Intravitreal bevacizumab as a treatment for choroidal neovascularisation secondary to myopia: 4-year study results

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ABSTRACT • RÉSUMÉ

Objectives: To report long-term follow-up results from intravitreal bevacizumab (IVB) treatment of choroidal neovascularisation (CNV) secondary to pathologic myopia (PM).

Design: The study was designed as a retrospective analysis of consecutive patients presenting with PM.

Participants: Twenty-one eyes were examined from 20 different patients.

Methods: The study was designed as a retrospective, consecutive, nonrandomised, interventional case series. Twenty-one eyes from 20 patients with CNV secondary to PM who were treated with bevacizumab were followed for a maximum of 52 months. Best-corrected visual acuity (BCVA), optical coherence tomography, and fluorescein and indocyanine green angiography were performed on each patient at baseline presentation and every 3 months thereafter for the entire follow-up period. The continuation therapy was based on dosing as needed regimen (PRN) for treatment assessment.

Results: Overall, 15 (71.4%) of the 21 eyes studied demonstrated an improvement of ≥1 line on the Snellen chart. A total of 3 (14.3%) eyes showed no change with this analysis, and 3 (14.3%) eyes lost 1 line of discrimination. After the 4-year study period, fluorescein angiography suggested absence of angiographic leakage or fibrotic lesions in 15 eyes, and 3 eyes showed partial regression of myopic CNV. The remaining 3 eyes demonstrated total regression of CNV.

Conclusions: Intravitreal bevacizumab appears to be an effective therapy for myopic CNV and its benefit may persist in a long-term follow-up, on the basis of PRN treatment compared to the natural history of the disease.

Objet : Compte-rendu des résultats du suivi du traitement à long terme par bevacizumab intravitréen (BIV) de la néovascularisation choroïdienne (NVC) secondaire à la myopie pathologique (MP).

Nature : L'étude a été conçue comme une analyse rétrospective de patients consécutifs présentant une MP.

Participants : Vingt-et-un yeux de 20 patients différents ont été examinés.

Méthode : L'étude a été formée d'une série rétrospective et non randomisée de cas d'intervention consécutifs. Vingt-et-un yeux de 20 patients atteints de NVC secondaire à une MP et traités au bevacizumab ont été suivis pendant un maximum de 52 mois. La meilleure acuité visuelle corrigée, la tomographie par cohérence optique et l'angiographie à la fluorescéine et au vert d'indocyanine ont été pratiquées sur chaque patient lors de sa présentation de base et ensuite à tous les trois mois pendant la période de suivi. La suite de la thérapie dépendait du dosage requis par l'évaluation du traitement pro re nata (PRN).

Résultats : En tout, 15 des 21 yeux étudiés (71,4 %) ont démontré une amélioration de ≥1 ligne à l'échelle Snellen. Un total de 3 yeux (14,3 %) n'ont pas montré de changement à l'analyse et 3 yeux (14,3 %) ont perdu 1 ligne de discrimination. Après une période d'étude de 4 années, l'angiographie à la fluorescéine suggérait l'absence de fuite angiographique ou de lésions fibrotiques dans 15 yeux et 3 yeux ont montré une régression partielle de NVC myopique. Les 3 autres yeux restant ont démontré une régression entière de la NVC.

Conclusions : Le bevacizumab intravitréen semble être une thérapie efficace pour la NVC myopique et ses avantages peuvent persister dans un suivi à long terme, sur la base d'un traitement PRN comparativement à l'histoire naturelle de la maladie.

