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Original Article

Combined therapy (intravitreal bevacizumab plus verteporfin photodynamic therapy) versus intravitreal bevacizumab monotherapy for choroidal neovascularization due to age-related macular degeneration: a 1-year follow-up study

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Abstract

Purpose—To assess the efficacy and safety of combined intravitreal bevacizumab and low-fluency-rate photodynamic therapy (PDT) in the treatment of choroidal neovascularization (CNV) associated with age-related macular degeneration (AMD) and to compare it with intravitreal bevacizumab monotherapy.

Methods—A total of 62 eyes of 62 patients with angiographic evidence of CNV were divided into 2 groups: the eyes of one group were treated with a combined therapy of 1 intravitreal bevacizumab injection (1.25 mg) and PDT within 7 days; the eyes of the other group received intravitreal bevacizumab monotherapy. Clinical evidence of complications, best-corrected visual acuity (BVCA) and fluorescein leakage were evaluated. Best-corrected visual acuity and optical coherence tomography (OCT) were tested monthly and followed for 12 months.

Results—In the combined group the mean BCVA increased from 0.61 logMAR before the treatment to 0.54 logMAR at 12 months' follow-up. In the monotherapy group the mean BCVA increased from 0.65 logMAR to 0.60 logMAR at 12 months' follow-up. There was no significant difference in visual acuity outcomes between groups ($P > 0.05$). In the combined group the mean number of treatments was 1.19 per patient; in the monotherapy group, 5.31 per patient ($P < 0.01$).

Conclusions—Combined therapy appears to be an effective option for CNV associated with AMD treatment allowing a significant reduction of intravitreal injections.

Introduction

Untreated age-related macular degeneration (AMD) complicated by choroidal neovascularization (CNV) is one of the most common causes of blindness among individuals >50 years of age in developed countries.[1] Neovascular AMD is a pathological disease involving multiple angiogenic agents to develop anomalous blood vessels arising from the choroid and disrupting the anatomy and the function of retinal tissue. Until recently, few therapeutic options were available for the treatment of AMD-associated CNV, the main treatments being photodynamic therapy (PDT) with verteporfin and intravitreal administrations of pegaptanib sodium (Macugen; Eyetech Inc, Cedar Knolls, NJ) or triamcinolone (Kanacort; Bristol-Myers Squibb, NJ).[2–9] Recently developments in producing humanized mouse monoclonal antibodies that bind all vascular endothelial growth factor (VEGF) isoforms has offered a new means to treat CNV due to AMD. Ranibizumab (Lucentis; Genentech, South San Francisco, CA), a Food and Drug Administration–approved monoclonal antibody that blocks VEGF, provides an effective treatment for neovascular AMD.[10,11] Bevacizumab (Avastin; Genentech) has also been used off-label as an intravitreal treatment for CNV.[12] Several uncontrolled studies and cases have reported visual improvements similar to those of ranibizumab. Intravitreal injections have been associated with improvements in visual acuity and reduction in both central retinal thickness (CRT) and angiographic leakage. Neverthe-

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Table 1. Inclusion and exclusion criteria for enrollment of patients

Inclusion criteria
• Age ≥50 years
• Presence of primary active choroidal neovascularization (CNV) attributable to age-related macular degeneration (AMD), as detected on fluorescein angiography
• Willing and able to return to the clinic for monthly visits
Exclusion criteria
• CNV with large hemorrhages (>1 optic disc diameter) at presentation
• Area of CNV larger than 1 optic disc diameter
• Long-standing CNV lesion at presentation (presence of fibrosis and symptoms occurred more than 6 months before diagnosis)
• Previously treated patients that had received laser and PDT treatment involving the central area of the retina or anti-VEGF treatment performed at least 6 months before baseline
• Vitreous hemorrhage or history of rhegmatogenous retinal detachment or macular hole in the study eye
• Any intraocular surgery before the screening or intraocular surgery planned during the study follow-up period
• History of uncontrolled glaucoma
• Active intraocular inflammation or ocular infection
• Concomitant eye disease in the study eye
• Cardiovascular, cerebrovascular or peripheral vascular event within 6 month prior the screening

less, monotherapy with intravitreal injections requires multiple intravitreal doses to maintain visual gain.[13,14] PDT with reduced light dose to avoid secondary choroidal atrophy, combined with intravitreal injections of antiangiogenesis drugs, has recently been suggested as an option for AMD to stabilize visual acuity, improve CRT, and reduce need for retreatment.[15–24] This study aimed to evaluate the efficacy of the combined treatment using bevacizumab and low-fluency-rate PDT in AMD-associated CNV by comparing it to intravitreal bevacizumab injections as monotherapy. Specifically, we wanted to determine whether combined therapy could decrease the number of injections.

