

# Temporal pattern of resolution/recurrence of choroidal neovascularization during bevacizumab therapy for wet age-related macular degeneration

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## Abstract

• **AIM:** To characterize temporal pattern of resolution and recurrence of naive choroidal neovascularization (CNV) secondary to wet age-related macular degeneration (AMD) treated with intravitreal bevacizumab on as needed regimen, and to analyze baseline risk factors for CNV resolution or recurrence.

• **METHODS:** Ninety-one eyes of 80 patients with newly diagnosed wet AMD were retrospectively studied. All eyes were treated with a round of three monthly intravitreal bevacizumab injections, followed by one additional 'bonus' injection after resolution of CNV activity. During follow-up, eyes were monitored with fluorescein angiography, optical coherence tomography, and best-corrected visual acuity (BCVA). In case of recurrences of CNV activity, eyes were retreated with other rounds of bevacizumab injections following the same treatment protocol.

• **RESULTS:** Over a median follow-up of 532d, the median resolution time of CNV activity in the first, second, and third treatment round was 98d, 126d, and 111d, respectively. The median recurrence time for the three rounds was 154d, 126d, and 151d, respectively. No significant difference in resolution time ( $P=0.09$ ) or in recurrence time ( $P=0.11$ ) was detected among treatment rounds. Age ( $P=0.0082$ ) and lens status ( $P=0.035$ ) were found to be associated with CNV resolution; for every

1-year increase in age there was 4% greater chance of CNV resolution; Phakic eyes demonstrated a 33% better chance to experience CNV resolution than pseudophakic eyes. For CNV recurrence, lens status ( $P=0.0009$ ) and gender ( $P=0.0446$ ) were found to be predictive; pseudophakic eyes had a 3.69-fold greater risk to experience recurrence of CNV activity compared to phakic eyes; males had a 2.19-fold greater risk to experience recurrence of CNV activity than females. No significant BCVA changes among three treatment rounds were noted ( $P=0.56$ ).

• **CONCLUSION:** Resolution time and recurrence time of CNV activity were not significantly different among treatment rounds, suggesting absence of tachyphylaxis to bevacizumab. A cautious decision should be made upon discontinuing treatment in wet AMD eyes of younger or pseudophakic patients, which showed slower response to bevacizumab. In addition, wet AMD eyes of male or pseudophakic patients should be evaluated more carefully after stopping the treatment, because they may have early reactivation of the CNV. BCVA was preserved by bevacizumab treatment despite multiple recurrences.

• **KEYWORDS:** bevacizumab; age-related macular degeneration; recurrence; anti-vascular endothelial growth factor therapy

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## INTRODUCTION

In current clinical practice, monthly injections of anti-vascular endothelial growth factors (VEGF) agents have become the standard of care for treatment of neovascular age-related macular degeneration (AMD)<sup>[1-4]</sup>; however most of these agents are expensive and difficult to sustain in the elderly population. Therefore, ophthalmologists started using a variety of regimen approaches, including pro re nata (PRN) protocols or the new "treat-and-extend" protocol<sup>[5]</sup>.

Pivotal clinical trials (ANCHOR Study Group<sup>[2]</sup> and MARINA Study Group<sup>[3]</sup>) showed that a monthly injection regimen of ranibizumab can obtain maximal outcome in preserving and improving best-corrected visual acuity (BCVA); however, recognizing concerns regarding ocular and systemic safety, total costs, and convenience for patients and physicians, subsequent studies with less intense injection regimens have been performed<sup>[6]</sup>. In the PIER study, ranibizumab was used on a quarterly basis after three injections every four weeks; the study showed that the visual improvement associated with more frequent therapy is lost by reducing the treatment to quarterly<sup>[7]</sup>. However, the PrONTO study showed that optical coherence tomography (OCT)-guided PRN retreatment regimen with ranibizumab was well accepted in clinic practice because of comparable visual results and less injection frequency than monthly treatment<sup>[6]</sup>. Aflibercept injections may be given every four weeks, but in clinical trials (VIEW1-2) one can reduce treatment to every eight weeks with good effect and maintenance of vision improvement<sup>[4]</sup>. Retrospective studies using the treat-and-extend regimen with bevacizumab have also been reported with favorable visual results, as well as less frequent patient visits and injections along with lower costs compared with a fixed, monthly dosing regimen<sup>[5]</sup>.

