

# Different conbercept injection strategies for the treatment of exudative age-related macular degeneration

## A retrospective cohort study

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### Abstract

Conbercept is a novel anti-vascular endothelial growth factor for the treatment of age-related macular degeneration (AMD). The most optimal injection strategy is unknown. To assess the effectiveness of intravitreal injection of conbercept using the 3 + pro re nata (PRN) and 3 + Q3M strategies for the treatment of exudative AMD.

From January 2015 to January 2018, patients confirmed with exudative AMD at Qilu Hospital of Shandong University were included in this retrospective study. Intravitreal injection of 0.5 mg of conbercept was conducted either with the 3 + PRN or 3 + Q3M strategy. Best-corrected visual acuity (BCVA), intraocular pressure, and optical coherence tomography were conducted at 1 and 2 weeks, then every month. fundus fluorescein angiography examination was conducted every 3 months.

There were 106 eyes from 106 patients. The number of follow-ups (3 + Q3M:  $12.4 \pm 1.3$  vs 3 + PRN:  $12.9 \pm 1.6$ ,  $P = .079$ ) and the follow-up time (3 + Q3M:  $12.7 \pm 0.6$  vs 3 + PRN:  $12.5 \pm 0.7$  months,  $P = .121$ ) were similar in the 2 groups. The number of injections was less in 3 + PRN than 3 + Q3M ( $5.3 \pm 1.0$  vs  $6.0 \pm 0.0$ ,  $P < .001$ ). The BCVA at months 7 and 9 to 12 in the 3 + Q3M ( $n = 51$ ) group were lower than for 3 + PRN ( $n = 55$ ) (all  $P < .05$ ). The CRT at months 9 to 12 in the 3 + Q3M group was lower than in the 3 + PRN group (all  $P < .05$ ). There were no differences between the 2 groups regarding the exudation area during follow-up. No serious treatment-related ocular complications or serious systemic adverse events were found.

The 3 + PRN and 3 + Q3M strategies of intravitreal injection of conbercept are effective in treating exudative AMD. The 3 + Q3M strategy needs more injection but is more effective in increasing visual acuity and reducing macular CRT than the 3 + PRN strategy.

**Abbreviations:** AMD = age-related macular degeneration, BCVA = best corrected visual acuity, CNV = choroidal neovascularization, CRT = central retinal thickness, FFA = fundus fluorescein angiography, IOP = intraocular pressure, log MAR = logarithm of the minimum angle of resolution, OCT = optical coherence tomography, VEGF = anti-vascular endothelial growth factor.

**Keywords:** best-corrected visual acuity, central retinal thickness, conbercept, exudative age-related macular degeneration, retrospective cohort study

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LG and YT contributed equally to this work.

The authors have no conflicts of interest to disclose.

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## 1. Introduction

Age-related macular degeneration (AMD) is a progressive chronic retinal disease affecting the aging eye, characterized by drusen (focal yellowish deposits of acellular, polymorphous debris), geographic atrophy of retinal pigment epithelium, and neovascularization that can lead to visual impairment.<sup>[1–3]</sup> There are about 30 million patients with AMD around the world, and about 500,000 of them become blind every year.<sup>[4]</sup> The prevalence of AMD is 3.1% to 5.4% in the United States and 5% in the United Kingdom.<sup>[5,6]</sup> There is no difference in prevalence between Asian and Caucasian populations.<sup>[7]</sup> AMD is strongly associated with age.<sup>[2]</sup> The incidence of AMD is also increasing each year in China, probably due to the aging of the population.<sup>[8,9]</sup>

AMD mainly consists of 2 types: exudative and atrophic AMD. The damages of exudative AMD is more serious to the visual acuity than atrophic AMD. In addition, exudative AMD is more difficult to treat, while the outcomes are poorer.<sup>[1–3]</sup> Exudation, bleeding, and fibrous scar caused by choroidal neovascularization (CNV) are the major causes of visual loss in exudative AMD.<sup>[10,11]</sup> The vascular endothelial growth factor (VEGF)