Pathologic myopia (PM) is a major cause of legal blindness in many developed countries.[1] The prevalence of PM was found to be 1.7%-2% in the United States.[2] Clinical signs seen in high myopic eyes includes areas of retinal pigment epithelium (RPE) and choroidal atrophy in the posterior pole, subretinal haemorrhages,[3,4] lacquer cracks, and choroidal neovascularisation (CNV).[5,6] Of these clinical signs, CNV is one of the most important vision-threatening complications in patients with PM.[7,8] Various studies documented CNV in up to 4%-11% of eyes with PM.[9,10] Based on the natural history of myopic CNV, several studies found that visual prognosis is generally poor on long-term follow-up.[8,11-13] Photodynamic therapy (PDT) with verteporfin has been considered to be the standard treatment for myopic CNV for the past decade. Various studies suggested that PDT reduced the risk of visual loss compared to placebo treatment.[14,15] However, the outcomes VIP Study Group looked at patients with CNV secondary to myopia, and observed no statistical difference at 2-year follow-up in visual acuity between the treatment and placebo groups.[16] Other investigators proposed a combination treatment with PDT and intravitreal triamcinolone injection, but the results of these studies did not demonstrate improved visual outcomes compared to PDT monotherapy.[17] Since 2007, various studies reported short-term efficacy of intravitreal bevacizumab (IVB) for CNV caused by PM.[18-22] Given these encouraging results, we aimed to investigate the long-term efficacy of IVB for the treatment of myopic CNV.

METHODS

We conducted a retrospective study using a group of 20 consecutive patients (14 female and 6 male) identified as

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Table 1—Characteristics of 20 patients with myopic CNV

Patients	Sex	Age	Refractive Error (D)	IVT Injections (n)	PDT	Location of CNV	Recurrence at 4 y	Follow-Up (mo)
1	F	61	−7.5	9	Yes	SF	No	49
2	F	73	−18	6	Yes	SF	No	51
3	F	33	−11	3	Yes	JF	No	47
4	F	48	−15	4	No	SF	Yes	50
5	F	65	−7.5	15	Yes	JF	Yes	52
6	F	38	−12	14	No	JF	Yes	50
7	M	56	−18	7	No	SF	No	50
8	F	64	−15	7	No	SF	No	47
9	F	62	−7	9	No	JF	No	46
10 (OD)	F	40	−15	2	No	SF	No	52
10 (OS)	F	40	−10.75	4	No	SF	No	52
11	M	70	−17.5	8	No	JF	Yes	46
12	F	62	−20	7	No	JF	Yes	46
13	M	67	−8	5	No	SF	No	52
14	M	59	−12	8	No	JF	No	49
15	M	64	−8.5	6	No	SF	No	49
16	F	87	−18	2	No	JF	No	48
17	M	53	−14	10	No	SF	Yes	40
18	F	70	−9	5	No	SF	Yes	48
19	F	63	−12	3	No	JF	Yes	43
20	F	43	−18.5	3	No	JF	No	52

Note: CNV, choroidal neovascularization; D, diopters; F, female; IVT, intravitreal; JF, juxtafoveal; M, man; PDT, photodynamic therapy; SF, subfoveal.

having CNV secondary to PM who were treated with at least 1 IVB. The mean age ± standard deviation (SD) of the patients was 58.9 ± 13.19 years of age. Five patients were younger than 50 years of age and 15 were older (range, 33-87 years). The mean ± SD of refractive error dioptres (D) was −13.05 ± 4.22 D (Table 1).

The inclusion criteria consisted of the following: spherical equivalent refractive error of −6.0 D or more, subfoveal or juxtafoveal location of CNV, best-corrected visual acuity (BCVA) of 20/400 or better, evidence of leakage secondary to CNV on fluorescein angiography (FA). Exclusion criteria included: CNV secondary to AMD, angioid streaks, trauma, choroiditis, hereditary diseases in the study or contralateral eye, previous argon or diode laser treatment in macular area, or previous surgery for retinal detachment with macular involvement.

Previous PDT was not considered as exclusion criteria for the study because the effect of PDT was not able to dry up the CNV lesion. Four of the 20 patients studied were previously treated with PDT: 1 eye 1 time, 2 eyes twice, and 1 eye 3 times.

