreatment needs, has proven effectiveness in improving vision and reducing treatment burden[15]. This prospective study provides novel real-world evidence demonstrating that intravitreal conbercept in a T&E regimen is effective for nAMD. The results also showed that both 2- and 4-week intervals had similar efficacy and safety, with fewer injections in the Δ4w group.

In this study, both treatment regimens effectively improved visual and anatomical outcomes in nAMD patients at 96wk (ΔBCVA: 5.19±6.58 letters and CRT: -118.97±106.97 μm in the Δ2w group; ΔBCVA: 5.91±5.51 letters and CRT: -134.98±128.77 μm in the Δ4w group). The change in CRT was significantly negatively correlated with BCVA improvement (r=-0.428). No significant differences were found between the two groups at any follow-up point (12, 24, 48, 72wk), which was consistent with previous large-scale anti-VEGF studies[16]. Noninferiority testing showed that the Δ4w regimen was noninferior to Δ2w in visual prognosis, offering better cost-effectiveness without compromising efficacy. In this study, the mean number of injections was 11.17±1.13 in the Δ2w group and 9.84±1.02 in the Δ4w group. However,

Table 3 Comparison of changes in BCVA letter score, CRT, SFCT, SVD, DVD, and LMVD between baseline and month 24 in the Δ2w and Δ4w groups

Variables	Month-3			Month-6			Month-12			Month-18			Month-24		
	Δ2w	Δ4w	*P*	Δ2w	Δ4w	*P*	Δ2w	Δ4w	*P*	Δ2w	Δ4w	*P*	Δ2w	Δ4w	*P*
ΔBCVA (letters)															
Mean±SD	5.31±7.99	7.13±7.36	0.290	7.44±7.63	7.88±7.05	0.811	7.50±7.03	6.38±6.39	0.495	6.08±6.72	6.13±5.59	0.978	5.19±6.58	5.91±5.51	0.528
Median (range)	6.00 (-15 to 25)	8.50 (-14 to 21)		9.00 (-11 to 28)	8.50 (-10 to 21)		8.50 (-6 to 27)	7.00 (-9 to 20)		6.00 (-5 to 25)	6.00 (-6 to 17)		5.00 (-6 to 24)	6.00 (-5 to 16)	
ΔCRT (μm)															
Mean±SD	-85.96±102.12	-88.49±95.96	0.726	-105.88±102.61	-123.43±112.61	0.313	-120.46±115.61	-111.86±110.74	0.841	-116.04±111.37	-124.94±120.64	0.570	-118.97±106.97	-134.98±128.77	0.406
Median (range)	-89.10 (-231.10 to 120.75)	-113.38 (-236.87 to 163.49)		-103.84 (-254.35 to 130.53)	-134.40 (-345.00 to 105.64)		-115.30 (-297.26 to 79.73)	-112.94 (-344.91 to 87.07)		-91.89 (-312.26 to 73.95)	-127.31 (-365.61 to 85.56)		-101.01 (-322.10 to 55.17)	-137.58 (-390.04 to 75.81)	
ΔSFCT (μm)															
Mean±SD	-24.47±23.29	-23.05±20.56	0.821	-19.42±20.28	-27.35±20.89	0.097	-28.86±19.81	-24.44±24.06	0.921	-28.56±20.11	-29.85±25.41	0.537	-30.03±17.48	-32.55±22.73	0.538
Median (range)	-34.76 (-50.60 to 30.80)	-30.42 (-45.85 to 34.57)		-27.69 (-43.03 to 24.89)	-31.27 (-51.62 to 27.75)		-37.62 (-50.33 to 18.29)	-32.81 (-55.07 to 39.43)		-33.69 (-52.25 to 10.87)	-34.34 (-65.33 to 24.52)		-35.39 (-52.84 to 2.80)	-35.94 (-69.13 to 13.51)	
ΔSVD (%)															
Mean±SD	-0.91±0.87	-1.58±0.94	0.003	-0.76±0.54	-1.10±0.98	0.010	-1.25±0.71	-1.85±1.22	0.015	-1.69±0.91	-1.73±1.30	0.902	-1.45±0.89	-1.87±1.44	0.149
Median (range)	-1.13 (-2.33 to 1.05)	-2.02 (-2.69 to 0.45)		-0.87 (-1.61 to 0.52)	-1.62 (-2.25 to 1.03)		-1.54 (-2.45 to -0.08)	-2.12 (-3.43 to 1.33)		-1.81 (-3.05 to 0.09)	-2.05 (-3.33 to 1.18)		-1.86 (-2.72 to 0.20)	-2.45 (-3.42 to 1.56)	
ΔDVD (%)															
Mean±SD	-0.95±0.92	-1.28±1.04	0.087	-0.41±0.51	-1.69±1.10	<0.001	-1.33±0.67	-1.13±1.18	0.216	-1.57±0.70	-2.06±1.43	0.068	-1.65±0.93	-1.87±1.68	0.487
Median (range)	-1.19 (-2.44 to 0.95)	-1.69 (-2.29 to 1.01)		-0.50 (1.35 to 0.79)	-1.94 (-2.93 to 1.25)		-1.27 (-2.48 to 0.46)	-1.44 (-2.70 to 1.56)		-1.76 (-2.73 to 0.02)	-2.54 (-4.01 to 1.37)		-1.78 (-3.21 to 0.41)	-2.53 (-3.69 to 2.48)	
ΔLMVD (%)															
Mean±SD	-1.75±0.63	-1.38±1.16	0.110	-1.58±0.55	-2.15±1.71	0.062	-1.83±0.85	-2.50±1.83	0.033	-1.98±0.87	-2.07±1.92	0.386	-2.34±0.76	-2.59±1.96	0.198
Median (range)	-1.89 (-2.63 to 0.39)	-1.94 (-2.46 to 1.75)		-1.67 (-2.40 to 0.26)	-2.78 (-4.27 to 2.50)		-1.87 (-3.47 to 0.22)	-3.01 (-4.80 to 2.20)		-2.03 (-3.37 to 0.05)	-2.72 (-4.03 to 2.87)		-2.55 (-3.57 to 0.22)	-3.29 (-4.47 to 2.06)	

