

## Continuing Medical Education:

# Intravitreal ranibizumab for choroidal neovascularization secondary to pathologic myopia: 12-month results

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### Learning objectives

Upon completion of this activity, participants will be able to:

1. Describe the epidemiology and current treatment of choroidal neovascularization in pathologic myopia
2. Identify the efficacy of ranibizumab in the treatment of choroidal neovascularization in the current study
3. Specify factors associated with a better response to ranibizumab in the current study
4. Describe the procedures and complications associated with ranibizumab therapy in the current study

### Authors/Editors disclosure information

AJ Lotery has disclosed that he has served as an advisor or consultant to Novartis Pharmaceuticals Corporation. Jordi M Monés has disclosed that he has served as an advisor or consultant to Notal Vision Ltd., Allergan, Inc., Novartis Pharmaceuticals Corporation, and Ophthotech Corp.

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# Intravitreal ranibizumab for choroidal neovascularization secondary to pathologic myopia: 12-month results

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## Abstract

**Aims** To determine the efficacy and safety of intravitreal ranibizumab in the treatment of choroidal neovascularization (CNV) secondary to pathologic myopia (PM).

**Methods** Prospective, consecutive, non-randomized, interventional case series of 23 eyes of 23 patients with CNV secondary to PM treated with intravitreal ranibizumab as needed, after the first injection (PRN: Pro Re Nata). Patients were followed-up monthly with best-corrected visual acuity (BCVA), biomicroscopy, fluorescein angiography, and optical coherence tomography.

**Results** There were 23 eyes of 23 patients, and the mean age was 51.08 (SD = 17.40) years. One patient was lost during the follow-up. At the 12-month follow-up, the mean VA improved by 9.53 letters ( $P < 0.05$ ). In all, 69% of patients increased at least one line, and 34.7% increased three or more lines. There were no cases of moderate vision loss (>3 lines) or severe vision loss (>6 lines). Favourable outcomes were obtained in all subgroups. Patients received an average of 1.52 injections. No serious ocular complications were noted.

**Conclusions** The 12-month results of this consecutive series of 23 patients suggests that a small number of injections of intravitreal ranibizumab may be safe and effective for both preventing and restoring visual loss in patients with CNV secondary to PM. Further studies to evaluate the safety and efficacy are justified.

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**Keywords:** choroidal neovascularization; neovascular membrane; pathologic myopia; ranibizumab; myopic CNV; anti-VEGF therapy

## Introduction

Pathological myopia (PM) is one of the leading causes of visual disability in the world from 20–50 years of age.<sup>1</sup> Choroidal neovascularization (CNV) is one of the most important vision-threatening complications of pathologic myopia (PM) and occurs in 5–10% of myopic patients, with a positive correlation between risk and degree of myopia. Among myopic patients with pre-existing CNV, more than 30% will develop CNV in the fellow eye within 8 years.<sup>2</sup>

Photodynamic therapy (PDT) with verteporfin (Visudyne, Novartis Ophthalmics, Basel, Switzerland) is, since 2001, the only approved treatment for subfoveal CNV in myopic eyes, and is able to stabilize best-corrected visual acuity (BCVA) of patients with subfoveal myopic CNV. At 12-month follow-up, 86% of the verteporfin-treated patients lost fewer than 15 letters of BCVA, in comparison to 67% of the placebo-treated patients.<sup>3</sup> However, its limitations, particularly for improving vision, are well known.

In 2005, Nguyen *et al*<sup>4</sup> reported good results with the use of systemic bevacizumab (Avastin, Genentech, San Francisco, CA, USA) in two myopic patients with CNV. Yamamoto *et al*<sup>5</sup> and Sakaguchi *et al*<sup>6</sup> were the first to report a short series of patients with the use of intravitreal bevacizumab for the treatment of subfoveal CNV secondary to PM, showing favourable

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results with no adverse events. The short-term results of both reports appeared promising with improvement in mean VA from 2 to 3.5 lines.

Ranibizumab (Lucentis, Novartis, Basel, Switzerland) is a humanized antibody fragment against VEGF-A that was specifically designed for intraocular use as a smaller antibody fragment to better penetrate through the retina.