Informed consent was obtained from all patients before treatment. Ethics Committee approval was obtained from University of Cagliari, and the study adhered to the tenets of the Declaration of Helsinki. Study patients were enrolled consecutively between June 2006 and June 2007. The BCVA was measured and the Snellen chart converted to the logarithm of minimal angle of resolution (logMAR) for statistical analyses. An ophthalmic examination was performed at each visit and included slit-lamp evaluation and funduscopic examination. Ocular imaging for each patient included FA and indocyanine green (ICG) angiography.

Optical coherence tomography (OCT) was performed at baseline as well as at the time of first IVB and at each subsequent follow-up visit. OCT imaging was performed using a Stratus OCT (Zeiss Meditec, Dublin, CA) in line mode with 5-mm vertical and horizontal scans over the fovea. Thereafter, scans were performed using a Cirrus OCT (Zeiss Meditec, Dublin, Calif.) in Raster mode with 512 × 128 and 200 × 200 cube scans for central foveal thickness (CFT). All patients were treated with intravitreal injections of 1.25 mg bevacizumab between June 2006 and October 2010 at the Eye Clinic University of Cagliari. Retreatment criteria were based on the discretion of the treating physicians (MF and EP), according to persistent angiographic leakage or presence of subintraretinal fluid on OCT and the therapy was applied in the same fashion of the first IVB, in the next 48 hours. The mean follow-up time was 48.52 ± 3.17 months (range, 40-52). Eleven of the myopic eyes studied demonstrated subfoveal CNV, and 10 eyes had juxtafoveal CNV. CNV was considered subfoveal if any portion of the new vessel was under the centre of the fovea. OCT, FA, and ICG were performed at the baseline, monthly until the lesion was considered silent and every 3 months thereafter for a maximum of 52 months. If a patient reported visual symptoms before their scheduled examination, a thorough, urgent examination including FA, ICG, and OCT was performed within 48 hours. Additional IVB was then applied in the next 48 hours (recurrence criteria), to eyes showing recurrence angiographic leakage, visual decrease, or distortion with or without OCT change based on the dosing as needed for (pro re nata [PRN]) treatment. If IVB reinjection was performed, the patient was again scheduled for monthly visits for the following 3 months until the lesion was considered to be silent. IVB therapy was performed in the operation

Table 2—Time recurrence in myopic CNV

Patients	Photodynamic Therapy	Recurrence			
		1 y	2 y	3 y	4 y
1	No	Yes (at 4 mo)	No	No	No
2	Yes	No	Yes (at 13 mo) Yes (at 24 mo)	No	No
3	No	Yes (at 12 mo)	Yes (at 24 mo)	No	No
4	No	No	Yes (at 18 mo)	No	No
5	No	No	Yes (at 18 mo)	No	No
6	No	No	Yes (at 13 mo)	No	No
7	No	No	Yes (at 13 mo)	No	No
8	No	No	Yes (at 24 mo)	No	No

Note: CNV, choroidal neovascularization.

room using topical anaesthesia under sterile conditions. 1.25 mg IVB (Avastin; Roche, Basel, Switzerland) was performed using a 30-gauge needle 4 mm posterior to the limbus. After injection, topical administration of antibiotic drops was recommended 4 times a day for 1 week. A complete ophthalmologic examination was performed on the first day after treatment. A total of 131 IVB were performed, with a range of 2-15 injections per eye (mean: 6.23 ± 3.50). No major adverse effects were observed in our series. Changes in BCVA at baseline, 1-year and 4-year follow-up were analysed using ANOVA and Bonferroni test; $p < 0.005$ was considered statistically significant.

Results

Twenty patients with CNV secondary to PM were followed for a period of 4 years at the Retina Center, Eye Clinic University of Cagliari. Twenty-one eyes from 20 patients were treated with IVB at baseline. During long-term follow-up, all patients required additional injections based on the evidence of angiographic leakage, OCT characteristics, or visual symptoms. The studied eyes received a mean 6.52 ± 3.5 injections, with a range of 2-15 injections based on PRN treatment. No significant adverse events were observed in any patient.

