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ORIGINAL RESEARCH

Only first intravitreal bevacizumab injection achieves statistically significant visual improvement in naïve myopic choroidal neovascularization

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Background: The aim of this study was to evaluate the efficacy of intravitreal bevacizumab when administered on an as-needed basis for the treatment of myopic choroidal neovascularization (CNV), and to assess visual changes upon treatment.

Methods: This study was designed as a retrospective, interventional case series, for which the inclusion criteria were pathologic myopia, and documentation of untreated active macular CNV on fluorescein angiography and optical coherence tomography. Monthly changes in best-corrected visual acuity (BCVA), visual gain after each treatment, and correlation with refraction, age, location, and dimension of CNV were considered. The data were analyzed using the one-tailed, paired Wilcoxon test.

Results: Nineteen naive eyes were found suitable for the study. The mean number of treatments was 3.32 ± 2.36 (confidence interval 2.25–4.37) during a mean follow-up period of 18.95 ± 8.3 months. At baseline, mean BCVA was 0.58 ± 0.37 logarithm of the minimum angle of resolution (logMAR) units. At 12 months, mean BCVA was 0.39 ± 0.35 logMAR and at 24 months was 0.39 ± 0.40. Mean improvement in BCVA from baseline was +0.17 ± 0.25 logMAR ($P < 0.05$) at month 12, +0.14 ± 0.25 logMAR ($P = 0.1$) at month 18, and +0.09 ± 0.32 logMAR ($P = 0.5$) at month 24. Improvement on pretreatment BCVA was significant (+0.16 logMAR, $P < 0.01$) after the first injection, but not after the second (–0.01 logMAR, $P = 0.5$) or third (+0.02 logMAR, $P = 0.5$) injections. There was a statistically significant correlation between age and number of treatments, and between improvement in BCVA of foveal versus extrafoveal location of CNV.

Conclusion: The use of intravitreal bevacizumab "as needed" is an effective treatment for myopic CNV, but visual gain is statistically significant only after the first injection and decreases in the second year.

Keywords: choroidal neovascularization, macular degeneration, pathologic myopia, bevacizumab, optical coherence tomography

Introduction

Actual therapeutic options for choroidal neovascularization (CNV) secondary to pathologic myopia consist of direct laser photocoagulation,[1] photodynamic therapy,[2] and intravitreal antivascular endothelial growth factor (anti VEGF) treatment with ranibizumab[3–7] or bevacizumab.[8–18] Intravitreal treatment with anti VEGF is now considered first-line therapy.[19] However, scientific debate continues regarding which of the two agents available is more efficacious and which is the preferable protocol for their administration, ie, a loading dose or retreatment for persistent CNV activity. Therefore, the aim of the current study was to evaluate the safety and efficacy of intravitreal bevacizumab administered on an as-needed basis for the retreatment

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of naïve myopic choroidal neovascularization. Moreover, although the effectiveness of anti VEGF is well known, visual changes in response to each treatment were analyzed on the basis of their statistical significance in the present study. Further, correlation between number of treatments, age or refraction, and influence of location and dimension of CNV were investigated.

Materials and methods

From January 2008 to June 2011, the charts of patients with myopic CNV were consecutively reviewed in this retrospective, interventional case series study. Inclusion criteria were as follows:

- pathologic myopia, defined as a spherical equivalent greater than 6.0 diopters (D) and/or presence of a typical area of retinal pigment epithelium (RPE) atrophy in the macular region, in association with peripapillary atrophy and axial length more than 26 mm
- FA documentation of active macular CNV, as identified by initial staining and late leakage, by means either of a digital fundus camera (ImageNet, Topcon, Tokyo, Japan) or a scanning laser ophthalmoscope (Spectralis, Heidelberg Engineering, Heidelberg, Germany).
- Time domain optical coherence tomography (OCT, Stratus, Carl Zeiss Meditec, Dublin, CA) or spectral domain OCT (Spectralis, Heidelberg Engineering, Heidelberg, Germany) confirmation of dome-shaped RPE elevation with or without retinal fluid in correspondence to the angiographic lesion.
- Onset of visual loss and metamorphopsia, both of less than one month in duration.

