Low fluence rate photodynamic therapy combined with intravitreal bevacizumab for neovascular age related macular degeneration.

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Abstract

Aims: to report efficacy and safety of intravitreal bevacizumab (IVB) alone *versus* IVB plus low fluence PDT in age-related macular degeneration (AMD) patients and to verify the occurrence of a synergistic effect of the combined approach on visual acuity, size and morphology of lesion, as well as on the treatment rate.

Method: prospective comparative interventional study on 85 patients with treatment naive classic, or predominantly classic, subfoveal choroidal neovascularisation (CNV) secondary to AMD. Patients were randomly assigned to Group 1 (IVB injections) and Group 2 (IVB plus low fluence PDT). In Group 2 the PDT with verteporfin was delivered with low fluence rate (300mW/cm^2 for 83seconds, 25 J/cm2). The follow-up was scheduled at 1-,3-,6-, 9- and 12-months.

Results: The eye without recurrence received a mean of 2.8 (Group1) vs 1.4 (Group2) IVB injections, whereas the eyes with recurrence received a mean of 3.2 (Group1) vs 2.2 (Group2) IVB injections. The difference in re-injections rate between the two Groups was statistically significant (P =0.03, ANOVA test). Visual acuity improvement was not statistically significant between the two Groups (P=0.31).

Conclusion: The combination of IVB with low fluence PDT for the treatment of classic or predominantly classic neovascular AMD works in a synergistic fashion with a significant reduction of IVB re-injections rate.

Introduction

The Macular Photocoagulation Study (MPS) provides guidelines for the evaluation and management of patients with choroidal neovascularization (CNV) secondary to age-related macular degeneration (AMD), ocular histoplasmosis, and idiopathic choroidal neovascularization.[1] According to the study, eyes with well-demarcated areas of extrafoveal or juxtafoveal classic CNV, as defined by fluorescein angiography, had a better visual prognosis when treated with laser photocoagulation than when managed by observation.[1] The subgroup analysis of this trial showed the importance of lesion component and size in treatment outcomes.

Photodynamic therapy (PDT) was the recommended treatment by the TAP study Group for patients affected by predominantly classic choroidal neovascularization (CNV) from AMD, with a benefit consisting in a vision loss fewer than 15 letters, over a period of 24 months. [2, 3, 4]

Although the clinical outcomes of verteporfin therapy have been established, the effects on choroid perfusion have revealed a significant reduction within the entire photosensitized area.[5] The tissue hypoperfusion is the common denominator and the major trigger of local angiogenesis stimulators,[6] inhibitors and proteolytic enzymes cooperatively participate in the progressive retinal pigment epithelium defect and growth of choroidal neovascular membranes in AMD.[7] Therefore the vaso-occlusive mechanism induced by PDT, that affected both CNV and the normal choroids,[8] may produce an angiogenic response with enhanced expression of vascular endothelial growth factor (VEGF) in human eyes. [9]

Intravitreal injection of a full-length humanized anti-VEGF antibody, as

Bevacizumab (IVB), has been associated with improvements in visual acuity and reduction of both central retinal thickness (CRT) and angiographic leakage in AMD.[10] Nevertheless, monotherapy with Bevacizumab requires multiple intravitreal injection, usually with a 4-week-interval, to maintain visual gain.[11]

Recently, PDT with a reduced light dose, to avoid choroid secondary change, combined with intravitreal injection of an anti-angiogenesis compounds, has been suggested as an effective option for AMD in terms of visual improvement, CRT diminution as well as reduced re-treatment rate. [12, 13]

Herein we report a comparative consecutive case series of AMD patients treated with IVB alone *versus* IVB plus low fluence PDT to verify the synergistic effect, if any, of the combined treatment on visual acuity, size and morphology of lesion, as well as on the re-treatment rate.

Patient and Methods

Study Design

A prospective comparative interventional study on 85 consecutive eyes of 85 patients (38: 47; male: female) aged 50 years or older has been performed. All subjects had a classic or predominantly classic subfoveal CNV secondary to AMD. The presence of blood had to account for <50% of the total area occupied by the subfoveal lesion. They were referred to one of the two centres (Università degli Studi di Brescia, Italy; Seconda Università degli Studi di Napoli, Italy) during the period between June 2007 and January 2008. The two local Human Subjects Review Committees (Brescia and Napoli) approved the project.

Patients and preoperative findings

The inclusion criteria consisted of, naive classic, or predominantly classic, subfoveal CNV, lesion size of >2 disk areas, lesions not exceeding 12 total disk areas (including blood, scar or atrophy, in presence of active neovascularization) and visual acuity in the fellow eye of 20/800 or better.

