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Conbercept therapy for neovascular age - related macular degeneration under the treat - and - extend regimen

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治疗-延长方案下康柏西普治疗新生血管性年龄相关性黄斑变性的疗效观察

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摘要

目的:评估在治疗-延长方案 treat-and-extend(T&E)下玻璃体腔注射康柏西普治疗新生血管性年龄相关性黄斑变性(nAMD)的疗效。

方法:回顾性分析 2020 年 5 月至 2022 年 5 月随访 2 年的 nAMD 患者临床资料。所有患眼均先接受康柏西普玻璃体腔注射 3 次、每月 1 次的负荷治疗,随后根据病灶活动度进入 T&E 方案:病情稳定者每次延长注射间隔 2 或 4 周,最长延长至 16 周;若病灶活动复发,则缩短注射间隔。根据既往治疗情况,将患者分为初治组和非初治组。比较 24 mo 随访期间两组患者最佳矫正视力(BCVA)、黄斑中心凹厚度(CMT)、注射次数及注射间隔等指标。

结果:共纳入 27 例患者(男 15 例,女 12 例,共 33 眼)。初治组 18 眼,平均年龄 65.72±12.32 岁。该组在治疗后 1、3、6 mo BCVA 较基线明显改善($P<0.05$),1、3 mo CMT 较基线明显降低($P<0.05$)。非初治组 15 眼,平均年龄 69.00±9.21 岁,该组在治疗后 3 mo BCVA 较基线显著改善($P<0.05$),而 CMT 变化无统计学差异($P>0.05$)。两组基线 CMT 差异无统计学意义($P>0.05$),但在多个随访时间点 CMT 差异具有统计学意义($P<0.05$)。两组总注射次数差异无统计学意义($P>0.05$)。注射间隔方面,初治组以 4 mo 为主,非初治组以 3-4 mo 为主。

结论:在 T&E 方案下进行玻璃体腔注射康柏西普治疗,初治患者较非初治患者可获得更好的视功能和解剖学改善效果。

关键词:治疗-延长方案;新生血管性年龄相关性黄斑变性;康柏西普;最佳矫正视力;黄斑中心凹厚度

Abstract

• AIM: To assess the efficacy of intravitreal conbercept for treating neovascular age-related macular degeneration (nAMD) under a treat-and-extend (T&E) regimen.

• METHODS: A retrospective analysis was conducted on nAMD patients followed over a 2-year period (May 2020 to May 2022). All eyes received three monthly loading intravitreal injections of conbercept, followed by a T&E regimen in which the injection interval was extended by 2 or 4 wk according to disease activity, up to a maximum of 16 wk. When disease activity recurred, the interval was shortened. Patients were divided into initial and non-initial treatment groups based on treatment history. Best-corrected visual acuity (BCVA), central macular thickness (CMT), injection frequency, and intervals between injections over the 24-month follow-up were compared.

• RESULTS: Totally 27 patients (15 males and 12 females, 33 eyes) were enrolled. In the initial treatment group (18 eyes, mean age 65.72 ± 12.32 y), BCVA significantly improved at 1, 3, and 6 mo ($P<0.05$), and CMT significantly improved at 1 and 3 mo ($P<0.05$). In the non-initial treatment group (15 eyes, mean age 69.00±9.21 y), BCVA improved significantly at 3 mo ($P<0.05$), whereas CMT remained stable ($P>0.05$). Baseline CMT was similar between the groups ($P>0.05$). However, significant differences were observed at multiple post-injection time points ($P<0.05$). The total number of injections did not differ between the groups ($P>0.05$). Intervals between injections varied, with the majority at 4 and 3-4 mo in the initial and non-initial treatment groups, respectively.

• CONCLUSION: Initiating intravitreal conbercept therapy under a T&E regimen results in superior visual and anatomical outcomes compared with non-initial treatment.

• KEYWORDS: treat-and-extend; neovascular age-related macular degeneration; conbercept; best-corrected visual acuity; central macular thickness
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INTRODUCTION

Neovascular age-related macular degeneration (nAMD) is a prevalent cause of vision impairment among individuals aged 50 y worldwide[1]. Despite extensive research, the exact etiology remains unclear, with potential associations with genetic, light-induced, nutritional, and metabolic factors. Currently, intravitreal injection of anti-vascular endothelial growth factor (VEGF) agents is the standard treatment for nAMD[2-3].