Δ indicates the change of each parameter from baseline. BCVA: Best-corrected visual acuity; CRT: Central retinal thickness; SFCT: Subfoveal choroidal thickness; SVD: Superficial vascular density; DVD: Deep vascular density; LMVD: Large-medium vascular density; SD: Standard deviation.

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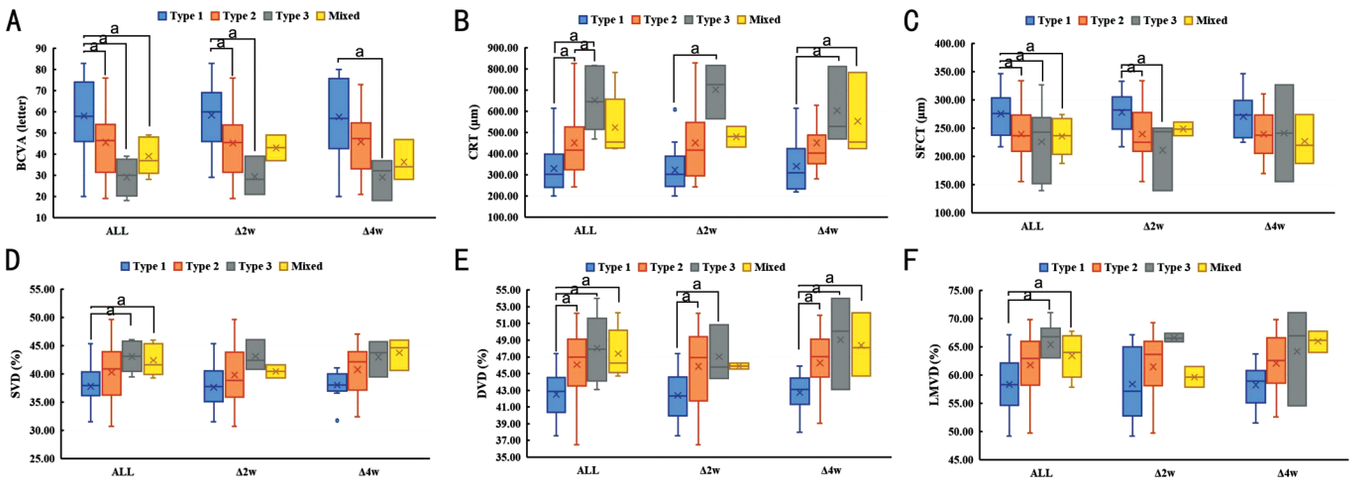