plays an important role in CNV and has become the major target for the treatment of CNV.<sup>[12,13]</sup> Currently, the most commonly used anti-VEGF drugs include ranibizumab, bevacizumab, and aflibercept. The injection strategies for the different drugs are different, which mainly include the 3 + pro re nata (PRN) strategy (1 injection every month in the first 3 months, followed by injection as-needed), 3 + Q1M strategy (1 injection every month in the first 3 months, followed by 1 injection every month), and 3 + Q2M strategy (1 injection every month in the first 3 months, followed by 1 injection every 2 months). Previous studies have demonstrated that the delay of each injection could possibly lead to decreased benefit of the visual improvement or even visual loss.<sup>[14–16]</sup> Therefore, re-examinations and repeated injection should be conducted for each patient every 1 to 2 months, which brings certain degrees of financial and psychological burdens to the patients. In addition, such frequent injections may also induce endophthalmitis and other ocular complications.<sup>[17]</sup> Therefore, how to increase the interval between the injections and reduce the frequency of drug application has become a research hot-spot in the anti-VEGF treatments.

Conbercept is the first anti-VEGF fusion protein developed by Chinese researchers and has the advantages of multiple targets, high affinity, and long effective time.<sup>[18,19]</sup> The phase I and II clinical trials of conbercept for the treatment of exudative AMD demonstrated that this treatment could effectively increase visual acuity, decrease CRT, and reduce the area of CNV. Specifically, the 3 + PRN and 3 + Q1M injection strategies have been used in the phase II trial, and the times of injection in the 0.5 mg 3 + PRN group was 7.73.<sup>[20,21]</sup> A recent multicenter, randomized, double-blind, sham-injection controlled phase III clinical trial (PHOENIX) has demonstrated that the 3 + Q3M injection strategy of conbercept is safe and effective for the treatment of exudative AMD (5.8 conbercept injections were conducted in the 3 + Q3M group).<sup>[22]</sup>

The number of injections in the 3 + Q3M strategy could be lower than in the 3 + PRN strategy, but no study has directly compared these 2 strategies yet. Therefore, the aim of the present study was to compare the effectiveness, injection times, and adverse effects of the 3 + Q3M and 3 + PRN strategies in patients with exudative AMD.

## 2. Material and methods

This retrospective cohort study was approved by the ethics committee of Qilu Hospital of Shandong University. Informed consent was waived because of the retrospective nature of the study.

### 2.1. Patients

From January 2015 to January 2018, the patients confirmed with exudative AMD by fundus fluorescein angiography (FFA) and indocyanine green angiography (ICGA) at Qilu Hospital of Shandong University were screened (n=125). For patients with lesions in both eyes, only the right eye was included in the analysis. The inclusion criteria were<sup>[23–26]</sup>:

- (1)  $\geq 50$  years of age;
- (2) received FFA and ICGA examinations due to AMD, which confirmed the presence of subfoveal CNV or any type of parafoveal CNV; and
- (3) were followed according to the treatment strategy.

The exclusion criteria were:

- (1) had been treated with intravitreal injection of another anti-VEGF drug or laser photocoagulation (n=0);
- (2) had a history of intraocular surgeries other than cataract operation (n=9);
- (3) CNV caused by any other reasons (n=2);
- (4) diabetic retinopathy or other retinal diseases (n=5);
- (5) serious systemic diseases that could affect the intravitreal injection (n=0); or
- (6) refracting media was unclear and affected the ocular fundus examinations (n=3).

Finally, 106 patients (106 eyes) were included, 51 in the 3 + Q3M group, and 55 in the 3 + PRN group.

### 2.2. Examinations

For all affected eyes, the examinations including the best-corrected visual acuity (BCVA), intraocular pressure (IOP), FFA, ICGA, and optical coherence tomography (OCT). The BCVA was examined using the International standard decimal visual acuity chart, and the results were converted to the logarithm of the minimum angle of resolution (logMAR) for analysis. A CT-80 non-contact ophthalmotonometer (TOPCON, Japan) was used for the measurement of IOP. A Visdcam (PRO NM, Germany) was used for fundus photography. A Spectralis HRA was used for FFA and ICGA. The same experienced physician assessed the area of exudation (Heidelberg Engineering Inc., Germany). A Cirrus HD-OCT 4000 was used for OCT. The same experienced physician measured the central retinal thickness (CRT) (Zeiss, Germany).