The exclusion criteria were: age younger than 50 years, severe systemic disease, pregnancy, any uncontrolled ocular disease and presence occult or minimally classic lesions, scarring or atrophy within the lesion.

Materials

Data collected from each recruited patient included diagnosis, visual acuity, fluorescein (FA) and indocyanine green angiography (ICG) angiographies, intraocular pressure and number of IVB injections. Best corrected visual acuity determination (BCVA), FA, ICG and optical coherence tomography (OCT) were recorded at baseline and, then, repeated the day before the IVB injection and at 1-,3-,6-, 9- and 12-month of follow-up. BCVA was determined with the ETDRS chart at distance of 4 m. FA and ICG (Heidelberg Retina Angiograph 2, Heidelberg, Germany) confirmed eligibility and appropriate classification of the lesions, which were graded according to the MPS system[1]. Only patients with classic and predominantly classic lesions were recruited.

Lesions were further investigated with OCT (OCT Stratus, Carl Zeiss Meditec, Dublin, CA). Linear scans of 6 mm length at 0° and 90° were obtained centred on the fovea. Retinal thickness, including intra- and sub-retinal fluid, was measured applying a calibre on the image; therefore the thickness of the neovascular complex was defined as a hyper reflective layer.

After the patients signed the consent form for the randomization and the identification number was recorded on the baseline data forms, they were randomly assigned to one of the two treatment groups (1 and 2 respectively).

At baseline patients included in Group 1 received 1.25 mg IVB. After the first IVB three patients dropped out from the trial and, therefore, they were not included into the study.

The patients of Group 2 were treated at baseline with a 1.25 mg IVB injection followed by PDT within a 2-week period. The PDT with verteporfin was delivered with low fluence rate (300 mW/cm^2 for 83 seconds, light dose of 25 J/cm2).

In both Groups, after the first injection, IVB re-injections were scheduled at least four weeks after initial treatment if one of the following criteria was fulfilled: i) drop of BCVA of at least five letters at two repeated tests ii) decrease of BCVA associated with increased leakage of the choroidal neovascularization, as assessed by FA iii) increase of central retinal thickness in OCT of more than 100 µm. [14]

The study was carried out for one year and the regimen treatment with IVB re-injections was followed for the first 6 months. After the first 6 months, in case of marked worsening or dissatisfaction, the patients abandoned the study.

Main outcome measure

The goal of the clinical trial was to verify the efficacy of a combined treatment (IVB + low fluence PDT) compared to IVB alone, in terms of functional results and changes of morphology of choroidal membrane, and advantage in terms of stabilization of the lesions and number of IVB re-treatments. For this purpose, changes in visual acuity, size and thickness of neovascular membrane, and macular thickness at each follow-up check as well the different re-injection treatment rates were recorded.

Visual outcomes analyzed were change in visual acuity from baseline to each follow up check: a) patients maintaining or gaining vision (gaining ≥ 15 letters); b) patients with moderate vision loss (loss of less than 15 ETDRS letters); c) patients with severe vision loss (measured as a losing of ≥ 15 ETDRS letters); d) risk of progression to legal blindness in the study eye (Snellen equivalent visual acuity of 20/200 or worse).

Statistical analysis

Statistical analysis was performed using the SPSS software 10.0 (SPSS, Chicago,IL, USA). A statistical ANOVA test was performed for analysis of variance on time difference among the covariates 'number of injections', 'age' and 'entity of initial value'. Unequal variance *t* test was used to compare the mean change in visual acuity from baseline to 12-months for each treatment Group**,** and between the two groups. A *P* value of ≤ 0.05 was considered to be significant.

Coefficient of correlation (ρ) was used to verify the relationship between VA and number of IVB injections. A *P* value of ≤ 0.05 was considered to be significant. Spearman's rank correlation coefficient (ρ) was used to describe the difference recorded in OCT parameters. A *P* value of ≤ 0.05 was considered to be significant.

Results

A total of 85 patients were enrolled and randomly assigned to both treatment groups. At the time of initial diagnosis all the patients presented a classic or predominantly classic subfoveal CNV lesion and no patient had been previously treated. The mean age in the first Group was 65.3 (SD=15), in the second Group it was 63.2 (SD=12) (P=0.2). Forty-five eyes (25 phakic, 20 pseudophakic) were treated with IVB injections (Group 1), whereas 40 eyes (22 phakic, 18 pseudophakic) with IVB plus low fluence PDT (Group 2). Patients were randomly assigned to one of the two Groups. (Table 1)

At baseline the mean ETDRS letter distance visual acuity was 50±12 and 55±14, respectively, in Group 1 and 2 (P = 0.06).