Here, we present the results of a 12-month prospective study that includes eyes with CNV secondary to PM treated with intravitreal injections of bevacizumab.

## Materials and methods

A prospective, consecutive, nonrandomized, interventional case series of 23 eyes of 23 patients with CNV secondary to PM was carried out. Patients with subfoveal or juxtafoveal CNV secondary to PM were recruited to receive intravitreal injections of ranibizumab as needed, after the first injection (PRN: Pro Re Nata). PM was defined as an eye with a minimum refractive error of  $-5$  D and retinal signs, such as lacquer cracks and peripapillary chorioretinal atrophy. CNV was confirmed with fluorescein angiography (FA) and/or optical coherence tomography (OCT). Patients could have received earlier treatments for CNV before being recruited for the study.

Patients were excluded from the study if they presented features of any condition other than PM associated with CNV that could suggest a different aetiology, such as age-related macular degeneration, angioid streaks, trauma, choroiditis, or hereditary diseases in the study or the fellow eye.

All patients underwent a complete ophthalmological examination at the time of inclusion in the study, including BCVA with ETDRS charts, biomicroscopic evaluation of the anterior and posterior segment, FA, and OCT. Patients with active CNV secondary to PM were offered treatment with intravitreal ranibizumab in an 'off-label' fashion. The potential benefits and side effects were discussed with patients and relatives. Patients willing to receive treatment provided written informed consent.

The need for treatment was based on the presence of recurrent intraretinal or subretinal fluid on OCT scans or leakage on FA. BCVA and presence of metamorphopsia were also used to decide the need for treatment when OCT scans or FA were questionable.

The procedure was carried out under sterile conditions as an office procedure. Patients were patched for 4 h and instructed to apply ciprofloxacin 0.03% (Exocin, Allergan) one drop, five times daily for 5 days after the procedure and fluormetolone 0.25%

(FML forte, Allergan) one drop, five times daily for 2 days after the procedure. Patients were contacted by telephone on the following day and instructed to come back for a consultation if symptoms of pain or significant loss of vision occurred.

Follow-up examinations were carried out every month. At each visit, another complete ophthalmic examination was carried out, including BCVA testing with ETDRS charts and fourier domain OCT scanning (3D OCT Topcon, Topcon, Japan).

The need for retreatment was based on the presence of recurrent intraretinal or subretinal fluid on OCT scans or leakage on FA. BCVA and presence or worsening of subjective metamorphopsia was also used to decide the need for retreatment when OCT scans or FA were questionable. The main outcome measures were mean change in BCVA. Secondary outcomes were angiographic cessation of leakage, and absence of intraretinal or subretinal fluid.

Data were analysed using the paired *t*-test. A *P*-value of 0.05 was considered significant.

## Results

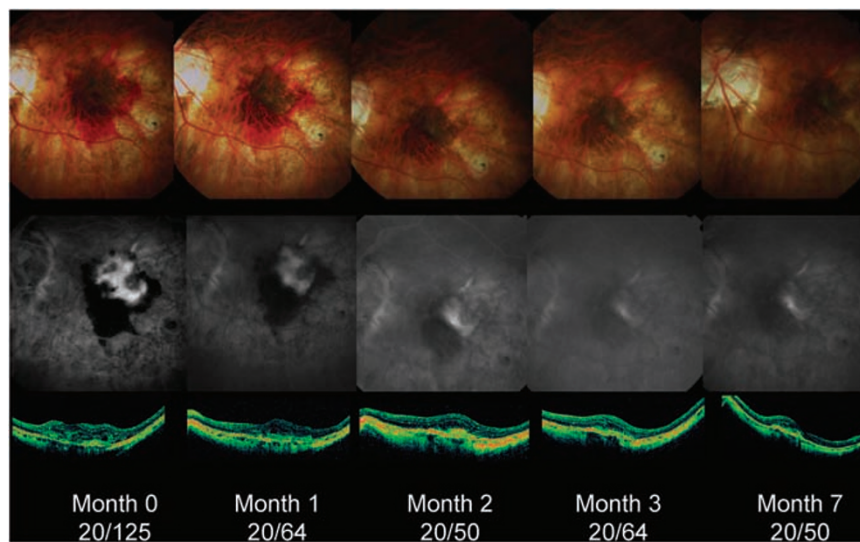
Table 1 shows the patient characteristics. In all, 23 eyes of 23 consecutive patients with CNV secondary to PM were included. Patients were enrolled between January 2007 and January 2008. Seventeen were females, and 6 were males. Mean age was 51.08 years (SD = 17.40). Twelve patients were older than 50 years. The mean spherical equivalent refractive error of the 23 eyes was  $-10.39$  D (SD = 10.39). Fourteen patients were treated earlier and 9 were naïve. Six eyes were treated earlier with PDT and intravitreal bevacizumab, four eyes with intravitreal bevacizumab alone, and four eyes with PDT alone. One patient was lost during the follow-up, at month 8 (patient no. 15). The patient was contacted by telephone after 4 months, and she had not received additional injections, without, at least, any worsening of her vision. Figure 1 shows the results in a 74-year-old woman with CNV secondary to PM that had been treated earlier with 2 intravitreal injections of bevacizumab.