Subjects and Methods

The study was performed in accordance with the tenets of the Declaration of Helsinki and was approved by our local ethics committee; informed consent was obtained from all subjects. This was a prospective, consecutive, comparative, interventional case series study in which we analyzed the outcomes of two therapeutic strategies. Patients treated for AMD-related CNV at the University Eye Clinic of Trieste within a 2-year period from December 2008 to December 2010 were enrolled. Patients were randomized into two groups—patients treated with intravitreal injection of bevacizumab followed by PDT (combined group), and patients who received only intravitreal bevacizumab injections (monotherapy group). Follow-up lasted 12 months for all patients. The major eligibility criteria are shown in Table 1.

At the screening visit, a careful medical history and complete ophthalmic evaluation with optical coherence tomography (OCT [Stratus OCT; Carl Zeiss Meditec, Dublin, CA]) and fluorescein angiography were performed. All patients were evaluated monthly for visual acuity and central retinal thickness (OCT examination). Visual acuity, fundus examination, fluorescein angiography, and OCT were performed at the fixed time points of follow-up (6 and 12 months). In both groups, the best-corrected visual acuity (BCVA) was determined according to the Early Treatment Diabetic Retinopathy Study (ETDRS) charts and converted to logMAR for data analysis.

The combined group was treated with combination therapy consisting of 1 injection of bevacizumab (1.25 mg) followed by a single PDT treatment delivered with a low-fluency-rate (300 mW/cm^2 for 83 sec, 25 J/cm^2) within 7 days of the injection. Bevacizumab (1.25 mg) was prepared and placed in a 1 ml syringe in sterile conditions by the hospital pharmacy. Injections were performed as an outpatient procedure under topical anesthesia after 5% povidone-iodine solution was placed on the globe and allowed to remain for at least 30–60 seconds. Using a 27-gauge needle, 0.05 ml of bevacizumab (Avastin; Genentech) was injected into the vitreous cavity. Topical ofloxacin 4 times daily for 7 days was prescribed after each injection. Patients were examined on

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Table 2. Baseline disease characteristics

Characteristic	Patients, no. (%)	Age, years		Sex		Baseline VA	
		<65 (%)	>65 (%)	Male (%)	Female (%)	LogMAR	*P* value
Lesion composition (n = 62)							
Classic	26 (41.9)	10 (16.1)	16 (25.8)	8 (12.9)	18 (29.03)	0.58	
Minimally classic	19 (30.6)	11 (17.7)	8 (12.9)	5 (8.0)	14 (22.58)	0.64	>0.05
Occult (no classic)	17 (27.4)	2 (3.2)	15 (24.19)	8 (12.9)	9 (14.5)	0.68	
Lesion location (n = 62)							
Subfoveal	50 (80.64)	11 (17.7)	39 (62.9)	18 (29.03)	32 (51.61)	0.61	
Juxtafoveal	5 (8.06)	3 (4.83)	2 (3.2)	1 (1.61)	4 (6.45)	0.6	>0.05
Extrafoveal	3 (4.83)	2 (3.2)	1 (1.61)	1 (1.61)	2 (3.2)	0.54	
Not available[a]	4 (6.45)		4 (6.45)	1 (1.61)	3 (4.83)	0.58	

[a]Angiograms not clearly interpretable.

the first and fourth day after injection. The combination therapy was performed with the same dosage of anti-VEGF drug and timing of postoperative examination.

The monotherapy group was treated solely with intravitreal bevacizumab injections (1.25 mg). Treatment was initiated with 3 consecutive monthly injections, followed by retreatment as needed, with monthly monitoring. The identical procedure described above was used for each injection.

Patients received additional treatment depending on their group (bevacizumab injection alone for the first group and bevacizumab injection plus PDT treatment for the second group) when active leakage on fluorescein angiography or intraretinal edema on OCT was detected. Retreatment criteria were loss of visual acuity and increase or permanence of intraretinal edema.