FA outcomes

The diagnosis of CNV secondary to PM was primarily made based on the FA and ICG, which are performed as standard diagnostic procedures in our clinic. During follow-up examinations, 8 of 21 eyes showed recurrence of CNV, and 1 of 8 eyes showed progression of myopic CNV from juxtafoveal to subfoveal with worsening of BCVA (Table 2). For this reason, eyes demonstrating recurrence received additional PRN IVB. At 4-year follow-up, the vascular network partially regressed in 3 eyes, completely regressed in another 3 eyes, and became fibrotic in the remaining 15 eyes. FA demonstrated late staining in 15 eyes, total regression of the lesion in 3 eyes, and persistence of leakage in the remaining 3 eyes. In our series, 7 of 21 eyes showed an increase in chorioretinal atrophy (CRA) in the macular area.

Visual outcomes

At baseline, the mean ± SD logMAR BCVA was 0.73 ± 0.40 (Snellen equivalent 20/100). At 1-year follow-up, the mean ± SD logMAR BCVA improved to 0.49 ± 0.40 (Snellen equivalent 20/60) (Figs. 1 and 2). At the final follow-up appointment, the mean ± SD logMAR BCVA showed stabilisation to 0.55 ± 0.43 (Snellen equivalent 20/60) (Figs. 2 and 3). During the follow-up examination period, 8 patients (8 eyes) complained of a reduction in BCVA with distortion in the study eye, and FA revealed a recurrence of myopic CNV in 100% of cases. At final follow-up, 15 patients (15 eyes) (71.4%) demonstrated improvements in BCVA from 1 to 5 Snellen lines, 3 eyes (14.3%) showed stabilisation of BCVA, and 3 eyes (14.3%) showed worsening from 13 to 3 Snellen lines. At final follow-up, patients with worsening BCVA presented with significant enlargement of CRA on FA, and 1 of the eyes showed persistent, active CNV. Patients that demonstrated an improvement or stabilisation in BCVA on FA, presented with CNV regression or fibrosis. ANOVA and Bonferroni tests indicated that there was no significant difference between the BCVA mean at baseline, 1-year, and 4-year follow-up after IVB. The BCVA at baseline, 1-year and final follow-up are listed in Table 3.

OCT outcomes

OCT scans were performed at baseline, at the time of first IVB injection, and at each follow-up visit. CFT was not considered to be sufficiently sensitive for statistical analyses in defining study outcomes. The reasons for this were severalfold. First, OCT scans were obtained with 2 different OCT systems with different software. Second, the poor quality of many images in myopic patients (opacity of optic media, difficult fixation, and the nature of staphyloma) critically influenced the measurements. In our protocol, we considered OCT analyses as qualitative in nature, and used the information only to determine the presence or absence of fluid in the retinal space.

Statistics on PDT subgroup

No statistical significance was found when comparing the mean injections ± SD of the untreated PDT sub-