The two-year CATT study results showed that both ranibizumab and bevacizumab treatment performed every four weeks for two years resulted in better visual outcomes than OCT-guided PRN regimen (2.4 letters difference,  $P=0.046$ )<sup>[8]</sup>. Moreover, the modest gains produced by monthly dosing vanished soon after switching regimens and reducing the frequency of the intravitreal injections. However, in that study, most of the eyes were treated based on time-domain OCT, which is less sensitive to detect fluid than spectral-domain (SD) OCT, resulting in undetected fluid in more than 30% of the examinations and therefore in missed treatments<sup>[9,10]</sup>. In cases of no residual fluid on OCT or leakage on fluorescein angiography or retinal hemorrhages, eyes were considered temporarily healed and thus further treatments were not necessary until recurrence of choroidal neovascularization (CNV) activity during monthly follow-up visits. However, the pattern of resolution and recurrence of the CNV activity during the PRN treatment regimen was not analyzed. Indeed, the response to anti-VEGF treatments and the time to recur after resolution may be related to the treatment regimen, to the preceding number of treatments, or to the baseline characteristics of the eye itself.

The purpose of the present study was to investigate whether eyes with wet AMD and multiple reactivations of CNV take longer to heal and a shorter time to recur than newly diagnosed CNV; in other words, we wanted to investigate if patients treated with bevacizumab develop tachyphylaxis to the intravitreal drug, defined as a decrease in the response to

bevacizumab after its administration. Baseline characteristics of the eyes were evaluated to correlate with resolution and recurrence intervals in order to investigate possible predictive factors.

## SUBJECTS AND METHODS

**Subjects** In this retrospective study, charts and imaging studies of all the eyes treated with bevacizumab for newly diagnosed wet AMD from March 2005 to January 2012 were reviewed at the University of California, San Diego Jacobs Retina Center. This study conformed to the Declaration of Helsinki for research involving human subjects and was approved by the Institutional Review Board of the University of California, San Diego.

A total of 91 eyes of 80 patients were studied with following inclusion criteria: 1) newly diagnosed CNV secondary to wet AMD, 2) treatment with intravitreal bevacizumab monotherapy guided by fluorescein angiography (FA) and SD-OCT using a confocal scanning laser ophthalmoscope (cSLO, Heidelberg Spectralis, Heidelberg Engineering, Carlsbad, CA, USA), 3) simultaneous FA/SD-OCT examination performed within 2 weeks prior to initial treatment and including at least one high-density raster scan, 4) minimum follow-up of 6 months. Patients with the following situations were excluded: 1) any prior treatment with photodynamic therapy or other anti-VEGF drugs, 2) prior vitrectomy for any reason, 3) CNV due to any reason other than wet AMD, 4) sub-retinal hemorrhage  $\geq 1$  disc diameter involving the fovea, 5) inactive lesion at baseline, including isolated pigment epithelium detachment (PED) or fibrotic scar without intraretinal fluid (IRF) or subretinal fluid (SRF), 6) concomitant retinal conditions that might affect visual acuity.

Demographic data, medical history, and lens status at the time of initial bevacizumab injection were documented by reviewing patients' charts. Baseline BCVA using standard Early Treatment Diabetic Retinopathy Study (EDTRS) charts and baseline imaging study data were also collected, as well as results of the same procedures performed every eight weeks regardless of symptoms until the resolution of CNV activity. The FA/SD-OCT images obtained within two weeks prior to initial treatment were used for the analysis of the baseline characteristics. All baseline SD-OCT images, including linear and raster scans centered on the macula, were evaluated to assess the presence of IRF only, SRF only, combined fluid (IRF+SRF), or PED.

**Methods** The treatment regimen that we used in the present study was a modified protocol from the PRN regimen used in the PrONTO study<sup>[6]</sup>. Once CNV was newly diagnosed, eyes were treated with a minimum of three monthly bevacizumab intravitreal injections; once no residual fluid was detected on SD-OCT, or leakage on FA, or significantly decreased BCVA as compared to the previous examination, one bonus

**Table 1** The mean time of resolution and recurrence

Rounds	Resolution <i>n</i> (%)	Recurrence <i>n</i> (%)	Mean resolution time: d±SD (median)	Mean recurrence time: d±SD (median)	No. of injections
1 <sup>st</sup>	75/91 (82.4)	53/75 (70.7)	172±18.7 (98)	266±30.9 (154)	5.2±3.2
2 <sup>nd</sup>	42/50 (84.0)	35/42 (83.3)	112±10.8 (105)	176±20.3 (126)	3.9±2.0
3 <sup>rd</sup>	26/32 (81.3)	20/26 (76.9)	148±20.1 (111)	170±18.9 (151)	5.0±3.0
Total	143/173 (82.7)	108/143 (75.5)	151±11.6 (99)	223±18.5 (147)	4.8±2.9

SD: Standard deviation.

injection of bevacizumab was performed and then the treatment was stopped. Patients were then seen every other month, and once a recurrence was noticed they were re-treated with a new round of bevacizumab injections according to the same PRN protocol.