Table 1: Demographic Characteristics of Study at baseline

Characteristic	Group 1 (45 eyes)	Group 2 (40 eyes)
No Male/female	20/25	18/22
Mean Age±SD	65.3 ± 15	63.2 ± 12
Phakic / Pseudophakic	25 / 20	22 / 18
Mean ETDRS letters ± SD	50±12	55±14
(Snellen equivalent)	(0.20±0.12)	(0.33±0.18)
Angiographic CNV greatest linear diameter ± SD (mm)	3.15 ± 1.2	3.85 ± 1.6
Central Macular Thickness ± SD (μm)	330 ± 98	321 ± 115
Hyper reflective area of CNV ± SD (μm)	110 ± 58	123 ± 35

CNV= Choroidal Neovascularization
IVB = Intravitreal Bevacizumab
SD= Standard Deviation

Functional outcomes

In Group 1, the mean visual acuity score (number of ETDRS letters read) improved from 50 (SD 12) ETDRS letters (Snellen equivalent 0.20±0.12) to 57 (SD 18) letters (Snellen equivalent 0.30±0.16) at 12 months. At the last check, 21 out of 45 eyes (47%) gained ≥ 15 ETDRS letters, 14 out of 45 eyes (31%) had lost less than 15 ETDRS letters, 10 out of 45 eyes (22%) measured as a losing of ≥ 15 ETDRS letters.

In Group 2, the mean visual acuity improved from 55 (SD 14) ETDRS letters (Snellen equivalent 0.25±0.19) to 61 (SD 16) letters (Snellen equivalent 0.33±0.18) at 12 months. At the last check, 14 out of 40 eyes (35%) gained ≥ 15 letters, 20 out of 40 eyes (50%) had lost less than 15 ETDRS letters, 6 out of 40 eyes (15%) measured as a losing of ≥ 15 ETDRS letters. (Table 2)

The improvement in visual acuity was greater in Group 2 than that recorded in Group 1, although the difference was not statistically significant ($P = 0.31$, unequal variance *t* test). The difference between baseline and 12-months follow-up VA was statistically significant in each group (Group 1; $P = 0.03$; Group 2; $P = 0.01$, unequal variance *t* test). The differences between the two groups were always not significant ($P = 0.15$ unequal variance *t* test). We did not find any correlation between VA and number of injections performed in both Groups ($R = 0.15$, $P = 0.3$).

Angiographic outcomes

The area of CNV and subretinal fibrous tissue/disciform scar remained stable over time on average in both Groups throughout the follow-up period (12-months). In each group the difference of CNV area size between baseline and 12-month check was statistically

significant (Group 1: $P = 0.01$; Group 2: $P = 0.001$, ANOVA test), whereas the difference between the two groups was, at the same time, not significant. (Table 2) (Figure 1, Figure 2)

Optical Coherence Tomography outcomes

The mean change from baseline in centre point thickness was approximately 107 µm (SD 35) in Group 1 and 77 µm (SD 44) in Group 2 through 12 months (Group 1*: P* = 0.002; Group 2: *P* =0.003, Spearman test). Overall, the macular thickness significantly decreased through the follow-up period in all subjects.

The hyper reflective area of the neovascular complex remained stable in both Groups during the first 12-months of follow-up. Correlation between baseline and 12-month follow-up macular thickness was statistically significant in both Groups (Group 1*: P* = 0.002; Group 2: *P* =0.001, Spearman test). (Table 2)

Re-injections Rate

After the first injection, patients were re-injected if recurrence was noted for an average of 3.6±0.8 injections in Group 1 and 1.8±0.4 injections in Group 2.

In total, at last check, in Group 1: 2 eyes (4.4%) had 2 IVB injections, 37 eyes (82,2%) had 3 IVB injections, 5 eyes (11%) had 4 IVB injections and 1 eye (2,2%) had more then 4 injections. In Group 2: 3 eyes (7.5%) had 2 IVB injections, 33 eyes (82,5%) had 2 IVB injections, 4 eyes (10%) had 3 IVB injections. (Table 2)

In Group 1, eyes with recurrence received a mean of 3.2 injections and eyes without recurrence received a mean of 2.8 injections. In Group 2 eyes with recurrence received a mean of 2.2 injections and eyes without recurrence received a mean of 1.4 injections The difference in re-injections rate between the two Groups with (*P* =0.035, ANOVA test)

and without recurrence (*P* =0.03, ANOVA test) was statistically significant. (Table 2)

Neither statistically significant changes in IOP, nor anterior chamber inflammation, retinal detachment, or endophthalmitis were documented. No patient developed myocardial infarction or thromboembolic event.

