INTRAVITREAL RANIBIZUMAB FOR MYOPIC CHOROIDAL NEOVASCULARIZATION

12-Month Results

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Purpose: The purpose of this study was to evaluate the safety and efficacy of intravitreal ranibizumab after 12 months in the treatment of choroidal neovascularization secondary to pathologic myopia.

Methods: This was a prospective, multicenter, consecutive, nonrandomized, interventional case series. The study included 34 eyes of 32 patients with choroidal neovascularization secondary to pathologic myopia; 13 eyes had previous photodynamic therapy, and 21 eyes had no previous treatment. The patients were followed for ≥12 months. Best-corrected visual acuity, optical coherence tomography, and the presence of metamorphopsia were assessed monthly.

Results: Mean visual acuity improved 8 letters from baseline to 12-month follow-up, and the difference was statistically significant ($P < 0.001$): 100% of the eyes lost <3 lines on the Early Treatment Diabetic Retinopathy Study chart, 24% of the eyes improved ≥3 lines, 44% improved ≥2 lines, 65% improved ≥1 line, and 79% improved ≥0 lines. Central retinal thickness decreased significantly from baseline to the 12-month follow-up ($P < 0.01$). A mean of 3.6 treatments were performed during the 12-month follow-up, and no systemic or ocular side effects were registered during that time.

Conclusion: One-year results of intravitreal ranibizumab for myopic choroidal neovascularization are very promising. Additional prospective studies are necessary to better determine long-term efficacy and safety.

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Although the natural course of myopic choroidal neovascularization (CNV) is highly variable, the long-term prognosis is known to be poor.[1–4] Photodynamic therapy (PDT) with verteporfin, the only treatment approved by regulatory authorities in Europe, for subfoveal myopic CNV[5,6] has also shown good efficacy in juxtafoveal lesions.[7]

However, in the verteporfin in PDT study,[5] a loss of ≥15 letters in visual acuity was observed in up to 13% of the treated eyes at 1 year of follow-up; only 6% of the eyes gained ≥3 lines, and 32% of the eyes gained ≥1 line. Preliminary results of intravitreal bevacizumab have been published and seem to be promising up to 1 year.[8–15]

We have published the first retrospective study with the short-term results of intravitreous ranibizumab for the treatment of myopic CNV.[16] The 1-year results of this study are presented herein.

Patients and Methods

Patients and methods were previously described.[16] This prospective, nonrandomized, multicenter, interventional, case series included 32 patients with 34

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myopic eyes with CNV, from 2 countries (Portugal and Spain), who had been followed-up and treated with ranibizumab by 5 ophthalmologists (R.M.S., J.M.R.-M., P.R., A.C., and L.R.) in their clinical practice. The short-term results of 26 of these 34 eyes already have been published.[16]

Thirteen eyes had previously undergone PDT at the time of inclusion in the study, and 21 eyes had no previous treatment. At baseline, all patients had evidence, on fluorescein angiography (FA), of leakage involving the fovea and potentially related with visual acuity decrease. No additional PDT was performed in any case during the follow-up. Inclusion and exclusion criteria were as follows.

Inclusion Criteria

- Pathologic myopia with axial length ≥25 mm and spherical equivalent ≥8 diopters
- Sub- or juxtafoveal CNV
- With or without previous PDT
- Visual acuity ≥20/400
- Age ≥21 years; signature required on a written informed consent form

Exclusion Criteria

- CNV resulting from causes other than myopic CNV, including ocular histoplasmosis syndrome, angioid streaks, multifocal choroiditis, and choroidal rupture
- Any retinal vasculopathies, including diabetic retinopathy, retinal vein occlusions, etc., in the study eye
- Previous treatment with other antiangiogenic drugs (such as bevacizumab or pegaptanib), intravitreal triamcinolone; or radiation; also, PDT with Visudyne administered <3 months before the inclusion
- Subfoveal or juxtafoveal laser scar
- Concomitant disease in the study eye, including uveitis, presence of pigment epithelial tears or rips, acute ocular or periocular infection, and central serous chorioretinopathy
- Advanced glaucoma (>0.8 cup-to-disk ratio) or intraocular pressure >21 mmHg in the study eye despite adequate treatment with medication
- Pregnancy or potential pregnancy (premenopausal women not using adequate contraception)

All patients signed an informed consent form to participate in this prospective study after a thorough discussion of all their therapeutic options and after the approval by the institutional review board of each center. The study was performed in accordance with the tenets of the Declaration of Helsinki.