### 2.3. Treatment and follow-up

For all affected eyes, the intravitreal injection of conbercept was conducted by the same experienced ophthalmologist according to the methods described before.<sup>[23]</sup> Ofloxacin (0.5%; Santen Pharmaceutical Co., Ltd, Osaka, Japan) was applied to the affected eyes (4times/d) for 3 days before treatment. Routine disinfection and draping were conducted in the operating room, according to the requirements of intraocular surgery. Oxybuprocaine hydrochloride eye drops (0.4%, Santen Pharmaceutical Co., Ltd) were used for topical anesthesia, and then 0.05 mL of conbercept (Kanghong Biological Co. Ltd, Chengdu, China) containing 0.5 mg of conbercept was intravitreally injected. The site of injection was pressed by a cotton swab for 10 seconds to avoid backflow. Tobramycin and dexamethasone ophthalmic ointment (ALCON CUSI, S.A., Spain) were applied, and the eyes were covered. Ofloxacin (0.5%) was applied to the eye (4times/d) for 3 consecutive days after treatment. BCVA, IOP, and CRT (measured by OCT) were conducted every month.

For the eyes in the 3 + Q3M group, 6 injections were conducted, with 1 injection every month for 3 consecutive months, followed by 1 injection every 3 months. For the eyes in the 3 + PRN group, 1 injection was conducted every month for 3 consecutive months, and then the injection was conducted again if 1 or more of the following conditions appeared:

- (1) OCT showed the presence or recurrence of subretinal or intraretinal effusion;
- (2) new bleeding in the macular area;
- (3) FFA examination showed the exudation of the CNV lesion increased, or new lesion appeared; and

(4) visual acuity decreased by >1, or the patients felt the visual acuity decreased.

FFA examination was conducted at the last follow-up to observe the changes of the exudation area of the CNV lesion. The numbers of injection, as well as the adverse events, were recorded.

### 2.4. Statistical analysis

SPSS 22.0 (IBM Corp., Armonk, NY) was used for statistical analysis. Continuous data are described as means and standard deviations and were analyzed using the Student *t*-test or the Mann-Whitney *U* test, while the Least-Significant Difference (LSD) *t* test was used for comparisons among different time points within the same group. Categorical variables are expressed as number (percentage) and were analyzed using the Chi-square or Fisher exact test. *P* < .05 was considered statistically significant.

## 3. Results

### 3.1. Characteristics of the patients

A total of 106 eyes from 106 patients were included in this study. Age, gender, and baseline ocular characteristics were not significantly different between the 2 groups (all *P* > .05) (Table 1). The number of injections in the 3 + Q3M group was fixed at 6, while the 3 + PRN group had 5.3 ± 1.0 injections (*P* < .001). The number of follow-ups (3 + Q3M: 12.4 ± 1.3 vs 3 + PRN: 12.9 ± 1.6, *P* = .08) and the follow-up time (12.7 ± 0.6 vs 12.5 ± 0.7 months, *P* = .12) were similar in the 2 groups.

### 3.2. Drug injection

Six injections were given to the 51 eyes in the 3 + Q3M group. The mean number of injection in the 55 eyes in the 3 + PRN group was 5.3 ± 1.0 (Table 1). Three eyes (5.5%) in the 3 + PRN group received 3 injection, 13 eyes (23.6%) received 4 injections, 23 eyes (41.8%) received 5 injections, 11 eyes (20.0%) received 6 injections, 4 eyes (7.3%) received 7 injections, and 1 eye (1.8%) received 8 injections.

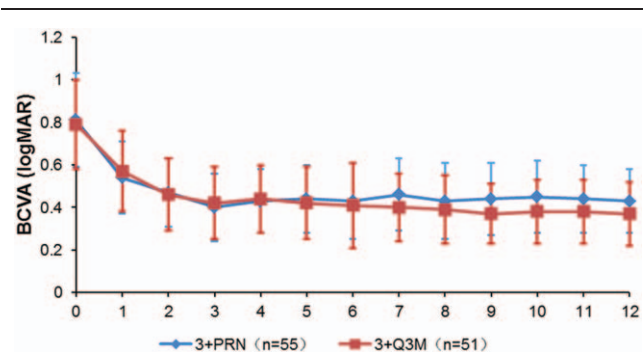
### 3.3. BCVA before and after treatment