Conbercept is a recombinant fusion protein composed of the second immunoglobulin (Ig) domain of vascular endothelial growth factor receptor 1 (VEGFR-1) and the third and fourth Ig domains of VEGFR-2, fused to the Fc portion of human IgG[4]. Owing to its unique molecular structure, conbercept can bind multiple VEGF isoforms, including VEGF-A, VEGF-B, and placental growth factor, thereby providing potent and sustained anti-angiogenic effects. Previous clinical studies have demonstrated that intravitreal conbercept is effective in improving visual acuity and reducing retinal thickness in patients with polypoidal choroidal vasculopathy (PCV), particularly in Asian populations[5].

Regarding treatment strategies, fixed dosing regimens ensure consistent VEGF suppression but are associated with high treatment burden and cost. In contrast, the *pro re nata* (PRN) regimen reduces injection frequency but requires intensive monitoring and may result in undertreatment in real-world practice. The treat-and-extend (T&E) regimen represents a proactive and individualized approach that aims to maintain disease control while minimizing treatment burden by gradually extending injection intervals based on disease activity. Increasing evidence suggests that the T&E regimen can achieve comparable or superior visual outcomes with fewer injections compared with PRN regimens[6-7].

Nevertheless, the optimal approach for anti-VEGF treatment remains debated, with key regimens, including fixed-interval protocols, PRN treatment, and T&E regimen[8]. Current studies have indicated that the T&E regimen is beneficial in reducing drug administration frequency and securing visual benefits for patientswith nAMD[9-10]. Therefore, the present study aimed to evaluate the long-term efficacy of intravitreal conbercept administered under T&E regimen in patients with nAMD, and to compare visual and anatomical outcomes between treatment-naïve patients and those previously treated with a PRN regimen.

PARTICIPANTS AND METHODS

Ethical Approval This retrospective study was approved by the Ethics Committee of the affiliated institution, and the requirement for informed consent was waived due to the retrospective nature of the study (Ethics Code: 2022-021). All procedures followed the Helsinki Principles.

Participants A retrospective investigation was conducted involving patients with nAMD who underwent treatment under the T&E regimen from May 2020 to May 2022, with a subsequent follow-up period of at least 2 y. Overall, 27 patients (15 males and 12 females) and 33 eyes (18 right and 15 left) were enrolled. Based on the patients' prior treatment history, the following two distinct groups were established: the "initial treatment" group, comprising patients with nAMD who had not received prior treatment and the "non-initial treatment" group, encompassing patients with nAMD previously treated under a PRN regimen. The "initial treatment" group included 16 patients (10 males and 6 females) and 18 eyes (8 right and 10 left). Among these, 5 eyes had artificial intraocular lenses, while 13 were phakic. This group had an average age of 65.72±12.32 y, with a best-corrected visual acuity (BCVA) before treatment 0.53±0.27 LogMAR. Moreover, the central macular thickness (CMT) before treatment was 343.67±134.53 μm. The "non-initial treatment" group comprised 13 patients (8 males and 5 females) and 15 eyes (10 right and 5 left). Patients in the non-initial treatment group had previously received anti-VEGF therapy under a PRN regimen, including ranibizumab or aflibercept, before switching to conbercept. The decision to switch to conbercept was made by the treating ophthalmologists based on insufficient treatment response, defined as persistent or recurrent intraretinal or subretinal fluid, unstable visual acuity, or the need for frequent injections under the PRN regimen. As this was a retrospective observational study, the treatment switch reflected real-world clinical decision-making rather than a predefined protocol. In this group, 2 eyes had artificial intraocular lenses, while 13 were phakic. This group had an average age of 69.00±9.21 y, with BCVA of 1.05±0.55 LogMAR before treatment and a pretreatment CMT of 441.13±201.57 μm.

Inclusion Criteria The following were the inclusion criteria: 1) age ≥50 y; 2) diagnosis of nAMD using fundus fluorescein angiography and indocyanine green angiography; 3) BCVA equal to or better than light perception; 4) clear ocular media not hindering fundus examination.

Exclusion Criteria The following were the exclusion criteria: 1) allergic history to mydriatics, local anesthetics, or other medications that may be used during diagnosis and treatment; 2) previous ophthalmic surgery (excluding cataract surgery), ocular trauma, or a history of retinal photocoagulation; 3) coexistence of other vitreoretinal diseases, including macular hole or retinal detachment; 4) excessive opacity in the refractive media obstructing fundus examination; 5) glaucoma or elevated intraocular pressure; 6) ocular conditions requiring surgical intervention during the follow-up period; 7) general health deemed inadequate; 8) poor compliance and uncooperative behavior toward treatment.