Statistical analysis was performed with SPSS Advanced Statistics software (Armonk, New York, IBM Corp). Groups were compared at baseline in order to verify homogeneity: sex, mean age, basal visual acuity, basal central retinal thickness (CRT) were analyzed with the χ^2 test, Fisher exact test, and the Mann-Whitney test. The variation of visual acuity and CRT after 6 and 12 months was analyzed with Friedman test. The mean number of injections in the two groups was analyzed using the Mann-Whitney test. The level of statistical significance was taken as 5% ($P < 0.05$).

Results

A total of 62 patients were included: 31 eyes of 31 patients (22 females; mean patient age, 77 ± 7.8 years) in the combined group and 31 eyes of 31 patients (19 females; mean patient age, 79 ± 7.3 years) in the monotherapy group. There was no statistical difference between groups in terms of mean patient age ($P < 0.05$), sex ($P < 0.05$), and basal BCVA ($P < 0.05$).

Pathological neovascularizations were classified according to lesion composition (classic, minimally classic and occult) and location (subfoveal, juxtafoveal, extrafoveal, not availed). Table 2 shows the morphology and anatomical characteristics.

At the end of the follow-up period, there were no active lesions in any patients (both groups).

In the combined group, 5 eyes had received previous treatments (laser, PDT, or intravitreal anti-angiogenic drugs). The remaining 26 patients had received no prior treatment. The mean BCVA was 0.61 ± 0.27 logMAR at baseline; 0.52 ± 0.33 logMAR, at 6 months' follow-up; and 0.54 ± 0.34 logMAR at 12 months' follow-up. The mean CRT was 299.6 ± 97.1 µm at baseline, 193.3 ± 95.3 µm at 6 months' follow-up, and 194.6 ± 103.3 µm at 12 months' follow-up. The mean number of combined treatments was 1.19 per patient.

In the monotherapy group, 6 eyes had received previous treatments (laser, PDT or intravitreal anti-angiogenic drugs); the rest of the group (25 patients) had not received prior treatment. The mean BCVA was 0.60 ± 0.31 logMAR at baseline; 0.57 ± 0.26 logMAR at 6 months' follow-up; and 0.60 ± 0.29 logMAR at 12 months' follow-up. The mean CRT was 259.5 ± 135.1 µm at baseline, 222.4 ± 142.8 µm at 6 months, and 216.1 ± 127.3µm at 12 months. The mean number of intravitreal injections was 5.31 per patient.

Only CRT before treatment was statistically different between groups: the mean CRT in the combined group was 299.6 ± 97.1 µm and in the monotherapy group was 259.5 ± 135.1 µm ($P = 0.036$ [Mann-Whitney]).

Table 3. Visual outcomes related to the efficacy of the treatment at 6 months and 12 months

	Improved + stable 6 months		Decresed 6 months		Improved + stable 12 months		Decresed 12 months	
	N	%	N	%	N	%	N	%
Combined therapy (n = 31)	21	67.74	10	32.26	20	64.51	11	35.49
Monotherapy (n = 31)	27	87.09	4	12.91	23	74.32	8	25.68
P value[a]		<0.05				<0.05		

[a]Differences between the two groups at 6 and 12 months in comparison to baseline; Mann-Whitney test.

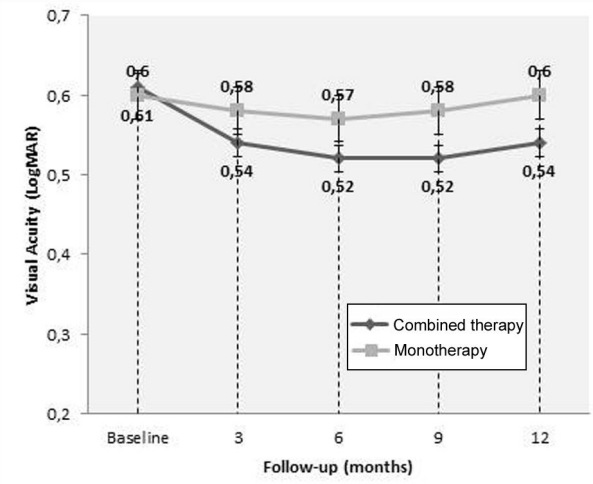

Figure 1. Best-corrected visual acuity (BCVA) in each group over time. The error bars indicate the mean best-corrected visual acuity. At 1 year's follow-up in combined group the mean BCVA was 0.54 logMAR; in the monotherapy group, 0.60 logMAR ($P < 0.05$).