The mean BCVA values before and at each time point after treatment are shown in Figure 1 and Table 2. The BCVA before treatment in the 3 + Q3M and 3 + PRN groups was 0.79 ± 0.21 and 0.81 ± 0.22 logMAR, respectively (*P* = .634). The BCVA in

**Table 1**  
Characteristics of the patients.

	3 + Q3M (n=51)	3 + PRN (n=55)	<i>P</i>
Sex, male (%)	26 (51.0%)	25 (45.5%)	.569
Age, yr	63.7 ± 7.6	65.4 ± 8.2	.272
Eyes, n	51	55	–
Right eye (%)	24 (47.1%)	27 (49.1%)	.834
BCVA at baseline, logMAR	0.79 ± 0.21	0.81 ± 0.22	.634
CRT at baseline, μm	451.19 ± 57.64	438.72 ± 61.23	.284
IOP at baseline, mm Hg	16.37 ± 3.01	17.14 ± 2.89	.182
Number of injections	6.0 ± 0.0	5.3 ± 1.0	<.001
Follow-up time, mo	12.7 ± 0.6	12.5 ± 0.7	.121
Number of follow-ups	12.4 ± 1.3	12.9 ± 1.6	.079

BCVA=best corrected visual acuity, CRT=central retinal thickness, IOP=intraocular pressure, PRN=pro re nata (as needed), Q3M=every 3 months.



**Figure 1.** Best-corrected visual acuity (BCVA) before and after treatment with conbercept. The BCVA in both groups at month 1 to 12 was significantly better than baseline (all *P* < .05). The BCVA at months 7 and 9 to 12 in the 3 + Q3M group were lower than in the 3 + PRN group (all *P* < .05). PRN=pro re nata (as needed), Q3M=every 3 months.

**Table 2**  
BCVA (logMAR) before and after treatment.

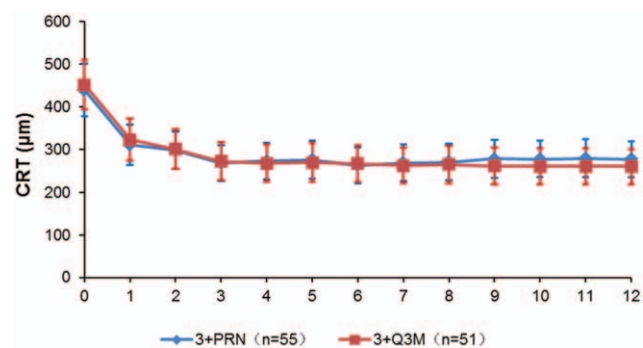
	3 + Q3M (n=51)	3 + PRN (n=55)	<i>P</i>
Before treatment	0.79 ± 0.21	0.81 ± 0.22	.634
1 mo after treatment	0.57 ± 0.19	0.54 ± 0.17	.393
6 mo after treatment	0.41 ± 0.20	0.43 ± 0.18	.589
12 mo after treatment	0.37 ± 0.15	0.43 ± 0.15	.042

BCVA=best corrected visual acuity, PRN=pro re nata (as needed), Q3M=every 3 months.

both groups at month 1 to 12 was significantly better than baseline (all *P* < .05). The BCVA values at months 7 and 9 to 12 in the 3 + Q3M group were lower than in the 3 + PRN group (all *P* < .05).

### 3.4. CRT before and after the treatment

The mean CRT before and at each time point after treatment are shown in Figure 2 and Table 3. The CRT before treatment in the 3 + Q3M and 3 + PRN groups was 451.19 ± 57.64 μm and 438.72 ± 61.23 μm, respectively (*P* = .284). The CRT values in both groups at months 1 to 12 were significantly better than



**Figure 2.** Central retinal thickness (CRT) before and after the treatment with conbercept. The CRT in both groups at months 1 to 12 were significantly better than baseline (all *P* < .05). The CRT at months 9 to 12 in the 3 + Q3M group was lower than in the 3 + PRN group (all *P* < .05). PRN=pro re nata (as needed), Q3M=every 3 months.