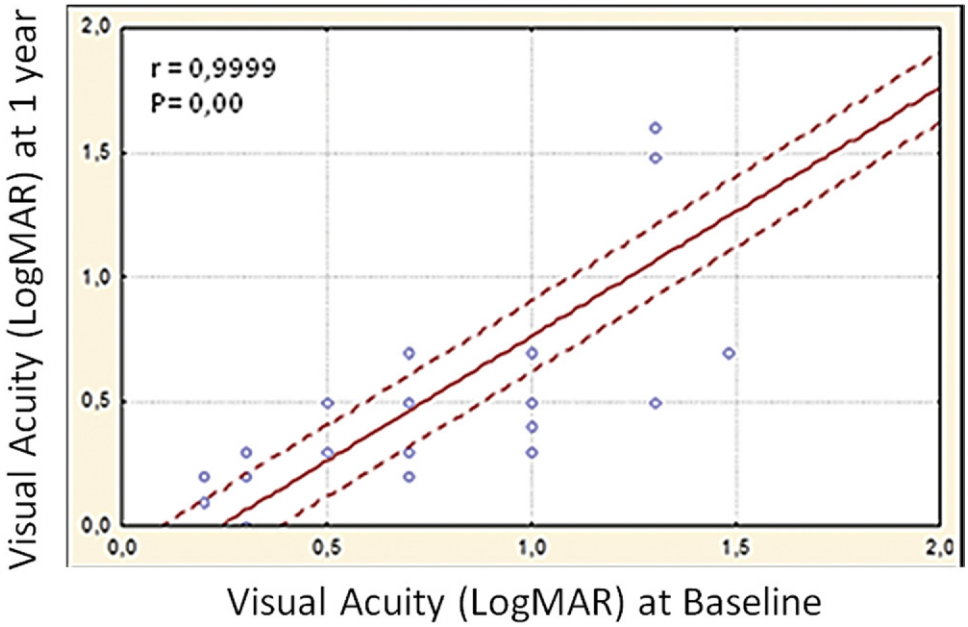

Fig. 1—Distribution of baseline visual acuity and visual acuity at 1-year follow-up.

group to the one that received PDT: 6.11 ± 3.15 versus 8.25 ± 5.10. Equally, no statistical difference in the mean improvement of BVCA for the whole untreated PDT subgroup, 0.79 ± 0.30 compared to 0.72 ± 0.37 in the PDT subgroup, was detected.

The number of recurrences in the untreated PDT subgroup was 7 versus 1 in the PDT subgroup (see Table 1).

Discussion

It is important to define the natural course of myopic CNV to establish the appropriate treatment. Yoshida et al.[13] followed 27 eyes with myopic CNV, 70.37% of which had BCVA superior to 20/200 at the baseline. At 3 years, 55.5% of those eyes maintained a BCVA of 20/200 or better and at 5 years it dropped to 20/200 or <88.8%.

PDT in PM compared to placebo showed some efficacy,[14,15] however, the outcomes did not significantly improve after 2 years.[16]

A recent therapeutic approach to myopic CNV using various anti-VEGF drugs has been studied with a maximum follow-up of 24 months and showed promising results compared to PDT.[18-25]

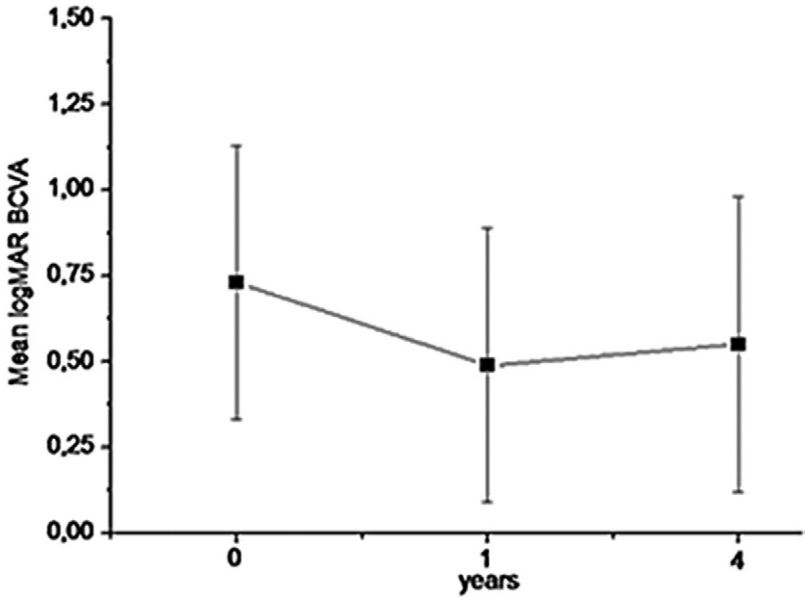

Fig. 2—Changes in mean LogMAR best-corrected visual acuity in our series of patients at baseline, at 1-year and at 4-year follow-up after intravitreal bevacizumab treatment. Bars represent the mean ± standard deviation (SD).