One of the authors (PM) classified the lesion as foveal or juxtafoveal if it was under the foveal avascular zone or closer to it by less than 200 microns. If it was further away, it was considered to be extrafoveal.

Lesion dimension was taken in consideration too, although approximately, comparing the diameter of the optic disk. Less than 200 microns was defined as "small", 200–500 microns as "medium", and >500 microns as "large". Exclusion criteria were other ocular diseases that could affect visual acuity, such as angioid streaks, trauma, choroiditis, drusen, and previous vitreoretinal surgery. Previous cataract extraction was not considered an exclusion criterion, nor was a history of cerebrovascular or cardiovascular accident.

All patients were treatment-naïve and had not undergone previous intravitreal treatment of any sort or associated photodynamic therapy. A complete ophthalmic examination was undertaken by certified optometrists for all patients at baseline and every month thereafter for the first 15 months after treatment, then every 3 months unless persistence or recurrence of CNV occurred. BCVA was reported using a Snellen chart, and measurements were then converted into the logarithm of the minimum angle of resolution (logMAR) units for statistical calculation.

Persistence of leakage on fluorescein angiography (FA) and persistent metamorphopsia were considered to be criteria for retreatment. Recurrence was defined as reappearance of the previously described signs from a previously closed CNV. All patients treated in our department were informed that bevacizumab was an off-label treatment, and written consent was obtained from each of them.

Bevacizumab injection

After topical anesthesia, povidone-iodine (5%) solution was applied to the conjunctiva and the fornices for at least 3 minutes under sterile conditions. A volume of 0.05 mL (1.25 mg) of bevacizumab was injected through a 30-gauge needle at 3.5 to 4.0 mm posterior to the limbus in the inferotemporal quadrant.

Statistical analysis

The data were analyzed by means of the one-tailed, paired Wilcoxon test. Correlation between number of treatments and age or refraction measurements was analyzed by the two-tailed Spearman test. One-tailed, paired Wilcoxon and Kruskal-Wallis tests were used to test the equality of median of change of BCVA versus location and dimension of CNV, respectively.

Results

Nineteen eyes from 19 patients (11 women and eight men) were suitable for the study. The mean patient age was 61.5 ± 15.4 (range 20–87) years. The mean spherical equivalent refractive error was −11.13 ± 5.11 D. A patient who presented with tilted disk syndrome and 3 D of astigmatism was included in the study on the basis of posterior pole staphyloma at OCT, and of peripapillary atrophy and macular RPE atrophy areas. Patients' demographic and CNV characteristics as well as follow-up details are shown in Table 1. Six patients were pseudophakic.

Our 19 patients received a mean 3.32 ± 2.36 treatments (confidence interval [CI] 2.25–4.37) during the total follow-up period, and a mean 2.84 ± 1.57 treatments (CI: 2.13–3.55) at month 12. At the end of respective follow-up, three eyes (15.8%) had not been retreated, six (31.6%)

Table 1 Intravitreal bevacizumab treatment for myopic choroidal neovascularization: patient demographics

Patient number	Gender	Age (years)	CNV location	CNV dimensions	Refraction (D)	Number of treatments on demand	Follow-up (months)
1	M	81	FJ	M	–6	9	33
2	F	42	EF	S	–15,5	1	24
3	M	56	FJ	L	–8	3	24
4	M	58	FJ	M	–6	2	24
5	M	55	FJ	M	–17	1	6
6	M	41	EF	S	–13	2	28
7	M	75	FJ	S	–23	4	12
8	F	66	EF	M	–15	2	31
9	F	64	FJ	M	–3	6	24
10	F	70	EF	S	–8	2	24
11	F	70	EF	S	–8,5	3	12
12	F	68	FJ	S	–14	2	9
13	F	50	FJ	L	–7	2	12
14	F	87	EF	M	–12	9	32
15	M	66	FJ	L	–9	4	12
16	F	70	FJ	L	–8,5	1	22
17	M	65	FJ	S	–12	3	15
18	F	20	EF	S	–16	3	9
19	F	65	EF	S	–9	4	21