Table 2 shows the mean change in VA. At the 12-month follow-up, the mean VA improved by  $+9.53$  letters ( $P < 0.05$ ). The VA improvement was higher in the untreated eyes ( $+12.78$  letters;  $P < 0.05$ ) than in the earlier treated eyes with PDT and/or intravitreal bevacizumab ( $+7.43$  letters;  $P < 0.05$ ). Patients with an age  $< 50$  years improved by a mean of  $+12$  letters ( $P < 0.05$ ), and patients older than 50 years improved by a mean of  $+7.25$  letters ( $P < 0.05$ ). Overall, 16 cases (69.5%) increased at least one line of VA (Table 3). Six eyes (27%) increased more than three lines of VA. There were no

**Table 1** Main data of patients included in the study

Patient no.	Sex	Age	Eye	D	Previous treatment (and how long ago)	Status fellow	Baseline VA letters (Snellen equivalent)	12-month VA letters (Snellen equivalent)	Number of injections
1	F	44	RE	-12	Three PDTs (6 m), one bevacizumab (2 m)	Scar	62 (20/50)	65 (20/50)	5
2	M	46	LE	-5	No	Normal	58 (20/63)	83 (20/20)	1
3	F	46	RE	-5	Three PDTs (6 m), three bevacizumab (1 m)	Scar	57 (20/63)	74 (20/32)	1
4	F	77	LE	-5	Three PDTs (9 m), three bevacizumab (5 m)	Scar	48 (20/100)	54 (20/80)	1
5	F	36	RE	-14	Two PDTs (12 m)	Normal	72 (20/32)	82 (20/20)	1
6	F	74	LE	-10	Two avastin (4 m)	Normal	41 (20/125)	62 (20/50)	2
7	F	35	RE	-14	Five PDTs(12 m), four bevacizumab (12 m)	Scar	38 (20/160)	61 (20/50-)	1
8	M	17	LE	-15	No	Normal	44 (20/125)	77 (20/25)	1
9	M	67	RE	-10	No	Normal	47 (20/100)	58 (20/63)	1
10	F	38	RE	-5	One PDT (8 m), one bevacizumab (6 m)	Normal	72 (20/32)	66 (20/40)	1
11	F	55	LE	-14	Two PDTs (12 m)	Scar	64 (20/50)	78 (20/25)	1
12	F	51	LE	-15	No	Scar	68 (20/40)	81 (20/20)	1
13	M	62	RE	-5	No	Normal	53 (20/80)	57 (20/63)	3
14	F	37	LE	-12	One bevacizumab (9 m)	Normal	42 (20/125)	48 (20/100)	1
15	F	65	RE	-13	Five bevacizumab (3 m)	Scar	3 (20/50)	Lost in follow-up 3 (20/40) at 3 months	1
16	F	62	RE	-10	No	Normal	47 (20/100)	44 (20/125)	2
17	M	50	RE	-18	Two PDTs (8 m), two bevacizumab (4 m)	Scar	42 (20/125)	42 (20/125)	1
18	F	49	LE	-10	One PDT (12 m)	Scar	58 (20/63)	69 (20/40)	1
19	F	17	LE	-5	No	Normal	73 (20/32)	83 (20/20)	3
20	F	65	RE	-10	No	Normal	56 (20/63)	62 (20/50)	1
21	F	55	RE	-10	One avastin (15 m)	Normal	77 (20/25-)	74 (20/32)	3
22	F	73	RE	-10	One PDT (15 m)	RD	32 (20/200)	34 (20/200)	1
23	M	54	LE	-12	No	Scar	66 (20/40)	82 (20/20)	1