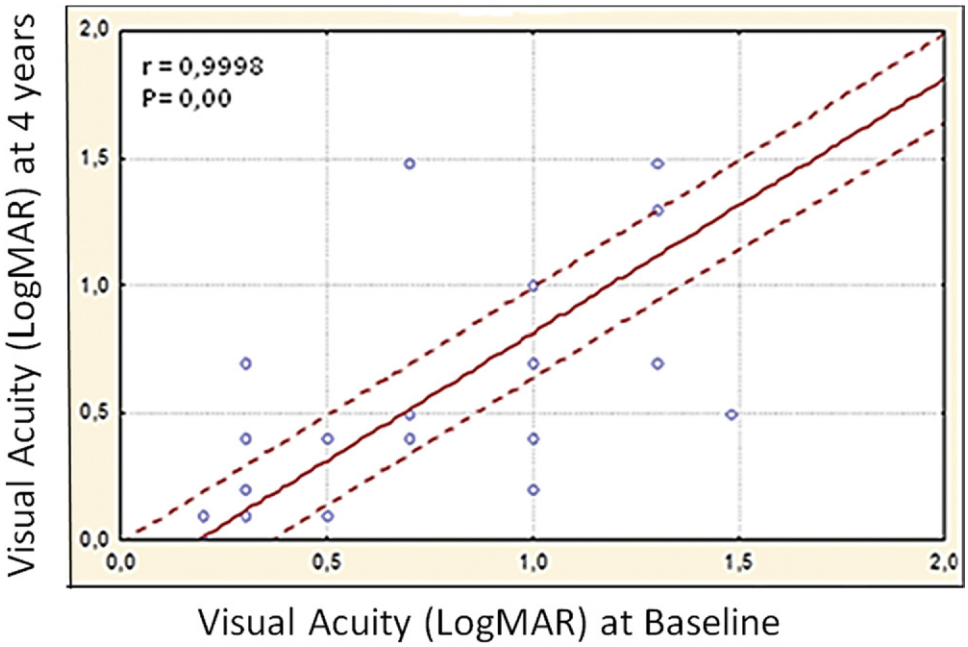

Fig. 3—Distribution of baseline visual acuity and visual acuity at 4-year follow-up.

Two studies at 1- and 2-year follow-up after IVB or PDT in myopic CNV evaluated the influence of both treatments on CRA formation.[24,25] These studies reported that PDT induces damage of collateral choroidal vessels and RPE compared to IVB. Discussion in this study speculates that PDT may increase the development of CRA in eyes with CNV secondary to PM. It seems as though IVB may result in less CRA compared to PDT, perhaps because bevacizumab decreases RPE cell migration and therefore may not facilitate CRA development.[24,25]

Table 3—Best-corrected visual acuity of 20 patients with myopic CNV

Patients	BCVA (Snellen) Baseline	BCVA (Snellen) Post-1 y	BCVA (Snellen) Post-Final Follow-Up
1	20/100	20/100	20/60
2	20/40	20/40	20/40
3	20/200	20/60	20/30
4	20/200	20/40	20/100
5	20/100	20/60	20/60
6	20/400	20/800	c.f.
7	20/100	20/30	20/50
8	20/600	20/100	20/60
9	20/60	20/60	20/25
10(OD)	20/30	20/25	20/25
10(OS)	20/200	20/100	20/200
11	20/100	20/200	20/50
12	20/60	20/40	20/50
13	20/400	20/300	20/400
14	20/40	20/30	20/25
15	20/400	20/60	20/100
16	20/200	20/50	20/50
17	20/100	20/100	20/600
18	20/40	20/40	20/100
19	20/40	20/20	20/30
20	20/30	20/30	20/20

Note: BCVA, best-corrected visual acuity; c.f., count fingers; CNV, choroidal neovascularization.