Abbreviations: D, diopters; F, female; M, male; FJ, foveal or juxtafoveal; EF, extrafoveal; S, small; M, medium; L, large; logMAR, logarithm of the minimum angle of resolution; CNV, choroidal neovascularization.

had received two treatments, four (21.8%) had received three treatments, and six (31.6%) had received more than three injections. Sixteen patients completed 12 months of follow-up, 11 patients completed 18 months, and nine patients completed 24 months. Overall, the mean follow-up was 18.95 ± 8.3 months (Table 2).

Visual outcomes

At baseline, mean BCVA was 0.58 ± 0.37 (median 0.4) logMAR. At 12 months, mean BCVA for 16 patients was 0.39 ± 0.35 (median 0.3) logMAR. For the 11 patients who completed 18 months of follow-up, mean BCVA was 0.35 ± 0.36 logMAR, and for the nine patients who completed 24 months of follow-up, BCVA was 0.39 ± 0.40 logMAR (Table 3 and Figure 1).

The mean BCVA improvement at month 12 was +0.17 ± 0.25 (median +0.2) logMAR. This improvement in BCVA was statistically significant ($P < 0.05$). The improvement from baseline was not statistically significant at 18 months (+0.14 ± 0.25 logMAR, $P = 0.1$) or at 24 months (+0.09 ± 0.32 logMAR, $P = 0.5$, Figure 2). At 12 months, nine patients (56%) had improved (mean +0.34 logMAR), six (37%) remained stable, and only one (6%) had visual loss (mean –0.3 logMAR). Of the nine patients who reached the 24-month follow-up, three (33%) had improved (mean +0.43 logMAR), four (44%) had remained stable, and two (22%) had experienced visual loss (mean –0.25 logMAR).

Given that follow-up was considerably more or less than 12 and/or 24 months for some patients, we believe it is appropriate to state the visual outcome at the end of each respective follow-up period (Tables 2 and 3). Ten patients (52.6%) showed improved BCVA, with a mean variation of +0.33 ± 0.18 logMAR. Five patients (26.3%) remained stable, and four patients (21.0%) had worsened. All but three patients showed complete resolution of fluorescein leakage; at the time of writing, the three exceptions remain under observation because CNV had still been active at their last check-up. The mean variation in this group was –0.22 ± 0.05 logMAR. Of these three patients, patient 14 experienced persistent CNV activity despite having received nine treatments, while patients 1 and 17 had recurrent CNV.

In the second year, ie, after month 12, BCVA measurements proved to be constant over the long term, with the exception of three patients. However, the size of the sample precludes generation of a conclusion. Three eyes showed recurrence of the same CNV, while two eyes were affected by different and newly detected CNV.

Table 4 shows measurements of logMAR BCVA before and after each treatment. Improvement on pretreatment BCVA was significant (+0.16 logMAR, $P < 0.01$) after the first injection, but not after the second (–0.01 logMAR, $P = 0.5$) or third

Table 2 Clinical data: characteristics and variation of logMAR best-corrected visual acuity

Patient number	Treatments (n)	BVCA baseline	Final BVCA	BVCA gain	Follow-up (months)	Clinical impression-FA leakage
1	9	1	1.3	–0.3	33	Recurrence, same CNV, still active
2	1	0.3	0.3	0	24	Closed
3	3	1	0.2	+0.8	24	Closed
4	2	0.4	0.2	+0.2	24	Closed
5	1	0.4	0.2	+0.2	6	Closed
6	2	0	0	0	28	Recurrence, same CNV, closed
7	4	0.6	0.2	+0.4	12	Closed
8	2	1	1.3	–0.3	31	Closed
9	6	0.3	0.3	0	24	Closed, secondary pucker, peeling
10	2	0.1	0.1	0	24	Closed
11	3	0.4	0.1	+0.3	12	Closed
12	2	0.4	0.1	+0.3	9	Closed
13	2	1	0.7	+0.3	12	Closed
14	9	0.2	0.4	–0.2	32	Recurrence, same CNV, still active
15	4	1	1	0	12	Closed
16	1	0.6	0.3	+0.3	22	Closed
17	3	0.7	1	–0.3	15	Recurrence, same CNV, still active
18	3	1.3	1	+0.3	9	Closed
19	4	0.4	0.2	+0.2	21	Two different CNV, closed

Abbreviations: BCVA, best-corrected visual acuity; CNV, choroidal neovascularization; FA, fluorescein angiography; logMAR, logarithm of the minimum angle of resolution.