A nonloading dose treatment regimen was assumed in all participating centers. Eligible patients received a baseline intravitreal injection of ranibizumab and were assessed every 4 weeks thereafter. Clinical evaluation after baseline included, in all cases, best-corrected visual acuity (BCVA) using an Early Treatment Diabetic Retinopathy Study chart, ocular pressure, biomicroscopy, fundoscopy, optical coherence tomography (OCT), and/or FA. The need for retreatment was determined by the presence of intra- or subretinal fluid in the 6 high-density, high-resolution radial diagonal scans produced by OCT (Stratus OCT, version 4.0.2, Carl Zeiss Meditec, Dublin, CA), metamorphopsia, and/or FA subfoveal or juxtafoveal leakage. Intravitreal injection of 0.5 mg of ranibizumab (Lucentis, Novartis, Switzerland) in a 0.05-mL volume of solution was administered using a 30-gauge needle 4 mm posterior to the limbus. The procedure was performed on an outpatient basis under strict aseptic technique and using topical anesthesia. Indirect ophthalmoscopy was performed before the procedure in all cases. Patients were given topical ofloxacin, 4 times daily, 3 days before and 3 days after each injection.

Patients with recent thromboembolic events (≤6 months) were not usually injected with ranibizumab, but the final decision was at the discretion of the treating physician. A reevaluation of all the patients was performed every 4 weeks after the first injection of ranibizumab, including the presence of metamorphopsia, BCVA, slit-lamp evaluation, biomicroscopic fundus examination, OCT, and/or FA. In doubtful cases, FA was performed for deciding the necessity of retreatment.

Measurements of visual acuity were performed at all visits with an Early Treatment Diabetic Retinopathy Study chart, and BCVA was obtained. Ocular imaging consisted of FA (performed at baseline in all cases and as needed during the follow-up) and/or OCT at each follow-up visit. Although the automated macular thickness map was obtained with the fast-mode low-density scans, central retinal thickness measurements were determined from manual measurements in high-density scans.

For statistical analysis, the Wilcoxon signed-rank test and the two-tailed *t*-test were used, comparing changes in BCVA and central retinal thickness on OCT. A P value <0.05 was considered statistically significant.

Results

A total of 34 eyes (17 right eyes and 17 left eyes) from 32 patients (20 women and 12 men; mean age,

54 years; standard deviation, 17 years) were treated with at least 1 injection of ranibizumab. Characteristics of all the eyes studied are summarized in Tables 1 and 2.

A significant improvement in visual acuity occurred at 3, 6, 9, and 12 months ($P < 0.001$). Treated eyes gained a mean of 8 letters at 12 months.

An improvement in visual acuity of ≥3 lines occurred in 8 eyes (24%) at 1 year (Tables 1 and 2); 15 eyes (44%) improved ≥2 lines, 22 eyes (65%) improved ≥1 line, and 27 eyes (79%) improved ≥0 letters. A decrease in visual acuity occurred in 7 eyes (21%) and was inferior to 2 lines in all cases. None of the treated eyes lost ≥3 Early Treatment Diabetic Retinopathy Study lines (15 letters). No systemic or ocular side effects were registered during the follow-up. A mean of 3.6 treatments were performed during the 12 months of follow-up.