F = female; LE = left eye; M = male; PDT = photodynamic therapy; RE = right eye; VA = visual acuity.



**Figure 1** Patient no. 6: A 74-year-old woman who had been treated with two intravitreal injections of bevacizumab recently—4 months ago. She had very active recurrence of CNV and was treated with intravitreal ranibizumab at the onset and at 1 month as leakage was still present at FA. Leakage resolved and vision improved four lines of ETDRS.

**Table 2** Mean change in visual acuity (letters score) from baseline to 12-month follow-up

	Baseline VA letters, mean (SD) (Snellen equivalent)	12-month VA letters, mean (SD) (Snellen equivalent)	Change (VA letters)	P-Value
All patients (n = 22)	53.04 (16.65) (20/80)	62.57 (19.27) (20/50)	+ 9.53	<0.05
Untreated patients (n = 9)	56.89 (10.28) (20/63)	69.67 (14.60) (20/40)	+ 12.78	<0.05
Treated patients (n = 13)	50.57 (19.68) (20/80)	58.00 (20.989) (20/63)	+ 7.43	<0.05
Age ≤ 50 years (n = 11)	56.18 (13.06) (20/63)	68.18 (13.79) (20/40)	+ 12.00	<0.05
Age > 50 years (n = 11)	50.17 (19.51) (20/80)	57.42 (22.57) (20/63)	+ 7.25	<0.05

VA = visual acuity; SD = standard deviation.

**Table 3** Main changes in visual acuity at 12-month follow-up

Change in visual acuity	Month 12; 22 eyes, n (%)
≥ 6-line increase	1 (4, 5)
≥ 3- < 6-line increase	5 (22, 7)
≥ 1- < 3-line increase	11 (50)
No change	2 (9, 1)
≥ 1- < 3-line decrease	3 (13, 6)
≥ 3-line decrease	0 (0)

cases of moderate vision loss (>3 lines) or severe vision loss (>6 lines).

The mean number of injections was 1.52. Six patients (26%) were retreated during the follow-up. One eye required five injections (patient no. 1), three eyes required three injections (patients no. 13, 19, and 21), and two eyes required two injections (patients no. 6 and 16). Four of them were older than 50 years, and three were treated earlier.

No ocular complications were noted after intravitreal injections, besides one patient with partial corneal desepithelization. One patient suffered angina 2 months after a single injection, although it seemed related to a marked anaemia secondary to a hip surgery.

## Discussion

Angiogenesis is regulated by several proangiogenic and antiangiogenic factors, many of which have now been identified. VEGF has been found to be one of the key elements in angiogenesis. Tong *et al*<sup>7</sup> showed that the VEGF concentrations in aqueous humour were markedly increased in patients with CNV secondary to PM when compared with the controls.

Several authors recently reported the benefit of intravitreal bevacizumab for myopic CNV. Yamamoto *et al*<sup>5</sup> reported a retrospective case series of 11 eyes from 9 patients injected with intravitreal bevacizumab. Bevacizumab led to both VA and anatomical improvements. These short-term results were very promising and average visual improvement was 3.5 lines

of gain, and 8 of 11 eyes achieved 20/50 or better vision. Sakaguchi *et al*<sup>6</sup> reported a prospective case series of eight eyes from eight patients. Six patients (75%) had an improved BCVA of two or more lines; in two (25%) patients, the BCVA remained the same. No ocular or systemic adverse events were reported.