(+0.02 logMAR, $P = 0.5$), although the improvement with respect to baseline was still statistically significant. It should also be noted that six patients needed more than three injections.

Age, number of treatments, and CNV characteristics

There was a discrete correlation (Spearman coefficient = 0.53, $P = 0.018$) between age and number of treatments, but not between age and visual outcome. An attempt to identify a possible threshold value revealed no age such that mean logMAR BCVA could have been considered different at month 12 ($P = 0.63$). In contrast, variation in BCVA from baseline proved to depend on CNV location. Table 5 shows that when CNV was foveal, there was a statistically significant improvement in BCVA until month 12 ($P < 0.01$), while the corresponding improvement in extrafoveal CNV was not significant. As a consequence, comparison of the respective medians for the two groups reveals significant differences ($P < 0.05$) throughout follow-up, with the exception of month 15. Improvement in BCVA was partially dependent on dimension, but the difference was not statistically significant.

There was no correlation (Spearman's correlation coefficient 0.26, $P = 0.29$) between refraction and number of treatments required. Furthermore, the median number of treatments was found to depend neither on CNV location (Wilcoxon test, $P = 0.89$) nor on its dimensions (Kruskal-Wallis test, $P = 0.44$).

Other than occasional subconjunctival hemorrhagic episodes, which resolved within a few days, no complications related to the injection procedure were observed. In one patient, BCVA stabilized after six treatments, but secondary macular pucker developed 7 months after the last injection, and uneventful vitrectomy was performed. No systemic side effects were recorded.

Discussion

Because photodynamic therapy shows reduced efficacy at 2 years, particularly when compared with intravitreal bevacizumab,[20–22] we currently use intravitreal anti VEGF agents for myopic CNV, on the basis of current therapeutic trends and without considering photodynamic therapy as the first therapeutic step. Given the "off-label" features of the treatment itself, we chose, as have other authors,[8–12,21] to retreat CNV on the basis of clinical and angiographic characteristics.

In our study, BCVA was significantly better than baseline every month until month 12 ($P < 0.05$), when the mean increased is +0.17 logMAR. In subsequent months, too, the mean BCVA increased from baseline by +0.14

Table 3 Measurements of logMAR best-corrected visual acuity during follow-up. LogMAR best-corrected visual acuity at baseline, and months one, 3, 6, 12, 18 and 24 (mean, SD, median, and variations with statistical significance of the changes versus baseline [pb] and versus previous month [pp] by Wilcoxon test)