Thirteen of the included eyes had undergone PDT previously (1–6 treatments). No additional PDT was performed after enrollment in the study. These 13 eyes were compared with the 21 naïve-to-treatment eyes regarding baseline characteristics (age, visual acuity, and central macular thickness) and response to intravitreal ranibizumab. No statistically significant difference ($P > 0.05$) was found between the PDT group of eyes and the non-PDT group of eyes regarding any of the mentioned baseline characteristics, the posttreatment number of letters gained or lost, or the number of treatments. Macular thickness was significantly higher at 12 months in the eyes treated with PDT. The eyes previously treated with PDT improved a mean of 6 letters in 12 months, after a mean of 4.2 intravitreal injections, and the difference was statistically significant compared with baseline visual acuity ($P < 0.05$) at 6, 9, and 12 months. Eyes with no previous PDT improved an average of 9 letters at 12 months, after a mean of 3.2 intravitreal injections; the difference was statistically significant at 3, 6, 9, and 12 months ($P < 0.01$).

Central macular thickness, evaluated manually in the high-density, high-resolution scans, decreased significantly from baseline to 12 months of follow-up in the full set of patients ($P < 0.01$) and in the group of naïve-to-treatment patients ($P < 0.001$) but not in those whose eyes underwent PDT previously ($P > 0.05$). None of the patients experienced systemic or ocular complications including endophthalmitis, retinal detachment, increased intraocular pressure, intraocular inflammation, or thromboembolic events.

Discussion

Ranibizumab is an antiangiogenic medication that blocks the effects of vascular endothelial growth factor. The efficacy of ranibizumab in the treatment of CNV caused by age-related macular degeneration is well established, and in many countries, ranibizumab is approved for this indication.[17,18] Bevacizumab, another antiangiogenic medication that similarly inhibits vascular endothelial growth factor action, is widely used for CNV caused by age-related macular degeneration but is not approved for this indication by any regulatory body. In theory, the efficacy of both ranibizumab and bevacizumab to cause regression of myopic CNV should be similar to the efficacy they have in causing regression of CNV caused by age-related macular degeneration. Reports of the use of bevacizumab in the treatment of myopic CNV have demonstrated promising results, and several reports have demonstrated bevacizumab to be superior to PDT with verteporfin for CNV in myopia.[8–15]

We have demonstrated a short-term benefit of treatment of myopic CNV with ranibizumab.[16] Our 1-year results of intravitreal ranibizumab in myopic eyes with CNV confirm the short-term efficacy and safety results. The entire set of treated eyes lost <3 lines, and 79% of them showed no letter loss. Treated eyes gained a mean of 8 letters at 12 months of follow-up, and the difference was statistically significant compared with baseline visual acuity.

Both eyes with and without previous PDT gained vision (6 and 9 letters, respectively) at 12 months, and the difference between the 2 groups was not significant. However, some differences between them were seen. The previous PDT group showed a significant gain in visual acuity at 6, 9, and 12 months ($P < 0.05$) but not at 3 months; visual acuity loss occurred in 31% of the cases; and only 8% achieved a visual acuity of ≥20/40, despite the significant improvement in mean visual acuity and the reduction in cases with visual acuity ≤20/200. Eyes with no previous PDT showed a significant improvement in visual acuity at 3, 6, 9, and 12 months ($P < 0.001$); visual acuity loss occurred only in 9% of the cases; the number of eyes with ≥20/40 visual acuity doubled from 24% at baseline to 48% at 12 months (Table 2); and the number of eyes with visual acuity ≤20/200 decreased from 29% to 10%. There are many possible explanations for the relatively inferior results in eyes with previous PDT, including choriocapillary atrophy resulting from PDT and the simple fact that the previous PDT eyes probably would have a more aggressive CNV with a poorer response to any treatment.

The relatively high percentage of eyes with some visual acuity loss at 12 months (21%) may be related to many factors, such as the nonloading dose regimen, the criteria for retreatment mainly based in OCT, and even the fact that eyes previously treated with PDT