Treatment The standard preoperative protocol involves the application of antibiotic eye drops. The medication is administered as follows: the procedure is performed in a sterile laminar flow operating room. The area around the eye is disinfected, drapes are applied, the eyelids are held open, and the conjunctival sac is rinsed with a saline solution. Using a 30-gauge injection needle, the flat part of the ciliary body,

located approximately 3.5-4.0 mm from the limbus, is vertically punctured. A 0.05-mL volume of conbercept is injected, with an initial loading dose of 2 mg.

Treat-and-extend All patients received an initial loading phase consisting of three consecutive monthly intravitreal injections of conbercept, followed by implementation of the T&E regimen. For patients with stable conditions, the treatment intervals are gradually extended (by 2 or 4 wk each time), up to a maximum of 16 wk. Treatment may be temporarily suspended in cases wherein patients remain stable after receiving injections at the maximum interval for 2 or 3 consecutive times, followed by reassessment at 3-4-week intervals. When disease activity reemerges, the treatment intervals are progressively shortened, with the likelihood of extension once stability is reestablished. The decision to extend treatment intervals by 2 or 4 wk was based on the treating physician's clinical judgment and individual disease stability. Due to the limited sample size, subgroup comparisons according to different extension strategies were not performed.

Criteria for Prolonging Treatment Intervals All of the following conditions should be met to extend treatment intervals: 1) visual stability: two consecutive BCVA assessments show a decrease of less than five letters (or one line); 2) retinal thickness stability: optical coherence tomography (OCT) measures a thickness increase in CMT of <50 μm;3) absence of sustained subretinal fluid (SRF), or when SRF is present, it remains stable over three consecutive follow-up visits[11]; 4) no new choroidal neovascularization (CNV) lesions; 5) no new macular hemorrhages[10].

Criteria for Maintaining Treatment Intervals The following conditions must be simultaneously satisfied to maintain treatment intervals: 1) visual decline of less than five letters (or one line); 2) no new SRF on OCT or the SRF volume is less than the previous follow-up result; 3) absence of new CNV lesions; 4) no new macular hemorrhages[10].

Criteria for Shortening the Treatment Intervals Any of the following situations warrant a reduction in treatment intervals: 1) visual decline of five or more letters (or one line); 2) recurrent SRF or persistent SRF with BCVA decline; 3) emergence of new CNV lesions; 4) appearance of new macular hemorrhages. Instability of the lesion activity even after extending the treatment intervals. When signs of disease activity, including 1) visual decline of 15 or more letters, 2) significant macular hemorrhage, 3) occasional highly active lesions including retinal pigment epithelial detachment[10], occur, regardless of the patient's previous treatment interval plan, the treatment interval should be immediately shortened to once every 4 wk as a rescue strategy.

Observation Parameters 1) BCVA: for all eligible patients, BCVA measurements are collected before treatment and at 1, 3, 6, 12, 18, and 24 mo post-treatment. The evaluations are conducted using the Early Treatment Diabetic Retinopathy Study (ETDRS) chart and are statistically analyzed by converting to LogMAR visual acuity. 2) OCT: CMT values are measured using Heidelberg OCT before treatment and at 1, 3, 6, 12, 18, and 24 mo post-treatment. 3) Number of injections: the total number of injections within 24 mo is calculated. 4) Interval duration: the time elapsed between the last administered treatment injection is recorded.

Statistical Analysis Statistical analysis was performed using Statistical Package for the Social Sciences (version 23, IBM, Armonk, NY, USA). Continuous variables were normally distributed and presented as mean±standard deviations. For the comparison of repeated measurements, repeated measures analysis of variance was employed, whereas independent sample t-tests were used to compare the two groups. Categorical data were expressed as counts (n) or percentages. Between-group comparisons for categorical data were made using the χ^2 test or Fisher's exact test, as appropriate. $P<0.05$ was considered statistically significant.

RESULTS

General Information Comparison of age and pretreatment CMT between the two groups revealed no statistical differences ($P>0.05$). However, a statistically significant difference in pretreatment BCVA was observed between the two groups ($P<0.05$, Table 1).