The time between initial treatment and inactivation of CNV was recorded as "resolution time", and the time between previous stabilization and subsequent recurrence of CNV activity was recorded as "recurrence time". "Resolution of CNV" was defined as the absence of leakage on FA and the resolution of all IRF and SRF on SD-OCT. The response of PED to therapy was not taken into consideration; eyes that had CNV with persistent PED were considered healed if there was no residual SRF or IRF. "Recurrence of CNV" was defined as new/recurrent fluid on SD-OCT and/or leakage on FA, accompanied with symptoms of worsening vision such as increased metamorphopsias or significantly decreased BCVA. In cases of multiple recurrences and resolutions of CNV activity, we analyzed the initial three treatment rounds.

**Statistical Analysis** The primary outcomes of the study were: 1) the time needed to obtain first, second and third resolutions of CNV activity; and 2) the time needed to detect first, second and third recurrences after resolution. The secondary outcome was the change in BCVA at first (group A), second (group B), and third resolution/recurrence of CNV activity (group C). We also analyzed predictors for resolution and recurrence of CNV activity, including baseline demographic characteristics such as age and sex, medical history (such as diagnosis of systemic hypertension, diabetes, hypercholesterolemia), lens status, BCVA, and OCT status.

Resolution and remission times were analyzed using survival analysis stratified by rounds of resolution or recurrence (first resolution round coded as "Round-1", second coded as "Round-2", and third coded as "Round-3"; the same coding was used for recurrence analysis). Eyes that did not achieve resolution of CNV after treatment were treated as censored for resolution analysis; likewise, eyes with healed CNV without recurrence were treated as censored for recurrence analysis. The probability of active or inactive CNV was analyzed using the cox proportional hazardous method by a stepwise selection of the baseline characteristics (using selecting entry  $P=0.15$  and selecting stay=0.1). Frailty modeling was used when performing the cox regression to adjust for clustering Continuous variables were expressed as

a mean±standard deviation (SD), and discrete variables as a fraction or percentage. Mixed model ANOVA with repeated measures analysis was used for BCVA changes analysis. Statistical analysis was performed using SAS statistical software version 9.3 (SAS Inc, Cary, NC, USA); the significance was determined based on an alpha error equal to or smaller than 5%.

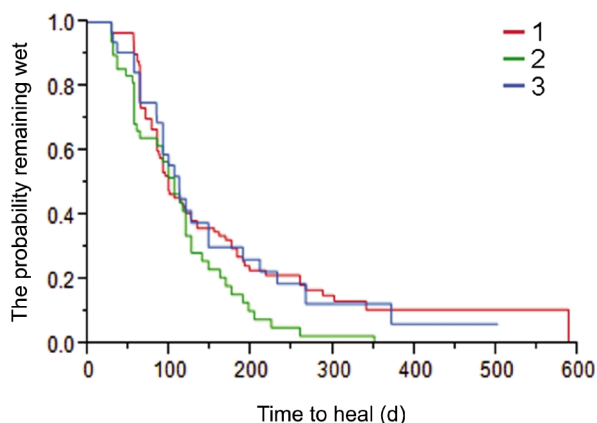
## RESULTS

Eighty consecutive patients (91 eyes; 26 males and 54 females) with a mean age of 80 years (range, 63 to 97 years) were included in this study. Eleven patients had both eyes included in the study; the second eye was included at least six months after the first eye completed the study. Thirty-five eyes (38.5%) were phakic and 56 (61.5%) were pseudophakic. The mean follow-up was 589±380.5d (median 532d). At baseline, concomitant PED on SD-OCT was seen in 69.9% of the cases, and concomitant subretinal scarring was present in 17.3% of the cases; 28 eyes (30.8%) showed IRF only, 40 eyes (43.9%) SRF only, and 23 eyes (25.3%) both IRF and SRF.