Both groups showed an improvement in visual acuity from baseline. Statistical analysis yielded a significant improvement in BCVA at the end of 1 year's follow-up ($P < 0.05$ [Friedman test]) but not at earlier follow-up ($P = 0.09$). BCVA data is summarized in Figure 1, which shows a progressive decrease in logMAR values that corresponds to a gain in visual acuity. Both groups showed a linear improvement in the first 6 months, which tends to reduce in the last months of follow-up. Despite the variation in visual function at the 6 and 12 months, which seems to be greater in the combined group, statistical analysis did not demonstrate a significant difference ($P > 0.05$). There was no statistical correlation between age, basal BCVA, and previous treatments and BCVA between groups at the end of the follow-up period.

The variations in BCVA during the 12-month follow-up were considered in order to compare the efficacy of the two treatments. The outcomes were divided into two categories following the trends of visual function: improved and stable or decreased. For the first category the variation considered was ≤ −0.1 logMAR; for the decreased outcomes the value was ≥ +0.1 logMAR. This further evaluation was performed for the 6- and 12-month of follow-up.

Table 3 illustrates the number and percentage distribution of the visual outcomes for each group at 6 and 12 months' follow-up, respectively, for each category. In both groups the majority of patients showed stable or improved outcomes, which reduced in the second semester. The percentage of decreased cases in the combined group improved 3%–4% in the second semester, whereas it doubled in the monotherapy group. Global comparison of the groups for these data yielded no statistical difference ($P = 0.15$ [Fisher exact test]). Visual outcomes were spliced into three categories (improved, stable, and decreased), and there were no statistical difference between groups at any time point during follow-up ($P = 0.08$).

Figure 2 shows change in mean central retinal thickness (CRT) from baseline to 12 months' follow-up. In the combined group the linear reduction of the CRT is remarkable and tends to plateau in the second semester. The monotherapy group follows a gradual reduction of the CRT over the course of the year. A significant difference was found between groups in CRT changes from baseline to month 12 ($P < 0.05$ [Friedmann test]).

Another parameter considered in this study was the mean number of injections for each group. In the combined group the mean number of injections was 1.19 ± 0.5; in the monotherapy group, 5.31 ± 1.5. Table 4 shows the range for each group, which varies from 1 to

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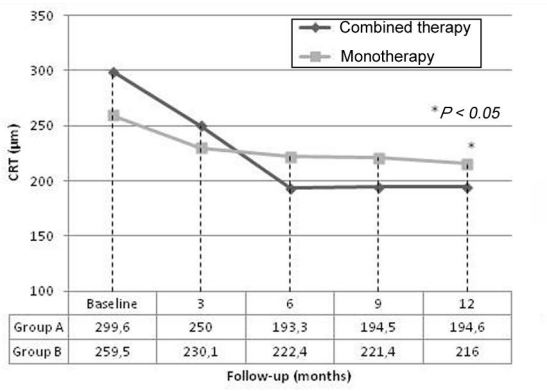

Figure 2. Mean central retinal thickness (CRT) in microns in each group over time. At 1 year's follow-up, in the combined group the mean CRT was 194.6 µm; in the monotherapy group, 216 µm ($P < 0.05$ [Friedmann test])

Table 4. Mean number of intravitreal injections of bevacizumab

No. injections	Combined group	Monotherapy group	*P* value
Minimal value	1	3	<0.01
Maximal value	2	9	<0.01
Mean	1.19 ± 0.5	5.31 ± 1.5	<0.01

2 injections in the combined group and from 3 to 9 injections in the monotherapy group B.

No serious ocular complications were reported up to 12 months after treatment, including endophthalmitis, severe ocular inflammation, retinal detachment, traumatic cataract, ocular hypertension (intraocular pressure >25 mm Hg), transient blurred vision, ocular hyperemia of the infusion site, or systemic adverse events.