Table 1. Patients Characteristics at Baseline and Follow-Up

Patient No.	Age, Years	Previous PDT Treatment (No.)	Initial VA Letters	1-Month VA Letters	1-Month VA Change Letters	3-Month VA Letters	6-Month VA Letters	9-Month VA Letters	12-Month VA Letters	12-Month VA Change Letters	No. of Treatments in 3 Months	No. of Treatments in 6 Months	No. of Treatments in 9 Months	No. Treatment in 12 Months	Initial OCT	12-Month OCT Thickness
1	63	Yes (6)	75	85	10	85	85	85	85	10	1	1	1	1	—	—
2	22	—	35	62	17	62	83	75	70	35	2	3	4	5	215	280
3	27	Yes (1)	47	37	−10	37	41	42	42	−5	2	3	4	5	340	400
4	80	—	70	75	5	75	73	75	70	0	2	2	2	3	298	222
5	41	—	40	49	9	49	54	54	45	5	3	5	5	5	215	163
6	69	Yes (1)	19	22	3	24	28	29	30	11	3	4	5	7	365	348
7	72	Yes (2)	49	65	16	70	66	65	64	15	1	1	1	1	257	157
8	84	—	74	77	3	84	84	84	84	10	2	2	2	2	406	215
9	50	—	35	55	20	55	56	52	52	17	2	3	4	5	490	186
10	20	Yes (1)	53	49	−4	49	49	68	68	15	2	3	4	5	348	232
11	62	Yes (2)	59	61	2	61	66	55	50	−9	2	4	5	6	440	430
12	54	Yes (6)	60	54	−6	60	56	53	55	−5	1	2	3	4	207	326
13	39	Yes (5)	50	60	10	60	60	60	60	10	1	1	1	1	—	—
14	54	—	65	65	0	65	70	75	72	7	2	3	4	5	406	319
15	73	Yes (3)	50	45	−5	45	47	47	44	−6	2	3	3	3	448	400
16	37	—	54	62	8	62	71	75	68	14	2	2	3	4	240	267
17	52	Yes (3)	35	48	13	56	59	60	55	20	3	4	5	6	315	268
18	32	—	62	56	−6	56	67	61	55	−7	2	3	4	5	282	154
19	45	Yes (3)	40	—	—	36	59	55	50	10	2	3	3	4	—	—
20	32	Yes (3)	47	50	3	49	52	56	50	3	3	4	5	6	298	378
21	51	—	64	69	5	70	70	65	67	3	3	2	3	3	232	180
22	54	Yes (4)	55	—	—	69	61	59	63	8	2	3	5	5	307	398
23	34	—	69	65	−4	65	68	72	75	6	2	3	4	5	307	255
24	89	—	30	35	5	35	55	55	55	25	1	1	1	1	307	178
25	67	—	52	40	−12	45	50	43	45	−7	1	2	3	4	—	—
26	57	—	20	25	5	25	25	35	25	5	3	3	4	4	254	204
27	55	—	80	80	0	80	80	83	80	0	3	3	3	4	201	201
28	48	—	72	75	3	74	74	70	65	−7	3	3	3	3	293	300
29	65	—	65	70	5	74	70	74	70	5	1	2	2	2	324	261
30	65	—	3	25	23	20	20	20	25	22	1	1	1	1	308	167
31	54	—	58	58	0	63	58	58	58	0	1	1	2	2	201	224
32	48	—	65	70	5	70	70	70	75	10	1	1	1	2	—	—
33	70	—	75	80	5	80	75	75	80	5	1	1	1	1	—	—
34	70	—	35	65	30	70	75	70	75	40	1	2	2	2	—	—
Mean	54.0	—	51.8	57.3	4.9	58.2	61.1	61.0	59.6	7.8	1.9	2.5	3.0	3.6	307.6	263.4
SD	17.3	—	18.1	16.6	9.3	17.2	15.9	15.5	15.8	11.6	0.8	1.1	1.4	1.8	79.2	85.3

VA, visual acuity.

Table 2. Eyes With and Without Previous PDT

VA	With Previous PDT	Without Previous PDT	*P*
Initial VA (letters)	20/100 (49 letters)	53 letters (20/100)	NS
12-month VA	20/80 (55 letters)	62 (20/63 letters)	NS
Initial thickness	335 μm	292 μm	NS
12-month thickness	326 μm	222 μm	<0.01
VA gain at 12 months	6 letters	9 letters	NS
Initial VA $\geq$20/40	1 (8%)	5 (24%)	—
Final VA $\geq$20/40	1 (8%)	10 (48%)	—
Initial VA $\leq$20/200	2 (15%)	6 (29%)	—
Final VA $\leq$20/200	1 (8%)	2 (10%)	—
Gain of $\geq$15 letters	3 (23%)	5 (24%)	—
Loss of $\geq$5 letters	5 (38%)	2 (10%)	—

VA, visual acuity; NS, not significant.

were also included (~one-third of the eyes with previous PDT and only 9% of the eyes with no previous PDT lost vision).