Best-corrected Visual Acuity In the initial treatment group, BCVA at 1, 3, 6, 12, and 24 mo was significantly different from pretreatment values ($P<0.05$). Moreover, BCVA at 1, 3, and 6 mo differed significantly from the previous time points; however, from 6 to 24 mo, no statistical differences were observed ($P>0.05$). In the non-initial treatment group, BCVA at 1 mo showed no statistical difference compared with the pretreatment value ($P>0.05$). However, BCVA at 3, 6, 12, and 24 mo exhibited statistically significant differences compared with pretreatment values ($P<0.05$). Furthermore, BCVA at 3 mo showed a statistically significant difference compared with BCVA at 1 mo; however, from 6 to 24 mo, no statistical differences were observed compared with previous time points ($P>0.05$, Table 2).

Table 1 General information $\bar{x}\pm s$

Parameters	Initial treatment group($n=18$)	Non-initial treatment group($n=15$)	t	P
Age (y)	65.72±12.32	69.00±9.21	0.89	0.38
Pretreatment BCVA (LogMAR)	0.53±0.27	1.05±0.55	3.36	<0.001
Pretreatment CMT (μm)	343.67±134.53	441.13±201.57	1.60	0.123
Number of injections	10.00±1.37	10.30±0.90	0.81	0.426

BCVA: Best-corrected visual acuity; CMT: Central macular thickness.

Central Macular Thickness In the initial treatment group, CMT at 1, 3, 6, 12, and 24 mo showed statistically significant differences compared with pretreatment values ($P<0.05$). Moreover, CMT at 1, 3 mo exhibited statistically significant differences compared with CMT at previous time points; however, from 6 to 24 mo, no statistical differences were observed ($P>0.05$). In the non-initial treatment group, CMT at 1 and 3 mo demonstrated no statistical differences compared with pretreatment values ($P>0.05$). However, CMT at 6, 12, and 24 mo exhibited statistically significant differences compared with pretreatment values ($P<0.05$). CMT at 1, 3, 6, 12, 18, and 24 mo showed no statistical differences compared with CMT at previous time points ($P>0.05$, Table 2). The comparison of CMT between the two groups at 1, 3, 6, 12, 18, and 24 mo showed statistically significant differences ($P<0.05$, Table 3).

Number of Injections The total number of injections over 24 mo was 10.00±1.37 and 10.36±0.93 in the initial and non-initial treatment groups, respectively. No statistically significant differences were observed between the two groups ($P>0.05$, Table 1).

Last Injection Interval In the initial treatment group, the injection intervals were 2, 3, 4, and 6 mo for 2, 4, 10, and 2 eyes, respectively. In the non-initial treatment group, the injection intervals were 3 and 4 mo for 4 and 11 eyes, respectively (Table 4).

DISCUSSION

nAMD is a major cause of blindness in the older adult population worldwide. According to statistical data, the number of patients with nAMD was 196 million in 2020 and is anticipated to increase to 288 million by 2040[12]. Currently, anti-VEGF therapy has become the first-line treatment for