Figure 3 Baseline ocular parameters across four MNV subtypes A: BCVA (letter); B: CRT (μm); C: SFCT (μm); D: SVD (%); E: DVD (%); F: LMVD (%). [a]*P*<0.05. BCVA: Best-corrected visual acuity; CRT: Central retinal thickness; SFCT: Subfoveal choroidal thickness; SVD: Superficial vascular density; DVD: Deep vascular density; LMVD: Large-medium vascular density; MNV: Macular neovascularization.

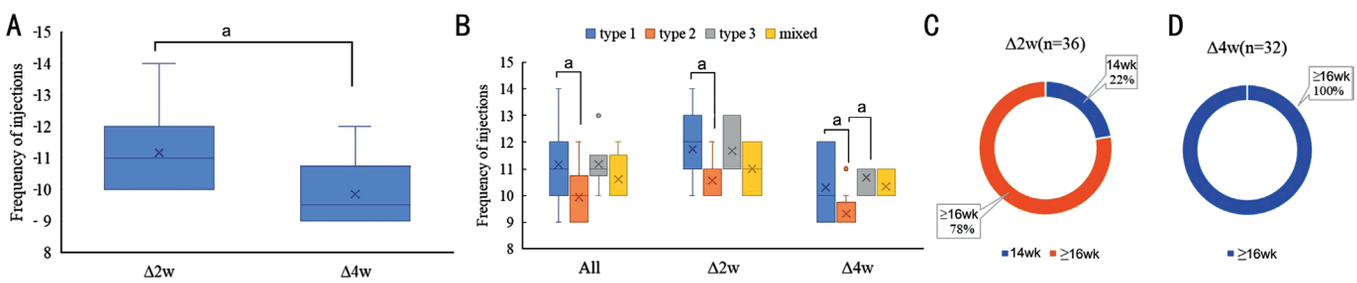


Figure 4 Injection frequency and interval analysis in two groups and four types of MNV A: Frequency of injections of two groups; B: Frequency of injections of four types of MNV; C: The last injection interval of Δ2w before month 24; D: The last injection interval of Δ4w before month 24. [a]*P*<0.05. MNV: Macular neovascularization.

the ALTAIR study found no significant difference in injection numbers between the two aflibercept T&E regimens[16]. The observed difference may be due to baseline visual acuity and MNV type. In this study, the baseline BCVA was 49.31 and 47.06 letters, with type 2 MNV comprising 44% and 50% of the total cases in the Δ2w and Δ4w groups, respectively. In contrast, the ALTAIR study had higher baseline BCVA (54.8 and 55.3 letters) and a lower proportion of type 2 MNV (28.5% and 34.1%). Poor initial visual acuity and type 2 MNV are risk factors for scarring[17-18]. Furthermore, frequent drug injections after scarring did not improve vision[19]. This study likely had a higher proportion of participants with irreversible fundus damage and stable visual acuity compared to the ALTAIR study, with a longer follow-up duration. Further research is needed to investigate the relationship between injection frequency and T&E regimens with treatment intervals.

At 96wk, 88.24% (60/68) of eyes reached a 16-week interval for the last injection, significantly higher than the 26.9%–46.0% in other T&E studies using ranibizumab and aflibercept[16,20]. The duration of VEGF inhibition is influenced by the drug's properties. Ranibizumab is a recombinant humanized monoclonal antibody fragment that neutralizes all forms of VEGF-A. Conbercept, like aflibercept, is a recombinant fusion protein with greater VEGF binding affinity than ranibizumab[7,21]. Conbercept has a unique structural domain 4 of VEGFR-2 compared with aflibercept, which increases its affinity toward VEGF and decreases extracellular matrix adhesion, potentially enhancing VEGF binding and prolonging its half-life[22]. Previous studies have shown that aflibercept has a half-life of at least 9d in the aqueous humor[23]. The duration of VEGF-A inhibition also varies between patients[24]. In this study, the majority of patients had type 2 MNV (47.05%, *n*=68), which was linked to better therapeutic response and fewer injections[25]. Poor initial visual acuity and type 2 MNV likely contributed to the high proportion achieving a 16-week injection interval.