Patient number	Month 0	Month 1	Month 3	Month 6	Month 9	Month 12	Month 15	Month 18	Month 21	Month 24	Month 27	Month 30
1	1	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7	1.3	1.3
2	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3		
3	1	0.3	0.3	0.2	0.2	0.2	0.2	0.2	0.2	0.2		
4	0.4	0.3	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2		
5	0.4	0.2	0.2	0.2								
6	0	0	0	0	0	0	0	0	0.1	0	0	
7	0.6	0.3	0.2	0.2	0.2	0.2						
8	1	0.7	0.7	0.7	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3
9	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3		
10	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1		
11	0.4	0.3	0.3	0.2	0.1	0.1						
12	0.4	0.2	0.1	0.1	0.1							
13	1	0.7	0.7	0.7	0.7	0.7						
14	0.2	0.5	0.3	0.2	0.3	0.2	0.4	0.4	0.4	0.4	0.4	0.4
15	1	1	1	1	1	1						
16	0.6	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3			
17	0.7	0.3	0.3	0.3	0.3	0.4	1					
18	1.3	1	1	1	1							
19	0.4	0.4	0.3	0.2	0.2	0.2	0.2	0.2	0.2			
Mean	0.58	0.41	0.38	0.36	0.41	0.39	0.41	0.35	0.37	0.39	0.75	1.00
SD	0.37	0.28	0.29	0.30	0.37	0.35	0.39	0.36	0.35	0.40	0.66	0.52
Median	0.40	0.30	0.30	0.20	0.30	0.30	0.30	0.20	0.30	0.30	0.85	1.30
DiffB		−0.17	−0.20	−0.22	−0.19	−0.17	−0.08	−0.14	−0.11	−0.09	0.20	0.27
pb		<0.01	<0.01	<0.01	0.01	0.03	0.36	0.10	0.36	0.5		
DiffP		−0.17	−0.04	−0.02	0.03	0.006	0.06	−0.02	0.03	−0.01	0.15	0
pp		<0.01	0.03	0.12	0.50	0.25	0.50	0.25	0.50	0.5		
n	19	19	19	19	18	16	12	11	11	9	4	3

Abbreviations: DiffB, variation versus baseline; DiffP, variation versus previous measure; n, number of patients; logMAR, logarithm of the minimum angle of resolution; SD, standard deviation.

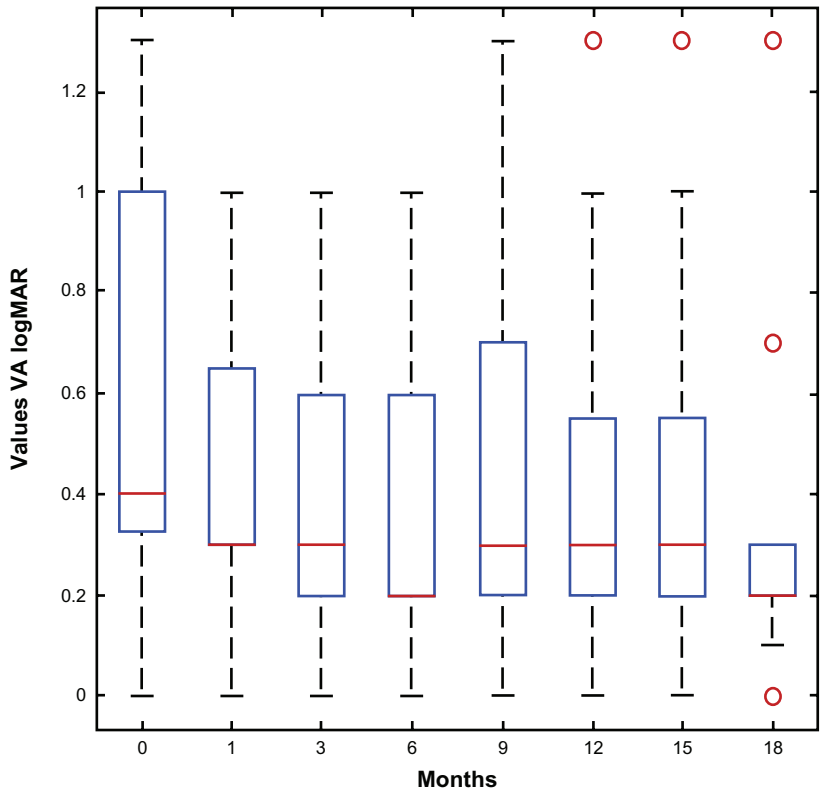

Figure 1 Median of best-corrected visual acuity (VA) in logMAR at baseline and subsequent follow-up.
Abbreviation: logMAR, logarithm of the minimum angle of resolution.