In our study series, 7 of 21 eyes (33.3%) showed an enlargement of CRA at 4 years after IVB treatment, 6 of them showed recurrence of myopic CNV during follow-up. These results suggest that, CRA may increase during long-term follow-up in patients with CNV secondary to PM. In addition, enlargement of atrophy in the macular area seems to be strictly correlated with recurrence of CNV.

Moreover, the whole group received between 2-15 IVB treatments and was followed over 3-month intervals for a maximum of 4 years. Out of the 21 eyes studied, 4 had been subjected to previous PDT, whereas the remaining 17 eyes were treated only with IVB. At 4-year follow-up, no significant differences in BCVA or CRA development were detected among patients treated or not treated with previous PDT. However, it is important to underline that although the number of eyes who received PDT was too small to draw definitive conclusions, the rate of recurrence in these eyes was lower (25%) than PDT-untreated eyes (41%). In our series, 57.14% of patients experienced increased BCVA immediately after IVB, and 71.42% of patients maintained consistent BCVA measurements throughout the follow-up period.

Some investigators have reported that the natural course of myopic CNV is dependent on age of onset.[10,23] Yoshida[12] studied 2 different age groups with CNV secondary to PM, and >50% of group 1 (≤40 years old) reported retained vision for >3 years, whereas in group 2 (≥40 years old), >50% of the patients experienced decreased vision. Ruiz-Moreno and Montero[23] published the results

of a study in which patients ≤50 years old experienced an increase in BCVA with no significant improvement in CFT after IVB, whereas patients ≥50 years showed improvement in CFT but no increase in BCVA at 12 months follow-up. These reports suggest that age is a critical factor in the prognosis of CNV secondary to PM. By comparison, in our study not only did 80% (4 of 5) of patients ≤50 years of age experienced an improved visual outcome, but also 80% (12 of 15) of patients ≥50 years showed improvement in BCVA at 4-year follow-up. Our results indicate that visual prognosis in CNV secondary to PM does not seem to be influenced by age of onset. The primary result from our study is the change in BCVA outcome: 38.09% of study patients (8 eyes) were observed to have a BCVA of 20/200 or less at the baseline. At 1-year follow-up, only 14.28% of studied eyes (3 eyes) were found to have vision of 20/200 or less, and only 19.04% (4 eyes) remained 20/200 or less at 4-year follow-up. In our series, all eyes received multiple IVB treatments, and 85.7% demonstrated improved or maintained BCVA up to the 52-month follow-up based on a 3-month follow-up and PRN treatment protocol. It is not known why some neovascular lesions improved with short-term treatment after only few injections whereas other lesions did not completely respond. Anti-VEGF is known to reduce vascular activity in myopic CNV, thereby decreasing damage at the level of the RPE and photoreceptors and promoting visual acuity in eyes treated over the long term. The primary follow-up examination in our study was FA, and any visual symptoms were carefully evaluated in each patient to determine the need for possible retreatment. OCT was used as a complementary examination to highlight the presence of fluid; however, this examination was interpreted with caution because the quality of OCT scans in myopic eyes is thought to be poor, and myopic neovascularisation is not always accompanied by frank subretinal fluid.[20] Our results collected over a maximum follow-up time of 52 months indicate that long-term IVB treatment is generally safe and contributes to stabilisation of visual acuity. These effects may help to prevent long-term impairment due to CNV, and our results are consistent with those reported in previous short-term studies. The optimum number of intravitreal injections needed to achieve myopic CNV closure is not known; however, in our study a total of 131 (mean, 6.23 ± 3.50) injections were carried out, with 2-15 IVB applied per eye. This study showed maintenance or improvement of vision in >85% of the eyes with myopic CNV. This is a significant improvement compared to the natural history of this disease.

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