The choroid accounts for over 70% of ocular blood flow, supplying oxygen, nutrients, and waste elimination, particularly for the foveal avascular zone[26]. While retinal pigment epithelium (RPE) and Bruch's membrane are well-studied, the choroid's role in AMD pathogenesis deserves further attention. Krytkowska *et al*[27] conducted a study involving 179 patients with wet AMD and 121 healthy participants as the control. They found increased choroidal thickness and volume under

Table 4 Group analysis based on MNV classification

Variables	Δ2w						Δ4w						All					
	Overall	1	2	3	Mixed	*P*	Overall	1	2	3	Mixed	*P*	Overall	1	2	3	Mixed	*P*
n	36	15	16	3	2		32	10	16	3	3		68	25	32	6	5	
ΔBCVA (letters)	5.19±6.58	4.60±6.18	6.81±7.39	-0.33±3.79	5.00±1.41	0.372	5.91±5.51	5.70±6.43	6.63±5.52	6.00±1.00	2.67±5.86	0.742	5.53±6.06	5.04±6.14	6.72±6.42	-2.83±4.26	3.60±4.39	0.345
ΔCRT (μm)	-118.97±106.97	-73.39±99.09	-152.26±115.30	-134.80±42.93	-170.72±69.86	0.187	-134.98±128.77	-69.66±104.95	-159.78±128.64	223.95±62.92	-134.81±203.70	0.208	-126.51±117.11	-71.90±99.21[a]	-155.71±120.22	-179.38±68.59	-149.17±149.51	0.013
ΔSFCT (μm)	-30.03±17.49	-30.74±18.09	-31.64±16.81	-13.64±18.28	-36.39±16.44	0.396	-32.55±22.73	-35.73±27.16	-34.29±21.48	-19.19±16.08	-26.09±23.77	0.687	-31.22±20.01	-33.00±21.77	-32.97±19.02	-16.42±15.70	-30.21±19.54	0.336
ΔSVD (%)	-1.45±0.90	-1.52±0.93	-1.35±0.93	-1.33±1.10	-1.92±0.07	0.836	-1.87±1.43	-1.73±1.63	-1.83±1.47	-2.71±0.46	-1.74±1.52	0.778	-1.64±1.19	-1.60±1.23	-1.58±1.24	-2.02±1.07	-1.81±1.08	0.853
ΔDVD (%)	-1.65±0.93	-1.83±0.83	-1.71±1.00	-0.71±0.79	-1.13±0.43	0.224	-1.87±1.68	-1.40±1.94	-2.22±1.59	-1.41±2.18	-2.06±0.82	0.649	-1.75±1.33	-1.66±1.36	-1.97±1.33	-1.06±1.51	-1.69±0.80	0.463
ΔLMVD(%)	-2.34±0.76	-2.23±0.80	-2.32±0.79	-2.78±0.68	-2.69±0.01	0.647	-2.58±1.96	-2.04±2.34	-2.89±1.71	-3.42±0.50	-1.97±3.07	0.596	-2.55±1.46	-2.46±1.45	-2.15±1.56	-2.60±1.34	-2.26±2.21	0.346

BCVA: Best-corrected visual acuity; CRT: Central retinal thickness; SFCT: Subfoveal choroidal thickness; SVD: Superficial vascular density; DVD: Deep vascular density; LMVD: Large-medium vascular density; MNV: Macular neovascularization. ΔBCVA, ΔCRT, ΔSFCT, ΔSVD, ΔDVD and ΔLMVD denote the changes from baseline to month 24 in the corresponding parameters. [a]*P*<0.05 between MNV 1 and MNV 3.