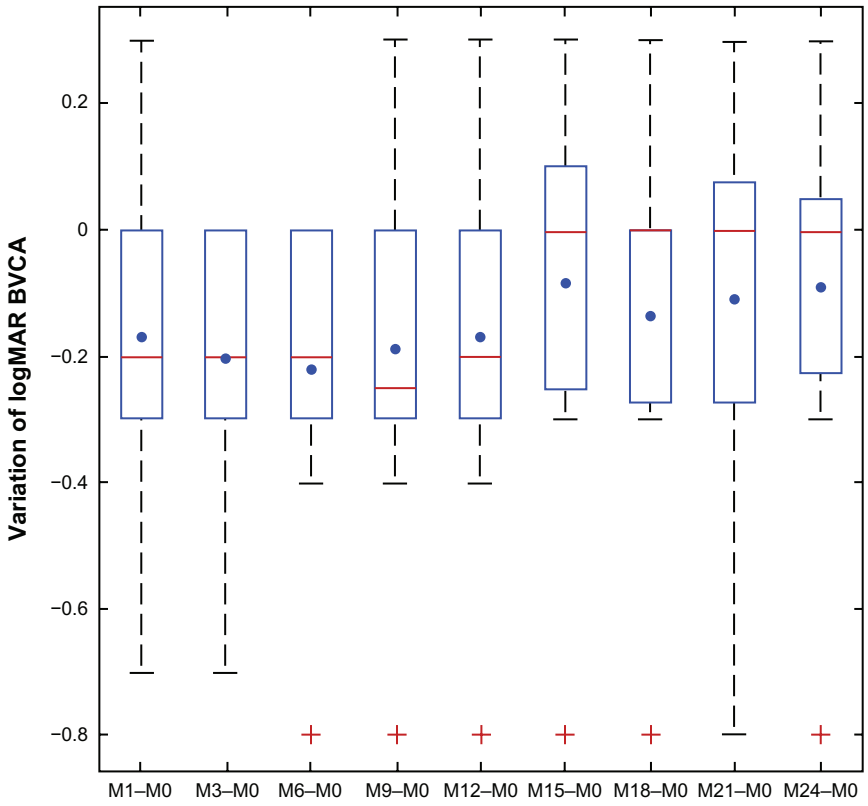

Figure 2 Boxplot of variation versus baseline in logMAR with respect to baseline.
Abbreviations: logMAR, logarithm of the minimum angle of resolution; BVCA, best-corrected visual acuity.

Table 4 Measurements of logMAR best-corrected visual acuity before and after treatments (mean, SD, median, and variations with statistical significance of the changes versus baseline [pb] and versus previous month [pp] by Wilcoxon test)

Patient number	T 1		T 2		T 3		T 4		T 5		T 6		T 7		T 8		T9	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1	1	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7	1.3	1.3	1.3	1.3	1.3
2	0.3	0.3																
3	1	0.3	0.3	0.3	0.3	0.3												
4	0.4	0.3	0.2	0.2														
5	0.4	0.2																
6	0	0	0	0.1														
7	0.6	0.3	0.3	0.2	0.2	0.2	0.2	0.2										
8	1	0.7	0.7	1.3														
9	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3						
10	0.1	0.1	0.1	0.1														
11	0.4	0.3	0.2	0.2	0.1	0.1												
12	0.4	0.2	0.2	0.2														
13	1	0.7	0.7	0.7														
14	0.2	0.5	0.5	0.2	0.2	0.3	0.3	0.5	0.3	0.2	0.2	0.3	0.2	0.2	0.2	0.4	0.4	0.4
15	1	1	1	1	1	1	1	1										
16	0.6	0.3																
17	0.7	0.3	0.7	0.7	0.7	0.4												
18	1.3	1	1	1	1	1												
19	0.4	0.4	0.4	0.3	0.3	0.3	0.2	0.2										
Mean	0.58	0.42	0.46	0.47	0.48	0.46	0.45	0.48	0.43	0.40	0.40	0.43	0.45	0.75	0.75	0.85	0.85	0.85
SD	0.37	0.28	0.31	0.38	0.34	0.32	0.33	0.32	0.23	0.26	0.26	0.23	0.35	0.78	0.78	0.64	0.64	0.64
Median	0.40	0.30	0.35	0.30	0.30	0.30	0.30	0.400	0.300	0.30	0.30	0.30	0.45	0.75	0.75	0.85	0.85	0.85
Mean DiffB		−0.16		−0.14		−0.22		−0.10		−0.01		−0.067		0.15		0.25		0
pb		<0.01		<0.05		<0.05		0.31										
Mean DiffP		−0.16		0.01		−0.02		0.03		−0.03		0.03		0.3		0.1		0
pp		<0.01		0.5		0.5		0.5										
N		19		16		10		6		3		3		2		2		2