In the present prospective, consecutive, nonrandomized, interventional case series, we report the real-life clinical experience with ranibizumab for CNV secondary to PM in 23 eyes of 23 patients. At the 12-month follow-up, the mean VA improved by 9.53 letters ( $P < 0.05$ ). A total of 77% of patients increased at least one line, and 4.5% increased more than six lines. There were no cases of moderate vision loss (>3 lines) or severe vision loss (>6 lines). Favourable outcomes were obtained in all subgroups. Patients received an average of 1.52 injections. No serious ocular complications were noted. The overall population and the smaller subgroups showed statistical significance.

Both untreated and previously treated eyes showed marked VA improvement at the end of follow-up. However, the benefit was more important in the untreated eyes. Naïve lesions may have less RPE and photoreceptors damage and an increased recovery potential.

The mean number of injections at 12 months was 1.52. Some patients showed a progressive improvement beyond 1 month after a single injection. These results suggest that at least in myopic CNV, PRN treatment from the first injection may achieve good clinical results, minimizing the number of needed injections and their potential related systemic and local complications.

Although the results of this consecutive series of 23 patients and earlier series of bevacizumab for myopic CNV do not show specific risks for myopic eyes, these eyes are at a potentially increased risk of suffering retinal tears and retinal detachment. Myopic eyes might also be at an increased risk of spontaneous chorioretinal atrophy after receiving treatments, such as laser or PDT. So far, we have not found any evidence of increased incidence of retinal pigment epithelium, choriocapillaris damage, and atrophy in this series of 23 patients.

However, this could change with a longer follow-up. Moreover, paninhibition of VEGF might impact in the survival of retinal neurons,<sup>8</sup> so it is desirable to administer the smallest number of injections possible, especially in myopic eyes.

A 77-year-old male patient suffered three angina pectoris 2 months after his first single injection. It seemed to be related to a marked anaemia secondary to a hip surgery.

The limitations of this study include its small number of eyes, the relatively short follow-up, and the absence of a control group. The number of patients is too small for further subgroup analysis of subtype lesion. However, all types of lesions showed a dramatic response to treatment, requiring very few injections. One patient was lost during the follow-up, at the 8th month (patient no. 15). As the series is small, a single patient with an unfavourable outcome might have driven the results to a different level of efficacy. The patient was contacted by telephone after 4 months, and she had not received additional injections, without, at least, any worsening of her vision. Therefore, this dropout does not appear to bias our favourable results.

In summary, the results are promising, with a small number of injections needed to preserve vision, and a large proportion of patients with marked gain. Longer follow-up with a larger number of patients is needed to further determine the safety and efficacy of intravitreal ranibizumab in the treatment of myopic CNV.

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1. Which of the following statements about the epidemiology and current treatment of choroidal neovascularization (CNV) in pathologic myopia (PM) is most accurate?

- A Most patients with myopia develop CNV
- B CNV is more likely to occur in patients with more severe myopia
- C Photodynamic therapy (PDT) with verteporfin improves visual acuity in most patients
- D Only systemic bevacizumab appears effective for patients with myopia with CNV

2. All of the following statements about the efficacy of ranibizumab in improving visual acuity are accurate, *except*:

- A The average improvement in visual acuity was 9.53 letters
- B Over two thirds of patients increased at least 1 line of visual acuity
- C Over one third of eyes increased more than 3 lines of visual acuity
- D No patients improved by more than 6 lines of visual acuity

3. Which of the following variables predicted a better response to treatment with ranibizumab?

- A Age over 50 years
- B Higher degrees of myopia
- C No previous treatment for CNV secondary to PM
- D Male sex

4. Which of the following statements about procedures and complications is most accurate?

- A The mean number of injections with ranibizumab was 4
- B Most patients required multiple injections during follow-up
- C Retinal pigment epithelium damage was common after injections
- D There were no cases of moderate or severe vision loss

### Activity evaluation

1. The activity supported the learning objectives.

Strongly disagree                      Strongly agree  
1                      2                      3                      4                      5

2. The material was organized clearly for learning to occur.

Strongly disagree                      Strongly agree  
1                      2                      3                      4                      5

3. The content learned from this activity will impact my practice

Strongly disagree                      Strongly agree  
1                      2                      3                      4                      5

4. The activity was presented objectively and free of commercial bias.

Strongly disagree                      Strongly agree  
1                      2                      3                      4                      5