Discussion

The first reports on combined therapy using PDT to treat CNV due to AMD were published in 2003 and 2004.[7,8] The development of a rational concept for treating exudative AMD through combination therapies is the result of pathophysiological and biomolecular studies that suggest the CNV is a result of multiple steps as inflammation, cell apoptosis, angiogenesis, and subretinal fluid accumulation. Synergy between more than one treatment offers the possibility of slowing or stopping the entire process involved with CNV, not just the vascular component.[13,14] This may not be possible with a single agent. Patients treated in studies of combined use of PDT and intravitreal triamcinolone seemed to show an improved visual acuity outcome and reduced treatment frequency compared with what would be expected from the use of PDT alone.[6] Promising results were also observed in 10 patients with neovascular AMD treated with combined PDT and intravitreal pegaptanib, with 90% of patients reported to have stabilized or improved vision at 3 months.[7] Combined intravitreal bevacizumab and PDT maintains or improves BCVA and reduces the number of retreatments needed to achieve vision stabilization, even at 12 months of follow-up.[19–25] In 2006 Dhalla et al[26] reported a study of 24 eyes with CNV secondary to AMD treated with PDT and 1.25 mg and bevacizumab. At 7-months' follow-up, visual acuity had stabilized in 83% of patients, and 63% required only a single combined treatment for CNV resolution. Ahmadieh et al[27] reported the efficacy of combined single-session with PDT and bevacizumab injection. A second injection was performed, based on fluorescein angiographic evidence of CNV leakage in 13 of 14 eyes, with a mean interval of 16.3 ± 5.9 weeks. The authors concluded that the combination therapy with a single session of PDT and bevacizumab injection could improve vision; repeat injections may maintain the visual gain from the initial combination therapy. In 2010 Costagliola et al[28] reported a prospective comparative interventional study on 85 patients affected by CNV for AMD. Patients were randomly divided into two groups—those treated with bevacizumab injections alone and those treated with bevacizumab injections plus low-fluency PDT. They concluded that there was no statistical difference between groups in terms of visual acuity and that the reinjection rate was statistically higher in the group treated with only injections. Kaiser et al[29] and Lazic et al[30] analyzed the outcomes of combined therapy (PDT plus bevacizumab injections) with two studies that enrolled a large number of patients and concluded that combination therapy was safe and effective and required a lower number of injections when compared to monotherapy anti-VEGF injections.

In the current study, the percentage of patients with stabilized and improved visual acuity at 6- and 12-months' follow-up did not differ statistically between groups ($P < 0.05$). This suggests that the combination treatment offers a similar possibility of improved visual acuity when compared to the bevacizumab monotherapy.

The CRT values at the end of the follow-up were reduced from baseline in both groups and the gain observed during follow-up is not statistically different between the two groups. Figure 2 shows the course of the CRT in the first year of follow-up. The combined group shows a higher reduction in the first semester,

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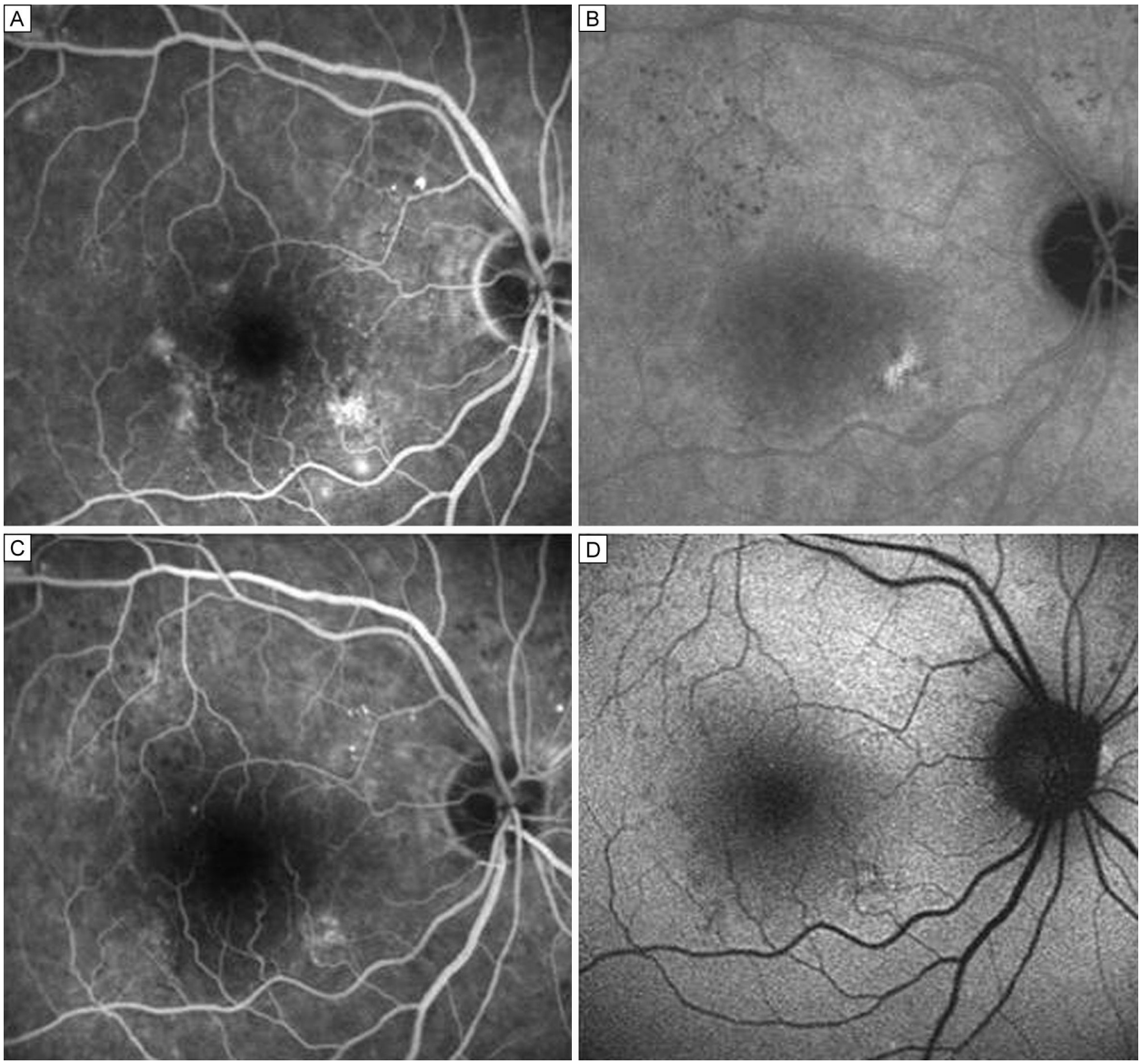