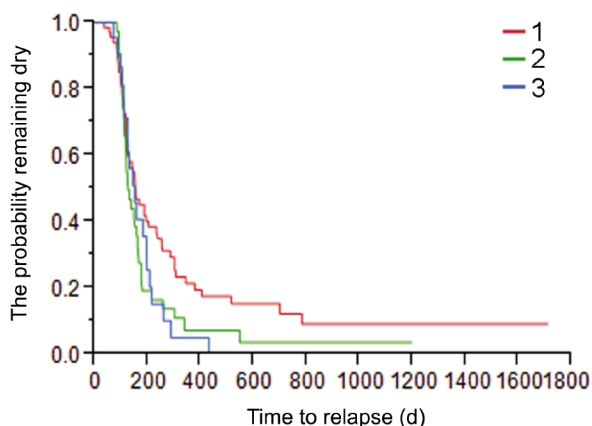
The median resolution time for the three rounds of treatment (Rounds 1, 2, and 3) was 98d, 105d, and 111d, respectively (Table 1); survival analysis (Figure 1) showed that there was no significant difference in resolution time among treatment rounds ( $P=0.09$  Log-Rank). Similarly, survival analysis of the recurrence time (Figure 2) did not show significant differences among the three rounds of treatment ( $P=0.11$  Log-Rank) with the median recurrence time for the three rounds of 154d, 126d, and 151d, respectively (Table 1).

In addition, we also compared resolution times and recurrence times among eyes that went through all 3 rounds of treatment (or 2 rounds of treatment at least), excluding 33 eyes that did not have recurrence and never went through rounds 2 and 3. The survival analysis showed similar results and no significant differences in resolution time and recurrence time among the three rounds of treatment, as shown in Figures 3 and 4. The median resolution time for the three rounds of treatment (Rounds 1, 2, and 3) was 84d, 105d, and 111d, respectively ( $P=0.32$  Log-Rank), and the median recurrence time was 123.5d, 123d, and 151d, respectively ( $P=0.60$  Log-Rank).

Cox regression analysis revealed that significant predictors for resolution time were age ( $P=0.0082$ , Table 2) and lens status ( $P=0.035$ , Table 2). For every year of age, the chance



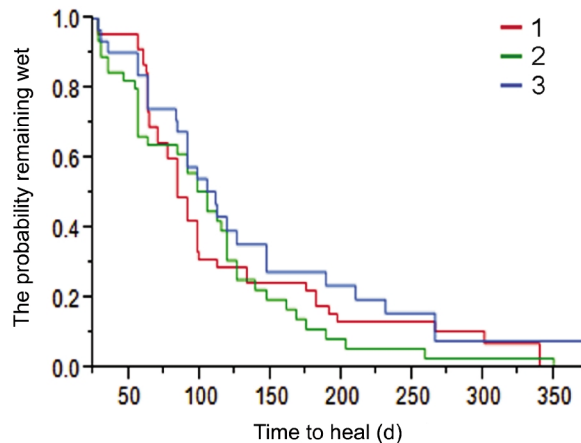
**Figure 1 Survival analysis of three resolution rounds in eyes with wet age-related macular degeneration after bevacizumab treatment** X-coordinate: Resolution time (d); Y-coordinate: Probability of persistent fluid. No significant difference ( $P=0.09$  Log-Rank) of resolution time was present among 3 treatment rounds (the median time of three groups were 98d, 105d, and 111d, respectively).



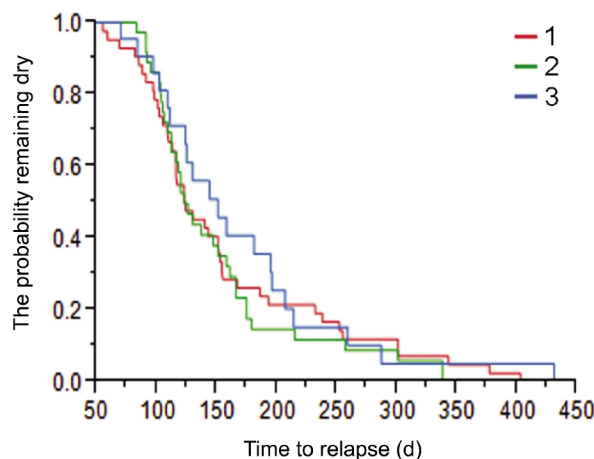
**Figure 2 Survival analysis of three recurrence rounds in eyes with wet age-related macular degeneration after bevacizumab treatment** X-coordinate: Recurrence time (d); Y-coordinate: Probability of remaining dry. No significant difference ( $P=0.11$  Log-Rank) of recurrence time was detected among 3 treatment rounds (the median time of three groups were 154d, 126d, and 151d, respectively).

for an eye to experience resolution of CNV activity (absorption of IRF or SRF) increased by 4%. Phakic eyes had 33% more chance to experience resolution of CNV activity than pseudophakic eyes. The resolution times for the treatment rounds (Rounds 1, 2, and 3) remained not significant after adjusting for the other baseline characteristics.