Table 5 Correlation analysis of indicators before and 24mo after treatment

Variables	*r*	*P*
ΔBCVA *vs* ΔCRT	-0.428	<0.001
ΔBCVA *vs* ΔSFCT	-0.596	<0.001
ΔBCVA *vs* ΔSVD	-0.188	0.124
ΔBCVA *vs* ΔDVD	-0.251	0.039
ΔBCVA *vs* ΔLMVD	-0.574	<0.001

BCVA: Best-corrected visual acuity; CRT: Central retinal thickness; SFCT: Subfoveal choroidal thickness; SVD: Superficial vascular density; DVD: Deep vascular density; LMVD: Large-medium vascular density. Symbols prefixed with Δ indicate changes of the above parameters from baseline to month 24.

the macula, alongside a reduced choroidal vascularity index in AMD patients. Choroidal thickness, choroidal volume, and choroidal vascularity index were negatively correlated with disease stage. The increase in choroidal thickness and volume could be attributed to choroidal vasodilatation, increased blood flow, and proinflammatory and pro-edematous effects caused by elevated intraocular VEGF levels[28]. This study followed wet AMD patients and found that SFCT decreased after anti-VEGF treatment, with changes in SFCT negatively correlated with BCVA. These findings are consistent with those of previous studies[29]. The study further demonstrated that SVD, DVD, and LMVD decreased after anti-VEGF treatment in wet AMD patients, with DVD and LMVD changes negatively correlated with BCVA. These alterations suggest changes in choroidal vascular permeability, affecting medium- and large-sized choroidal vessels.

This study found variations in observational indexes and injection frequency across nAMD subtypes. Type 1 MNV had higher baseline BCVA, thinner CRT, thicker SFCT, and smaller DVD, requiring more injections. Type 2 MNV had the lowest BCVA and fewest injections, while type 3 MNV had the lowest BCVA and a higher injection frequency. Mixed MNV had intermediate baseline BCVA and injection needs. Several explanations for these findings are possible.

The first may be related to the anatomical features of neovascularization for each subtype. Type 1 MNV originates from choroidal capillaries and remains sub-RPE, type 2 crosses the RPE into the subretinal space, type 3 originates from the deep retinal capillary plexus and can rupture the RPE, while mixed MNV displays characteristics of multiple lesion types[30]. These variations affect disease progression and symptom severity[31]. Deeper anatomical locations increase the difficulty of anti-VEGF drugs reaching the lesions[32]; requiring more frequent injections to maintain efficacy. Consistent with this study, a U.S. retrospective trial found type 1 MNV patients, with a baseline BCVA of logMAR 0.542, had a better visual prognosis but required more injections (mean: 52.4

injections over 6y). Type 2 patients, with a baseline BCVA of logMAR 0.845, needed fewer injections (mean: 46.2 injections over 6y)[25]. However, other studies have reported that type 2 patients required more frequent treatments to preserve vision[33], possibly due to subretinal fibrosis and scarring[34].

Another hypothesis is anti-VEGF resistance, with tissues becoming less responsive due to vascular remodeling and reduced dependence on angiogenic factors[35]. Type 1 MNV patients, with longer disease courses, are more likely to develop resistance, requiring more frequent injections.

Our study extends previous findings by demonstrating that, despite differences in injection frequency and baseline anatomical parameters among MNV subtypes, the functional outcomes (BCVA) and most OCT/OCTA metrics at week 96 did not differ significantly across subtypes. Only a mild difference was observed in CRT changes among subgroups. Collectively, these observations indicate comparable long-term treatment responses to the Δ2w and Δ4w regimens across different MNV subtypes. These exploratory data also provide direct prospective evidence linking MNV subtype to injection burden and morpho-functional outcomes in this prospective, randomized cohort.

In summary, considering MNV subtype when designing treatment regimens may help optimize resource allocation and patient management. Further studies are warranted to confirm these findings and refine individualized therapy for different nAMD subtypes.

Limitations This study's small sample size, particularly for type 3 and mixed-type nAMD, may have influenced data. A 2-year follow-up may be insufficient to assess long-term drug efficacy, and single-center data limit generalizability. Additionally, nearly 20% of enrolled participants were lost to follow-up (76 enrolled *vs* 61 completed), which may introduce attrition bias and further affect the reliability of our results. All OCTA segmentation corrections were performed by a single senior ophthalmologist with no reproducibility tests, and potential subjective bias cannot be ruled out.

In conclusion, T&E regimens with 2- and 4-week intervals of intravitreal conbercept were effective in improving visual function in nAMD patients, with similar efficacy and safety profiles. The Δ4w group required fewer injections and was noninferior to the Δ2w group in visual prognosis, offering a more cost-effective approach. The MNV type should be fully considered when developing a treatment regimen to maximize patient benefit.