Abbreviations: DiffB, variation versus baseline; DiffP, variation versus previous measure; n, number of patients; logMAR, logarithm of the minimum angle of resolution; SD, standard deviation; T, treatment.

Table 5 Variation of logMAR best-corrected visual acuity versus baseline with respect to the location of CNV at 24 months (mean, SD, median, and variations, with statistical significance of the changes within each group (p) and between the two groups [p2] Wilcoxon test)

Location	Month 1	Month 3	Month 6	Month 9	Month 12	Month 15	Month 18	Month 21	Month 24
Extrafoveal									
Mean	–0.05	–0.10	–0.13	–0.05	–0.01	0.05	0.02	0.07	0.10
SD	0.18	0.12	0.13	0.19	0.18	0.16	0.15	0.16	0.13
Median	0.00	–0.10	–0.13	0.00	0.00	0.00	0.00	0.07	0.05
P	0.62	0.12	0.12	0.99	0.99	0.99	0.99	0.65	0.50
Foveal									
Mean	–0.25	–0.28	–0.29	–0.30	–0.29	–0.22	–0.32	–0.32	–0.33
SD	0.20	0.19	0.22	0.23	0.24	0.37	0.29	0.29	0.34
Median	–0.30	–0.30	–0.30	–0.30	–0.30	–0.25	–0.30	–0.30	–0.25
P	<0.01	<0.01	<0.01	<0.01	<0.01	0.37	0.12	0.12	0.25
p2	<0.05	<0.05	<0.05	<0.05	<0.05	0.0703	<0.05	<0.05	<0.05

Abbreviations: SD, standard deviation; logMAR, logarithm of the minimum angle of resolution; CNV, choroidal neovascularization.

logMAR at month 18 (11 patients), by +0.11 logMAR at month 21 (11 patients), and by +0.09 logMAR at month 24 (nine patients). However, these findings should be interpreted with caution, because only a limited number of patients completed 24 months of follow-up, and the statistical validity is impaired by the high *P* value. Overall, visual gain was highest in the first month after treatment, and at one year was consistent with those reported by Ikuno et al,[8] Hayashi et al,[20] and Ruiz-Moreno et al,[16] who to date have used as-needed treatment in the greatest numbers of naïve patients (63, 43, and 75, respectively) reported in the literature. They achieved one-year BCVA improvements of +0.24, +0.23, and +0.18 logMAR, respectively, with 2.4 ±1.4, 1.6 ± 0.7, and 1.8 ± 1.2 injections. Accordingly, it must be taken into account that various differences in BCVA improvement are reported in the literature by several investigators, because the finding of Voykov[13] is +0.17 logMAR (24-month follow-up), that of Wu and Chen[12] is +0.5 logMAR (14-month follow-up and with 2.5 mg of bevacizumab), and that of Hayashi et al is +0.19 logMAR (15-month follow-up).[10]

Variable results and hence efficacy have likewise been reported by authors whose therapeutic protocol comprised a loading phase of three initial, consecutive, monthly injections, ie, +0.24 logMAR and +0.25 logMAR by Chan et al who treated 29 and 22 eyes in two different studies,[14,15] +0.36 logMAR by Gharbiya et al for 20 eyes,[23] but +0.17 and +0.14 logMAR by Ruiz Moreno et al for 29 and 19 eyes.[17,18] In our opinion, this variability could derive not only from the extension of follow-up in the studies cited, but also from a range of other factors, including previous photodynamic therapy (frequently carried out prior to intravitreal bevacizumab), age, onset of symptoms, and baseline BCVA. Although baseline BCVA is in fact intuitively an important predictive factor for the final visual outcome, data from the studies differ because some authors have demonstrated that better visual gain corresponds to a higher BCVA at baseline,[8] whereas other authors have found that the greatest gains are associated with low BCVA baseline values.[12,23,24]