Cox regression analysis of probability for a healed CNV to recur showed that lens status ( $P=0.0009$ , Table 2) and gender ( $P=0.0446$ , Table 2) were significant covariates. Eyes with intraocular lens (IOL) implants demonstrated a 3.69-fold greater risk to recur compared to phakic eyes; the median recurrence time for pseudophakic eyes was 124 days, and was 164 days for phakic eyes. In addition, males showed a 2.19-fold greater risk to experience recurrence of CNV activity than their female counterparts.



**Figure 3 Survival analysis of three resolution rounds considering only eyes that went through all 3 rounds of treatment (or 2 rounds of treatment at least)** X-coordinate: Resolution time (d); Y-coordinate: Probability of persistent fluid. No significant difference ( $P=0.32$  Log-Rank) of resolution time was present among the three treatment rounds (the median time of three groups were 84d, 105d, and 111d, respectively).



**Figure 4 Survival analysis of three recurrence rounds considering only eyes that went through all 3 rounds of treatment (or 2 rounds of treatment at least)** X-coordinate: Recurrence time (d); Y-coordinate: Probability of remaining dry. No significant difference ( $P=0.60$  Log-Rank) of recurrence time was detected among 3 treatment rounds (the median time of three groups were 123.5d, 123d, and 151d, respectively).

**Table 2 Analysis of maximum likelihood estimates**

Parameter	Pr>ChiSq	Hazard Ratio	95% CI
CNV resolution			
Age	0.0082	<sup>1</sup> 1.038	1.010-1.066
Lens status	0.0350	<sup>2</sup> 0.660	0.457-0.972
CNV recurrence			
Gender	0.0446	<sup>3</sup> 2.190	1.019-4.708
Lens status	0.0009	<sup>4</sup> 3.694	1.709-7.984

CNV: Choroidal neovascularization; CI: Confidence interval; IOL: Intraocular lens. <sup>1</sup>Every year of age was associated with 3.8% higher probability of CNV resolution; <sup>2</sup>Pseudophakic eyes, compared to phakic eyes; <sup>3</sup>Males, compared to females; <sup>4</sup>Pseudophakic eyes, compared to phakic eyes.

Table 3 shows changes in BCVA during the study. After the first treatment round, BCVA increased 6.6 ETDRS letters

**Table 3 Visual acuity at baseline, at resolution, and at recurrence**

Rounds	n	BCVA (letters±SD)			<sup>2</sup> P
		At baseline <sup>1</sup>	At resolution	At recurrence	
1 <sup>st</sup>	91	43.0±18.2	50.7±16.4	43.6±17.6	<0.0001
2 <sup>nd</sup>	50	46.9±12.6	53.5±14.3	45.1±17.4	<0.0001
3 <sup>rd</sup>	32	45.4±16.0	53.7±15.4	47.4±16.4	<0.0001
P		0.84	0.68	0.48	
Total		44.5±16.4	52.0±15.6	44.7±17.3	<0.0001

<sup>1</sup>Before each round of treatment; <sup>2</sup>Between baseline BCVA and BCVA at resolution. BCVA: Best-corrected visual acuity; SD: Standard deviation.

from baseline (from 44.5 ±16.4 to 52.0 ±15.6 letters,  $P < 0.001$ ); however, it deteriorated to the baseline score when the CNV reactivated (44.7 ±17.3 letters). No difference in BCVA among treatment rounds was observed ( $P = 0.56$ ).

### DISCUSSION

To the best of our knowledge, the present study is the first that evaluated resolution/recurrence intervals and vision changes after multiple rounds of intravitreal bevacizumab, and also the first to incorporate a "bonus" injection in the PRN regimen in the attempt to prolong the duration of a healed CNV. We also were careful to use SD-OCT only, evaluating multiple scans through the macula to permit detection of subtle changes suggestive of early recurrence of CNV. For this reason, we typically detected reactivation of CNV prior to loss of BCVA although patients often described subtle subjective symptoms of reactivation. Other investigators have noted this phenomenon as well<sup>[11-13]</sup>.