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REFERENCES

1 Loo CY, Fenwick EK, Man REK, *et al*. Utilisation of patient-centred outcome measures in age-related macular degeneration research and clinical practice: a systematic review. *Clin Exp Ophthalmol* 2025;53(2):161-174.

2 GBD 2021 Global AMD Collaborators. Global burden of vision impairment due to age-related macular degeneration, 1990-2021, with forecasts to 2050: a systematic analysis for the Global Burden of Disease Study 2021. *Lancet Glob Health* 2025;13(7):e1175-e1190.

3 Singh M, Negi R, Alka, *et al*. Age-related macular degeneration (AMD): pathophysiology, drug targeting approaches, and recent developments in nanotherapeutics. *Medicina* (*Kaunas*) 2024;60(10):1647.

4 Mettu PS, Allingham MJ, Cousins SW. Incomplete response to anti-VEGF therapy in neovascular AMD: exploring disease mechanisms and therapeutic opportunities. *Prog Retin Eye Res* 2021;82:100906.

5 Antal R, Benyó Z, Nagy ZZ, *et al*. Recent advances in treating age-related macular degeneration and diabetic retinopathy: current therapies and emerging novel approaches. *Geroscience* 2025. Online ahead of print.

6 Jia HX, Lu B, Yuan YZ, *et al*. A randomized, controlled trial of treat-and-extend *vs*. *pro re nata* regimen for neovascular age-related macular degeneration. *Front Med (Lausanne)* 2022;9:852519.

7 Li XX, Xu GZ, Wang YS, *et al*. Safety and efficacy of conbercept in neovascular age-related macular degeneration results from a 12-month randomized phase 2 study: AURORA study. *Ophthalmology* 2014;121(9):1740-1747.

8 Zhang M, Yu DC, Yang C, *et al*. The pharmacology study of a new recombinant human VEGF receptor-Fc fusion protein on experimental choroidal neovascularization. *Pharm Res* 2009;26(1):204-210.

9 Liu K, Song YP, Xu GZ, *et al*. Conbercept for treatment of neovascular age-related macular degeneration: results of the randomized phase 3 PHOENIX study. *Am J Ophthalmol* 2019;197:156-167.

10 Zhao XY, Wen Y, Yang ZY, *et al*. Development and validation of a deep learning model to predict visual and anatomical prognosis of anti-VEGF therapy for neovascular age-related macular degeneration (KongMing Study): a prospective, nationwide, multicentre study. *Lancet Digit Heal* 2026;8(4):100971.

11 Rosenberg D, Deonarain DM, Gould J, *et al*. Efficacy, safety, and treatment burden of treat-and-extend versus alternative anti-VEGF regimens for nAMD: a systematic review and meta-analysis. *Eye* (*Lond*) 2023;37(1):6-16.

12 Chen YS, Chang HC, Chi SC, *et al*. Different aflibercept regimens for wet age-related macular degeneration: a systematic review and network meta-analysis. *J Chin Med Assoc* 2026;89(5):347-353.

13 Koh A, Lanzetta P, Lee WK, *et al*. Recommended guidelines for use of intravitreal aflibercept with a treat-and-extend regimen for the management of neovascular age-related macular degeneration in the Asia-Pacific region: report from a consensus panel. *Asia Pac J Ophthalmol* (*Phila*) 2017;6(3):296-302.

14 Heier JS, Khanani AM, Quezada Ruiz C, *et al*. Efficacy, durability, and safety of intravitreal faricimab up to every 16 weeks for neovascular age-related macular degeneration (TENAYA and LUCERNE): two randomised, double-masked, phase 3, non-inferiority trials. *Lancet* 2022;399(10326):729-740.

15 Qi YY, Cheng AX, Xu JY, *et al*. Real-world outcomes of aflibercept 2 mg using a treat-and-extend protocol for neovascular age-related macular degeneration: a 24-month retrospective study in a Chinese population. *Drug Des Devel Ther* 2026;20:601668.

16 Ohji M, Takahashi K, Okada AA, *et al*. Efficacy and safety of intravitreal aflibercept treat-and-extend regimens in exudative age-related macular degeneration: 52- and 96-week findings from ALTAIR. *Adv Ther* 2020;37(3):1173-1187.