**Table 3**  
CRT ( $\mu\text{m}$ ) before and after the treatment.

	3 + Q3M (n=51)	3 + PRN (n=55)	P
Before treatment	451.2 $\pm$ 57.6	438.7 $\pm$ 61.2	.284
1 mo after treatment	322.8 $\pm$ 49.2	310.1 $\pm$ 47.8	.183
6 mo after treatment	266.4 $\pm$ 43.5	262.5 $\pm$ 41.9	.643
12 mo after treatment	259.8 $\pm$ 41.2	276.8 $\pm$ 42.1	.039

CRT=central retinal thickness, PRN=pro re nata (as needed), Q3M=every 3 months.

baseline (all  $P < .05$ ). The CRT at months 9 to 12 in the 3 + Q3M group was lower than in the 3 + PRN group (all  $P < .05$ ).

### 3.5. Exudation area of CNV

FFA and ICGA at month 12 showed that the exudation had completely disappeared in 32 (62.7%) and 31 (56.4%) eyes in the 3 + Q3M and 3 + PRN groups, respectively. In addition, the exudation had decreased in 15 (29.4%) and 18 (32.7%) eyes in the 3 + Q3M and 3 + PRN groups, respectively. The area of exudation remained unchanged or increased in 4 (7.8%) and 6 (10.9%) eyes in the 3 + Q3M and 3 + PRN groups, respectively. The differences between the 2 groups were not statistically significant ( $P = .764$ ) (Table 4).

### 3.6. Adverse events

Subconjunctival hemorrhage or transient IOP increase was found in some patients after treatment (Table 5). During follow-up, no serious treatment-related ocular complications such as retinal detachment, retinal tear, persistent IOP increase, and endophthalmitis, as well as serious systemic adverse responses, were found.

## 4. Discussion

Conbercept is a novel anti-VEGF for the treatment of AMD,<sup>[18,19]</sup> but the most optimal injection strategy is unknown. Therefore, this study aimed to assess the effectiveness of intravitreal injection of conbercept using the 3 + PRN and 3 + Q3M strategies for the treatment of exudative AMD. The results strongly suggest that the 3 + PRN and 3 + Q3M strategies of intravitreal injection of conbercept are effective in treating exudative AMD. The 3 + Q3M strategy needs more injection but

**Table 4**  
Exudation area of choroidal neovascularization.

	3 + Q3M (n=51)	3 + PRN (n=55)	P
Exudation disappeared	32 (62.7%)	31 (56.4%)	.764
Exudation area decreased	15 (29.4%)	18 (32.7%)	
Exudation area increased	4 (7.8%)	6 (10.9%)	

PRN=pro re nata (as needed), Q3M=every 3 months.

**Table 5**  
Adverse events after conbercept injection.

	3 + Q3M (n=51)	3 + PRN (n=55)	P
Subconjunctival hemorrhage	11 (21.6%)	13 (23.6%)	.892
Transient intraocular pressure increase	2 (3.9%)	3 (5.5%)	

PRN=pro re nata (as needed), Q3M=every 3 months.

is more effective in increasing visual acuity and reducing macular CRT than the 3 + PRN strategy.

The most optimal injection strategies for anti-VEGF drugs for the treatment of exudative AMD are still under examination. For instance, the 3 + PRN, 1 + PRN, and 3 + Q1M strategies for ranibizumab injection, and the 3 + Q2M strategy for aflibercept injection have been applied, all of which with certain advantages and disadvantages. The AURORA study has shown that in the critical period of conbercept treatment, 1 injection every month for 3 consecutive months could effectively increase the visual acuity. When followed by 1 injection every month (3 + Q1M) or injection as-needed (3 + PRN) in the extended treatment period, the 12-month visual acuity of the patients increased by 9.31 and 14.3 letters, respectively ( $P > .05$ ). These findings suggested that both injection strategies in the extended treatment period could maintain treatment effectiveness. Therefore, an individualized injection strategy could be applied according to the various disease conditions to meet the individualized requirements.<sup>[20]</sup> The PHOENIX study also demonstrated that the 3 + Q3M strategy of conbercept treatment is safe and effective in treating exudative AMD.<sup>[22]</sup>