Table 2 Intra-group comparison of BCVA and CMT in the two groups $\bar{x}\pm s$

Parameters	Initial treatment group($n=18$)						Non-initial treatment group($n=15$)					
	BCVA (LogMAR)	t	P	CMT(μm)	t	P	BCVA (LogMAR)	t	P	CMT(μm)	t	P
Pretreatment *vs* 1st month	0.53±0.27	3.38	0.004	343.67±134.53	4.05	<0.001	1.05±0.55	1.94	0.073	441.13±201.57	1.49	0.158
	0.45±0.26			271.28±133.99			1.01±0.54			422.73±214.46		
Pretreatment *vs* 3rd month	0.53±0.27	−4.73	<0.001	343.67±134.53	−4.98	<0.001	1.05±0.55	−3.17	0.007	441.13±201.57	−0.71	0.49
	0.35±0.18			231.78±96.01			0.89±0.46			426.67±234.57		
Pretreatment *vs* 6th month	0.53±0.27	2.88	0.012	343.67±134.53	5.22	<0.001	1.05±0.55	5.93	<0.001	441.13±201.57	3.10	0.008
	0.28±0.17			218.30±61.55			0.84±0.49			399.93±199.83		
Pretreatment *vs* 12th month	0.53±0.27	3.89	0.002	343.67±134.53	4.81	<0.001	1.05±0.55	5.78	<0.001	441.13±201.57	2.94	0.011
	0.28±0.19			209.78±36.91			0.85±0.53			397.07±205.17		
Pretreatment *vs* 24th month	0.53±0.27	4.64	<0.001	343.67±134.53	5.07	<0.001	1.05±0.55	6.00	<0.001	441.13±201.57	3.88	0.002
	0.28±0.2			203.50±36.36			0.82±0.50			389.87±199.84		
1st month *vs* 3rd month	0.45±0.26	3.42	0.003	271.28±133.99	2.39	0.029	1.01±0.54	3.13	0.007	422.73±214.46	−0.24	0.816
	0.35±0.18			231.78±96.01			0.89±0.46			426.67±234.57		
3rd month *vs* 6th month	0.35±0.18	3.72	0.002	231.78±96.01	1.48	0.157	0.89±0.46	3.19	0.07	426.67±234.57	1.83	0.089
	0.28±0.17			218.30±61.55			0.84±0.49			399.93±199.83		
6th month *vs* 12th month	0.28±0.17	−0.57	0.579	218.30±61.55	1.13	0.274	0.84±0.49	−0.12	0.91	399.93±199.83	0.57	0.576
	0.28±0.19			209.78±36.91			0.85±0.53			397.07±205.17		
12thmonth *vs* 18th month	0.28±0.19	1.46	0.163	209.78±36.91	1.46	0.163	0.85±0.53	1.27	0.225	397.07±205.17	0.89	0.391
	0.27±0.2			203.50±36.36			0.82±0.49			390.53±198.64		
18th month *vs* 24th month	0.27±0.2	−1.00	0.331	203.50±36.36	−0.05	0.962	0.82±0.49	1.87	0.082	390.53±198.64	0.15	0.882
	0.28±0.2			203.56±36.92			0.82±0.50			389.87±199.84		

BCVA: Best-corrected visual acuity; CMT: Central macular thickness.

Table 3 Inter-group comparison of CMT in the two groups ($\bar{x}\pm s$, μm)

Parameters	Initial treatment group($n=18$)	Non-initial treatment group($n=15$)	t	P
Pretreatment	343.67±134.53	441.13±201.57	1.60	0.123
1st month	271.28±133.99	422.73±214.46	2.38	0.026
3rd month	231.78±96.01	426.67±234.57	3.01	0.007
6th month	218.3±61.55	399.93±199.83	3.39	0.004
12th month	209.78±36.91	397.07±205.17	3.49	0.003
18th month	203.50±36.36	390.53±198.64	3.60	0.003
24th month	203.56±36.92	389.87±199.84	3.56	0.003

CMT: Central macular thickness.

Table 4 Time interval for the last treatment

Groups	2 mo	3 mo	4 mo	6 mo
Initial treatment(n=18)	2 (2/18)	4 (4/18)	10 (10/18)	2(2/18)
Non-initial treatment(n=15)	0 (0/15)	4 (4/15)	11 (11/15)	0(1/15)

nAMD, with key medications, including aflibercept, ranibizumab, and bevacizumab[2-3]. Early fixed monthly dosing regimens, as initially proposed by researchers, including Rosenfeld *et al*[13] and Brown *et al*[14], demonstrated promising results but were accompanied by high treatment costs. The PRN regimen was introduced to alleviate the financial burden on patients. However, this approach demanded strict follow-up requirements that several patients found challenging to meet, making it difficult to achieve the most optimal treatment outcomes[5-6]. In contrast, the T&E regimen, a tailored proactive treatment approach[15], has been supported by several studies for its effectiveness in maintaining treatment outcomes, reducing the frequency of follow-up visits, reducing the financial burden on patients, and relieving healthcare service pressures[16-18]. Nevertheless, comparative research on the T&E regimen for patients with nAMD who are newly initiating treatment and those who have previously undergone PRN therapy is relatively limited.

Compared with other anti-VEGF agents, conbercept possesses a broader binding spectrum and a higher binding affinity to VEGF isoforms, which may contribute to its sustained therapeutic effect[19]. Previous studies have reported favorable visual and anatomical outcomes with conbercept using various dosing strategies, including fixed and PRN regimens[20]. However, evidence regarding the application of conbercept under a T&E regimen, particularly in patients with different treatment histories, remains limited. In the present study, treatment-naïve patients demonstrated earlier and more pronounced visual and anatomical improvement compared with previously treated patients. This finding suggests that early initiation of conbercept therapy under a T&E regimen may optimize treatment response, possibly by preventing irreversible retinal structural damage associated with delayed or insufficient anti-VEGF exposure.