Age is generally considered a critical factor for prognosis in myopic CNV, and the critical age seems to be 50–60 years but, to our knowledge, Gharbiya et al[23] and Ruiz-Moreno et al[16] are the only authors to demonstrate that patients younger than 50 years experience a significantly better BCVA outcome after intravitreal bevacizumab. In our study, statistical analysis showed a reasonable correlation only between age and number of injections (Spearman coefficient = 0.53, $P = 0.018$), suggesting that age might have a role.

In terms of efficacy, the results yielded by the loading phase protocol do not appear to exceed those of the as-needed protocol. Moreover, our study included a total of 10 patients (52%) who had clinical and angiographic remission of CNV and underwent two or fewer injections, and in a study with a larger number of patients,[16] 60% of patients achieved recovery with one injection only.

Taken together, these findings lead us to the opinion that use of the as-needed protocol should be taken in consideration in order to avoid apparently useless reinjections, with a subsequent cumulative risk of retinal detachment as the number of injections increases. To support this finding, subanalysis of treatment-by-treatment visual gain shows that functional improvement, which is statistically significant (+0.16 logMAR, $P < 0.01$) after the first injection, tends to diminish, both in terms of visual gain and of statistical significance after the second and third injections

(respectively, –0.01 logMAR, $P = 0.5$, and +0.02 logMAR, $P = 0.5$), although overall improvement over baseline remains statistically significant (+0.22 logMAR, $P < 0.05$) up to the third treatment.

It becomes evident subsequently that the most effective injection is the first, because 11 patients (59%) were treated twice by month 3, while the remaining eight (42%) were treated only once as required no further treatment. Accordingly, although patients who persistently show clinical and fluorescein angiographic evidence of CNV activity commonly receive treatment, it seems that BCVA does not increase by much. In fact, in our study, the visual gain accrued during the first 6 months tended to stabilize over time but not to improve further, as some authors have already reported.[8,16]

Similarly, two recent studies with 2-year follow-up showed that BCVA gains in naïve patients tended to diminish after the first 12 months and to lose statistical validity. Ikuno et al[21] reported that BCVA was significantly better than baseline in 11 patients at 12 months (+0.17 logMAR, $P < 0.05$), but not at 18 or 24 months (+0.12 logMAR, $P = 0.29$ and $P = 0.38$, respectively). Likewise, at 24 months, 16 patients in a study by Voykov et al showed a mere +0.07 logMAR improvement, along with a statistical validity ($P = 0.8$) that is at least as debatable as ours.[13] Accordingly, Iacono et al reported that in their series of 30 eyes, no significant improvement over baseline was demonstrated after the first month examination onwards.[25] Our study reveals clearer improvement in foveal and juxtafoveal CNV than in extrafoveal CNV. We intuitively believe this could be attributable to retinal disorganization secondary to CNV, that would result worse when CNV is close to the fovea, and hence to cones and rods.

The relatively small number of patients and variable follow-up are acknowledged limitations of our study, but our results signal the overall efficacy of intravitreal bevacizumab. It is noteworthy that 15 patients (78%) demonstrated an improvement or stabilization in BCVA at the end of their respective follow-ups. Of the four patients whose BCVA deteriorated, two were over 80 years of age, and a third presented a tilted optic disk with staphyloma, which appears to be a negative prognostic factor.[26] Also, nowadays we should consider treating patients with ranibizumab, because the results appear very promising in both the short term and the long term,[3–7] although a randomized prospective study that compared the efficacy of both the monoclonal antibodies could not determine a statistically significant difference.[27]

Conclusion

Pending clarification of the optimal dose and interval of administration, as-needed use of intravitreal bevacizumab is a safe and effective treatment for myopic CNV, but visual gain is statistically significant only after the first injection and decreases in the second year.

Disclosure

The authors report no conflicts of interest in this work.

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