In the present study, we treated patients aggressively until there was a complete resolution of fluid on SD-OCT and clearance of leakage on FA within a 1 500µ m radius in the macula. During the median follow-up period of 532d (mean 589? 80d), 82.7% of the cases responded to the anti-VEGF treatment with documented fluid resolution. Among these cases, 75.5% presented a recurrence of CNV activity after resolution. The median resolution time of CNV activity was 99d, and the mean resolution time 151 ±12d. The median recurrence time (from CNV resolution to reactivation) was 147d, and the mean recurrence time 223.3±18.5d. Interestingly, we found no difference in resolution time among the three treatment rounds ( $P = 0.09$ ), even considering only eyes that went through at least two rounds of treatment ( $P = 0.32$ ). This suggests that even in eyes with multiple recurrences, an aggressive treatment regimen can result in complete fluid resolution without evidence of tachyphylaxis. Similarly, no difference in recurrence time was observed over the three treatment rounds ( $P = 0.11$ ), even considering only eyes that went through at least two rounds of treatment ( $P = 0.60$ ). This indicates that bevacizumab is able to keep a CNV inactive for a similar period among treatment rounds; in other words, recurrences of CNV activity do not occur earlier in

patients with a prior history of healed CNV. Dadgostar *et al*<sup>[11]</sup> reported that three injections of ranibizumab in 3.5 months are necessary to achieve a "dry" macula on OCT for eyes receiving PRN injections. Horster *et al*<sup>[14]</sup> showed that recurrence intervals for 29 eyes treated with PRN regimen of intravitreal ranibizumab ranged from 41d to 17 months (mean 5.5±3.4 months, median 4.5 months). These studies evaluated only one recurrence and one round of treatment. In contrast, our study addressed the hypothesis that recurrences of CNV activity may become more difficult to treat; however, based on our results, recurrences manifested a similar response to bevacizumab in terms of resolution time. The observation of tachyphylaxis, which has been reported by others, was not seen by us possibly because our aggressive treatment regimen included a 'bonus' injection given after complete resolution of CNV activity<sup>[15-17]</sup>.

We also analyzed baseline risk factors that might affect the response to treatment and the recurrence time. We found that lens status was an important risk factor affecting both resolution and recurrence of CNV. Pseudophakic eyes experienced late CNV resolution and early CNV recurrence compared to phakic eyes. This may be explained with faster clearance and shorter half-life of intravitreally injected anti-VEGF agents following open lens capsule and vitreous liquefaction<sup>[18]</sup>. In addition, an interesting finding was that older age was associated with better treatment response or easier resolution of CNV activity. We hypothesize that this finding may be due to a possible age-related variation of VEGF production; VEGF production in elderly patients may be less than in younger patients because the aging of retinal pigment epithelium cells leads to impaired cellular functions such as cytokines production, including the VEGF<sup>[19]</sup>. Further studies are needed to confirm our finding using a similar study design. In addition, the current study showed also that males had higher risk of recurrence of CNV activity than females though the  $P$ value was close to borderline. The validity of this finding needs to be further investigated with larger sample studies.

We also found that, during a median of 532d of follow-up, our patients did not show permanent vision loss after multiple

reactivations; the BCVA after the last recurrence of CNV activity was similar to the BCVA before the very initial treatment (mean change,  $-1.4 \pm 14.1$  letters,  $P=0.35$ ). And moreover, the BCVA following resolution of CNV activity after the first cycle of therapy was not different from the visual outcome after the third treatment round. This indicates that, using our modified PRN regimen, vision potential does not reduce with multiple reactivation of the CNV. We acknowledge as limitations of this study the retrospective nature and the modest sample size. Also, since patients were not imaged monthly, there was a possibility that recurrence of CNV activity could have been detected earlier.

In summary, analyzing multiple resolution/recurrence intervals during bevacizumab therapy for wet AMD, we demonstrated that there is no risk of tachyphylaxis to this intravitreal drug. In addition, younger AMD patients and eyes with intraocular lens should be evaluated more carefully and with a closer follow-up because they may experience slower response to anti-VEGF treatment. Similarly, male AMD patients and eyes with intraocular lens may experience earlier recurrence of CNV activity than expected.

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