Regarding BCVA, our study results indicate the following: in the initial treatment group of patients with nAMD, the pretreatment BCVA was 0.53±0.27. After the first month, BCVA began to improve to 0.45±0.26, reaching 0.28±0.17 at the sixth month, a significant improvement compared with that at baseline ($P<0.05$). Beyond the sixth month, BCVA remained relatively stable. This finding aligns with those of international researchers, including Jaggi *et al*[21] and Soliman *et al*[22], who also observed that patients with nAMD treated with the T&E regimen experienced gradual BCVA improvement within the first 6 mo, followed by a relatively stable vision. However, Augsburger *et al*[23] suggested that under the T&E regimen, patients with nAMD demonstrated the most significant BCVA improvement in the first 2 mo, followed by a period of relative stability.

In the non-initial treatment group of patients with nAMD, BCVA values before treatment and at the first month were 1.05±0.55 and 1.01±0.54, respectively, with no statistically significant difference compared with BCVA at baseline ($P>0.05$). However, at 3, 6, 12, and 24 mo, BCVA showed statistically significant differences compared with that at baseline ($P<0.05$). This finding suggests that, under the same medication and dosage conditions, patients with nAMD in the initial treatment group responded more promptly to anti-VEGF drugs. This finding aligns with the study by Riecke and Valmaggia[24], who categorized patients on the basis of their nAMD progression and prior treatment. Their results revealed that patients with nAMD who had not received treatment exhibited a significantly greater improvement in BCVA than those with a disease duration of <6 mo who had undergone the PRN regimen. However, patients with a disease duration of >6 mo who had received the PRN regimen showed no BCVA improvement after transitioning to the T&E regimen, which may be attributed to macular fibrosis. Hatz and Prünte[25], Jørstad *et al*[26], and Seguin-Greenstein *et al*[27] reported that patients with nAMD previously treated with either the PRN or T&E regimen did not exhibit significant BCVA improvements at the 1-year follow-up after switching to aflibercept. Jørstad *et al*[26] even noted a decrease in BCVA during the second-year follow-up. Studies such as those by CATT[28] and Corazza *et al*[29] have indicated that patients with nAMD treated with the PRN regimen maintained relatively stable vision during the initial 2-year follow-up but experienced an annual decline after 2 y, ultimately falling below baseline levels by the fifth year, likely owing to structural damage to the retina. However, Kvannli and Krohn[30] reported contrasting results. They believed that regardless of whether patients with nAMD were in an active disease phase, transitioning from the PRN regimen to a strict T&E regimen for over 8 y and receiving up to 39 intravitreal injections led to varying degrees of BCVA improvement. This improvement may be attributed to inadequate treatment under the PRN regimen. Kim *et al*[31] reported similar outcomes to Kvannli and Krohn[30]. They suggested that under the T&E regimen, BCVA improved across different types of CNV treated with anti-VEGF therapy, with no statistically significant difference in BCVA changes between the persistent SRF (+) and persistent SRF (-) groups of various CNV types. Furthermore, Jia *et al*[32] identified a special subtype of nAMD in patients with PCV who exhibited poor responses to

anti-VEGF treatment under the T&E regimen. In contrast, Li *et al*[33] suggested that both the "3+Q12W" and "3+T&E" regimens could enhance the visual and anatomical outcomes of patients with PCV. However, the "3+Q12W" regimen more significantly reduced PCV bleeding areas and required fewer injections on average.

Regarding CMT, in the initial treatment group, the pretreatment CMT value was 343.67±134.53 μm. After the first month, it significantly decreased to 271.28±133.99 μm. Compared with that at baseline, CMT at 3, 6, 12, and 24 mo showed statistical differences (P<0.05). However, from 6 mo onward, CMT remained relatively stable with no significant differences compared with CMT at previous time points (P>0.05). This finding indicates a substantial reduction in CMT during the first 3 mo; however, CMT remained relatively stable after the 3rd month.