17 Daniel E, Toth CA, Grunwald JE, *et al*. Risk of scar in the comparison of age-related macular degeneration treatments trials. *Ophthalmology* 2014;121(3):656-666.

18 Mathis T, Holz FG, Sivaprasad S, *et al*. Characterisation of macular neovascularisation subtypes in age-related macular degeneration to optimise treatment outcomes. *Eye* (*Lond*) 2023;37(9):1758-1765.

19 Parodi MB, Cascavilla M, Papayannis A, *et al*. Intravitreal bevacizumab in advanced-stage neovascular age-related macular degeneration with visual acuity lower than 20/200. *Arch Ophthalmol* 2012;130(7):934-935.

20 Mitchell P, Holz FG, Hykin P, *et al*. Efficacy and safety of intravitreal aflibercept using a treat-and-extend regimen for neovascular age-related macular degeneration: the ARIES study: a randomized clinical trial. *Retina* 2021;41(9):1911-1920.

21 Xu D, Kaiser PK. Intravitreal aflibercept for neovascular age-related macular degeneration. *Immunotherapy* 2013;5(2):121-130.

22 Wang LP, Zhang CW, Hua R. Clinical effectiveness of ranibizumab and conbercept for neovascular age-related macular degeneration: a meta-analysis. *Drug Des Devel Ther* 2018;12:3625-3633.

23 Avery R, Diack C, Holekamp N, *et al*. Ocular half-life: what it does and does not mean for intravitreal anti-angiogenic drug durability. *Ophthalmol Ther* 2026;15(4):1195-1204.

24 Fauser S, Schwabecker V, Muether PS. Suppression of intraocular vascular endothelial growth factor during aflibercept treatment of age-related macular degeneration. *Am J Ophthalmol* 2014;158(3):532-536.

25 Mrejen S, Jung JJ, Chen C, *et al*. Long-term visual outcomes for a treat and extend anti-vascular endothelial growth factor regimen in eyes with neovascular age-related macular degeneration. *J Clin Med* 2015;4(7):1380-1402.

26 Farazdaghi MK, Ebrahimi KB. Role of the choroid in age-related macular degeneration: a current review. *J Ophthalmic Vis Res* 2019;14(1):78-87.

27 Krytkowska E, Grabowicz A, Mozolewska-Piotrowska K, *et al*. The impact of vascular risk factors on the thickness and volume of the choroid in AMD patients. *Sci Rep* 2021;11(1):15106.

28 Chhablani J, Barteselli G. Clinical applications of choroidal imaging technologies. *Indian J Ophthalmol* 2015;63(5):384-390.

29 Koizumi H, Kano M, Yamamoto A, *et al*. Subfoveal choroidal thickness during aflibercept therapy for neovascular age-related macular degeneration: twelve-month results. *Ophthalmology* 2016;123(3):617-624.

30 Kataoka K, Watanabe Y, Kumagai M, *et al*. Sub-retinal pigment epithelium features as predictors for limited interval extension of faricimab in treatment-naïve neovascular age-related macular degeneration. *Graefes Arch Clin Exp Ophthalmol* 2026. Online ahead of print.

31 Xie H, Ju H, Lu J, *et al*. Comparative study on the efficacy of Conbercept and Aflibercept in the treatment of neovascular age-related macular degeneration. *Sci Rep* 2024;14(1):11997.

32 Park SJ, Oh J, Kim YK, *et al*. Intraocular pharmacokinetics of intravitreal vascular endothelial growth factor-Trap in a rabbit model. *Eye* (*Lond*) 2015;29(4):561-568.

33 Izquierdo-Serra J, Martin-Pinardel R, Moll-Udina A, *et al*. Macular neovascularization type influence on anti-VEGF intravitreal therapy outcomes in age-related macular degeneration. *Ophthalmol Retina* 2024;8(4):350-359.

34 Daniel E, Pan W, Ying GS, *et al*. Development and course of scars in the comparison of age-related macular degeneration treatments trials. *Ophthalmology* 2018;125(7):1037-1046.

35 Yang SQ, Zhao JK, Sun XD. Resistance to anti-VEGF therapy in neovascular age-related macular degeneration: a comprehensive review. *Drug Des Devel Ther* 2016;10:1857-1867.