Figure 3. Representative patient treated with one combined treatment of bevacizumab and photodynamic therapy. Fluorescein angiography (A) and indocyanine green angiography (B) at baseline. Fluorescein angiography (C) and autofluorescence image (D) after 1 year of follow-up.

with plateau in the second semester, whereas the monotherapy group demonstrated a linear gradual reduction of retinal thickness throughout the year.

All angiograms and the OCT scans collected were evaluated for the presence of subretinal fibrosis in the lesion area after treatment. There was no evidence of differences in terms of atrophy and retinal fibrosis between groups at 1 year's follow-up. In particular, patients who underwent PDT treatment (Figure 3) did not demonstrate greater subretinal degeneration compared to those of the monotherapy group.

The main difference between groups was the number of injections. The combined group patients received a mean of 1.19 injections versus 5.31 injections for monotherapy group patients at the end of the follow-up period ($P < 0.01$). There was no correlation between BCVA and the number of injections performed in either group.[28]

PDT is an established modality to treat CNV secondary to AMD, although the release of a wide variety of potent mediators (such as acute phase proteins, proteases, peroxidases, radicals, leucocyte chemoattractants, cyto-

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kines, etc), including vasoactive substances, growth factors, and other immunoregulators have been documented after its use.[31] All these compounds, together with the PDT induced hypoxia, increase VEGF levels, as suggested by Schmidt-Erfurth et al.[18] Therefore, bevacizumab injections plus PDT treatment would both ablate established vessels (PDT) and inhibit regrowth due to increased expression of VEGF (bevacizumab).

Overall improvement in vision with a good efficacy in fluorescein leakage from CNV and fewer bevacizumab reinjections throughout the study suggest that a possible synergistic effect may arise from the combination of intravitreal bevacizumab with low-fluency PDT for CNV due to AMD.[28] These findings are promising and further studies are needed to investigate dosage and timing of administration of therapeutic agents in combination for CNV.[31,32]

Possible limitations of this study include the small number of patients in each group, the limited follow-up time, which may be too brief to take into account long-term efficacy of treatment, and the fact that our results are not directly comparable to those of previous reports.

A larger, controlled, prospective, randomized, study with a longer follow-up period will be required in order to fully compare differences in treatment efficacy between anti-VEGF monotherapy and combination therapy. Although preliminary, our outcomes suggest that combined therapy appears to be a useful therapeutic choice for maintaining good visual outcomes while offering a reduced number of intraocular injections. Patients may also benefit from a reduction of discomfort and risk of complications and from the lower cost of procedures.

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