In the non-initial treatment group, the baseline CMT valuewas 441.13±201.57 μm. After treatment, CMT at 6, 12, and 24 mo was significantly reduced compared with that at baseline (P<0.05). However, no statistical differences in CMT were noted when comparing each time point from 3 mo onward (P>0.05), suggesting that the CMT of the non-initial treatment group gradually increased at the sixth month and eventually stabilized. We also compared the CMT between the two groups and revealed no statistical differences in CMT before treatment (P>0.05). However, at different time points after treatment, statistically significant differences in CMT were noted between the two groups (P<0.05), indicating that under the T&E regimen, the initial treatment group had a significant advantage in anatomical structure recovery compared with the non-initial treatment group. Our findings align with those of Soliman *et al*[22], who revealed that the initial CMT of patients with nAMD at baseline was 347±117 μm, which decreased to 254±68 and 246±55 μm at 6 and 12 mo, respectively, all showing statistical differences compared with the baseline CMT value (P<0.05). However, no statistically significant differences were noted when comparing CMT at 6 and 12 mo (P>0.05), with the first 3 mo displaying a more substantial decrease in CMT.

Seguin-Greenstein *et al*[27] reported that patients with nAMD previously unresponsive to ranibizumab under the PRN regimen showed anatomical improvement and reduced CMT after switching to aflibercept under the T&E regimen at the 1st year of follow-up. Riecke and Valmaggia[24] investigated three groups of patients with nAMD, including those who underwent initial treatment, those with a disease duration of <6 mo with prior PRN regimen, and those with a disease duration of >6 mo with prior PRN regimen. They observed no statistical differences in CMT changes among the three groups (P>0.05). Fallico *et al*[34] suggested no significant difference in CMT reduction between patients with nAMD treated with the T&E regimen and those on a fixed regimen. Kim *et al*[31] proposed that under the T&E regimen, the CMT change was not significantly different between the persistent SRF (+) and persistent SRF (−) groups for every macular neovascularization(MNV) type (P>0.05).

Regarding the number of injections, this study compared the two groups and revealed no statistically significant differences (P>0.05). These findings agree with those of Riecke and Valmaggia[24], who concluded that under the T&E regimen, no significant differences in the number of injections, recurrence rates, follow-up durations, and the proportion of eyes achieving a 12-week treatment interval were observed between the initial and non-initial treatment groups during the 24-month follow-up (P>0.05). Furthermore, researchers, including Fallico *et al*[34], noted that the T&E group required significantly fewer injections than the fixed treatment group. Regarding the last injection interval, in the initial treatment group, 10 eyes (12/18) had 4-month intervals, and 2 eyes (2/18) had 6-month intervals. In the non-initial treatment group, 11 eyes (11/15) had 4-month intervals. Kertes *et al*[35] discovered that at 24 mo, 73.7% of patients extended the treatment interval to ≥8 wk, and 43.1% of patients could extend it to 12 wk. This finding highlights the favorable outcomes of the T&E regimen in terms of the number of injections and the duration between treatments, alleviating the burden on patients and minimizing the wastage of clinical resources.

Previous studies have primarily focused on short-term outcomes or simplified treatment strategies for nAMD. In contrast, the present study provides real-world evidence on the long-term efficacy of intravitreal conbercept administered under T&E regimen with a 24-month follow-up. Moreover, by comparing treatment-naïve patients with those previously treated under a PRN regimen, this study offers additional insights into the impact of treatment history on visual and anatomical outcomes, highlighting the potential benefits of early initiation of conbercept therapy in nAMD management.

Althoughthe initial treatment group demonstrated significant advantages in terms of visual improvement and anatomical recovery when using the T&E regimen for intravitreal conbercept therapy in patients with nAMD, we acknowledge several limitations of this study. First, a retrospective clinical control design was employed, which has inherent limitations in establishing causal relationships and may be subject to potential confounding factors affecting the results. Second, the sample size of this study was relatively small, which may constrain the reliability of the outcomes. Although the initial treatment group exhibited more favorable results, these findings should be substantiated through larger scale sample verification. Therefore, for a more comprehensive assessment of the effectiveness and safety of this treatment regimen, we recommend conducting larger multicenter randomized controlled clinical trials with long-term follow-up studies to

further validate the benefits of this therapeutic regimen.

We would like to express our sincere gratitude to all individuals and organizations who contributed to the successful completion of this research on the efficacy ofconbercept therapy for nAMD under the T&E regimen. Our heartfelt appreciation goes to the participants for their valuable involvement and cooperation as well as to the medical staff and institutions that supported and facilitated the study. Additionally, we acknowledge the guidance and insights provided by our mentors, colleagues, and the broader scientific community. Their collective contributions have been instrumental in advancing our understanding of this critical medical intervention.

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Data Availability Statement: The data supporting the findings of this study are available upon reasonable request from the corresponding author.

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