Nevertheless, this injection strategy has not been compared with conventional treatment strategies yet. Therefore, we retrospectively compared the treatment effectiveness of the 2 injection strategies, namely 3 + PRN and 3 + Q3M. After 12 months, the logMAR BCVA of the patients with exudative AMD increased from 0.86 $\pm$ 0.39 to 0.51 $\pm$ 0.26, and the CRT decreased from 416 $\pm$ 68  $\mu\text{m}$  to 257 $\pm$ 44  $\mu\text{m}$  in the 3 + PRN group, while in the 3 + Q3M group, the logMAR BCVA increased from 0.82 $\pm$ 0.37 to 0.32 $\pm$ 0.24, and the CRT decreased from 419 $\pm$ 71  $\mu\text{m}$  to 225 $\pm$ 40  $\mu\text{m}$ . The mean BCVA was significantly higher, while the CRT reduction was significantly lower in the 3 + Q3M group than the 3 + PRN group at 3, 6, and 12 months. The FFA at the last follow-up showed that the macular exudation area was 93% in the 3 + Q3M group and 87% in the 3-PRN group. These findings strongly suggest that both the 3 + PRN and 3 + Q3M strategies of intravitreal injection of conbercept are effective in treating exudative AMD, but the 3 + Q3M strategy was more effective in increasing the visual acuity and reducing macular CRT.

Frequent intravitreal injection of anti-VEGF drugs could increase the risks of geographic atrophy of the macular area, atrophy of retinal pigment epithelium, and choriocapillary atrophy,<sup>[27,28]</sup> and also lead to complications such as endophthalmitis, retinal detachment, retinal pigment epithelium tear, retinal pigment epithelium detachment, short-term or persistent IOP increase, subretinal hemorrhage, and vitreous hemorrhage,<sup>[17]</sup> and even thrombotic events.<sup>[29]</sup> Selecting which treatment strategy could achieve treatment effectiveness with the lowest number of injections is critical, but the study results are still controversial. The AURORA study<sup>[20]</sup> compared the "PRN" and "Q1M" strategies for the intravitreal injection of conbercept in treating exudative AMD, resulting in comparable treatment effectiveness after 12 months of treatment. Nevertheless, the mean number of injection in the 3 + PRN group was 7.73, while the mean number of injection in the "3 + Q1M" group was 11.34 ( $P < .05$ ). The PHOENIX study<sup>[22]</sup> reported that the mean number of injection in the 3 + Q3M group was 5.8; the number of injection in the 3 + Q3M group was 6, while the mean number of injection in the 3 + PRN group was 4.1 $\pm$ 0.3, and the difference was statistically significant. The number of injection in the 3 + Q3M group varied greatly when comparing with the AURORA



study, which could be associated with a referral bias. As the follow-up time of the present study was relatively short, 13% of the eyes in the 3 + PRN group were with increased macular exudation area at 12 months after treatment, which required further injections. We speculated that with the increase of the follow-up time, the times of the injections in the 3 + Q3M group could be lower than in the 3 + PRN group, which needs to be further verified in studies with longer follow-up time.

Conbercept has good tolerability, and no serious systemic events were found in the present study. The most common ocular adverse events were subconjunctival hemorrhage at the injection site and transient IOP increase. The molecular weight of conbercept is relatively high (143 kDa), which restrains the drug from passing the blood-ocular barrier. Compared with systemic drug therapy, the incidence of systemic adverse events was lower, and the effective time was longer.<sup>[30]</sup> No serious treatment-related ocular complications such as retinal detachment, retinal tear, persistent IOP increase, and endophthalmitis, as well as occurred during follow-up.

There are several limitations to this study. This was a single-center retrospective cohort study, with inherent biases and limitations. The patients were from a single-center, and the sample size is, therefore, limited. The outcomes were observed over only 1 year, which is short considering that AMD is not a life-threatening condition and that the disease will not limit the lifespan of the patients. Because of those biases, the differences in the efficacy between the 3 + Q3M and 3 + PRN groups could not be compared. More RCTs with larger sample sizes are needed for further investigation.

In conclusion, using the 3 + Q3M strategy for the intravitreal injection of conbercept in treating exudative AMD involves a higher number of injections than the 3 + PRN strategy, but the improvements of the visual acuity and CRT are more substantial.

## Author contributions

**Conceptualization:** Lei Gao, Yuan Tao.

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