The mean number of treatments required in the entire set of eyes was 3.6 at 12 months. The mean number of injections was 1.9 in the first 3 months, 0.6 between 3 and 6 months, 0.5 between 6 and 9 months, and 0.6 between 9 and 12 months. Our criteria for retreatment was based on the presence of fluid observed on OCT and/or leakage on FA and the presence of metamorphopsia.[16] A nonloading dose regimen was adopted in all study centers. This decision was based on the assumption that the greater improvement in visual acuity is achieved after the first injection of ranibizumab[16,18] and the fact that CNV is generally less extensive in myopic eyes than in eyes with age-related macular degeneration. Myopic eyes with CNV, in general, have less intra- and subretinal fluid, which may contribute to a better response to intravitreal ranibizumab. In fact, in our series, the greater improvement in visual acuity occurred after the first injection (5 letters), whereas additional improvements in visual acuity occurred at 6 and 9 months. At 3 months, 26 eyes (76%) had received <3 injections, and at the 12-month evaluation, 11 eyes (32%) had been treated with only ≤ 2 injections. We believed that the adoption of a loading-dose regimen would be excessive and unnecessary. However, we could not exclude the possibility that a greater improvement would have been achieved with a more intense treatment regimen.

A comparison between eyes gaining and losing vision at 12 months showed no significant difference regarding age, initial visual acuity, OCT central macular thickness, number of injections, or previous PDT ($P > 0.05$). Twenty-two eyes gained vision after the first visit. Twenty of them (91%) maintained some gain in visual acuity at 12 months. Seven eyes lost vision after the first injection (cases 3, 10, 12, 15, 18, 23, and 25). Five of them (cases 3, 12, 15, 18, and 25) lost ≥ 5 letters at 1 month and did not recover by the 12-month follow-up visit. The other 2 eyes lost <5 letters and gained additional visual acuity during the follow-up. Eyes losing vision at the 1-month follow-up (after the first treatment) had a worse prognosis. They had a much higher possibility of maintaining a negative score at 12 months ($P < 0.001$) compared with eyes that initially showed some gain. These results suggested that the response to the first injection may be a good predictor of efficacy.

No cases of endophthalmitis, stroke, or retinal detachment were registered during the follow-up. Particular care was taken to observe the peripheral retina before treatment, and prophylactic topical antibiotics were administered before and after the injection.

Limitations of our study were related to its multicenter and nonrandomized design. An effort was made to use similar standardized procedures in the five centers. Patients were observed each month with clinical examination, BCVA assessment, and OCT (and FA, as needed). Best-corrected visual acuity was obtained with Early Treatment Diabetic Retinopathy Study charts, and the score was registered. Even so, some bias may have been introduced in the study. However, its potential impact would have been minimal, considering that visual acuity results are consistent and associated with anatomical improvement that is confirmed by OCT. In fact, a significant central macular thickness was registered at 12 months and was associated with significant improvement in visual acuity.

In conclusion, the 1-year results of intravitreal ranibizumab for myopic CNV using a routine clinical care regimen were positive. Nearly one-fourth of the eyes showed a significant improvement in visual acuity at 12 months, one-third of the eyes had vision that allowed patients to drive or read, and no cases of severely decreased visual acuity were registered. Significant improvement in visual acuity also occurred in eyes with

previous PDT, although the results were less impressive. Additional prospective long-term studies will be necessary to evaluate the safety and efficacy of intravitreal ranibizumab in the treatment of myopic CNV.

Key words: Lucentis, myopia, ranibizumab, antiangiogenic drugs, CNV, photodynamic therapy, verteporfin, bevacizumab.

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