Table 2 . Results at 12-months follow-up in Group 1 (IVB alone) vs Group 2 (IVB+PDT with low fluence rate)

	Group 1 (45 eyes)	Group 2 (40 eyes)	*P* value
Mean ETDRS letters ± SD (Snellen equivalent)	57±18 (0.30±0.16)	61±16 (0.33±0.18)	0.31
Gained ≥ 15 ETDRS	21 (47%)	14 (35%)	0.08
Lost ≤ 15 ETDRS	14 (31%)	20 (50%)	0.09
Lost ≥ 15 ETDRS	10 (22%)	6 (15%)	0.12
Angiographic CNV greatest linear diameter ± SD (mm)	2.80 ± 0.75	2.65 ± 1.2	0.35
Central Macular Thickness ± SD (µm)	223 ± 72	244 ± 60	0.21
Hyper reflective Thickness of CNV ± SD (µm)	78 ± 24	81 ± 15	0.15
Mean no. of IVB with recurrence	3.2	2.2	0.035
Mean no. of IVB without recurrence	2.8	1.4	0.03

CNV= Choroidal Neovascularization
IVB = Intravitreal Bevacizumab
SD = Standard Deviation

Discussion

Combined intravitreal bevacizumab and PDT for AMD effectively maintains or improves VA and reduces the number of re-treatments needed to achieve a vision stabilization, even at 12 months of follow-up. In 2006, Dhalla et al reported a retrospective series of 24 eyes with juxtafoveal or subfoveal CNV secondary to AMD treated with PDT and 1.25 mg of IVB.[15] All patients were naïve to treatment and had either treatment within a 14-day interval. At 7-month follow-up, 20 out of 24 (83%) patients had stabilization of visual acuity, 16 out of 24 (67%) had improvement in visual acuity. Fifteen eyes (63%) required only a single combined treatment for CNV resolution.[15]

In a prospective case series of 14 eyes**,** Ahmadieh et al reported the efficacy of combined single-session with PDT and IVB injection for treatment of neovascular AMD.[16] A second IVB injection was performed based on fluorescein angiographic evidence of CNV leakage in 13 out 14 eyes (93%) with a mean interval of 16.3+/-5.9 weeks. At a mean follow-up of 52.4+/-15.2 weeks the BCVA improved from 0.80+/-0.42 logMAR to 0.62+/-0.47 logMAR (p=0.006) and the mean central macular thickness reduced from 308+/88 µm to 186+/-53 µm (*P*=0.003). The author concluded that the combination therapy with single-session PDT and IVB can improve vision and reduce CMT in neovascular AMD. Repeat IVB injections may maintain the visual gain from the initial combination therapy.[16]

Photodynamic therapy combined with IVB tends to be more effective compared to the monotherapy by reducing the post-PDT increased expression of VEGF-A, inflammatory mediators and reactive oxygen species.[18] On the other hand, the

simultaneous combination of PDT with bevacizumab in patients with neovascular AMD may enhance the photochemical stress in normal choroid with prolonged and magnified hypofluorescence in ICG, due to ischemia in normal choriocapillaries.

Recently**,** Rouvas et al reported the case of enlargement of post PDT spot in a patient with retinal angiomatous proliferation that was treated with PDT combined with an IVB injection. The post PDT hypofluorescent treatment spot had an enlargement from 1,4 μm at the day of the treatment, to 5,3 μm at the 6-week visit that still was persisting at the 10-month follow-up.[17]

In light of such considerations**,** the IVB combined with a low fluence PDT may avoid the enlargement of hypofluorescent treatment spot reducing the collateral alteration of the physiologic choroids. Our comparative case series of AMD patients showed a synergistic effect of the combined treatment on the visual acuity, size and morphology of the lesions, as well as reduction of treatment rates.

These findings of ours demonstrate that the improvement in visual acuity was greater in Group 2 than in Group 1, although the difference was not statistically significant (P = 0.31, t-test of unequal variance). The difference between CNV area size recorded at baseline and at the 12-month check was statistically significant in both Groups (Group 1: P = 0.01; Group 2: P =0.001) as well as the macular thickness (Group 1: P = 0.002; Group 2: P =0.001).

The main difference between the two groups was the IVB re-injections rate. The eye without recurrence received a mean of 2.8 (Group 1) vs 1.4 (Group 2) IVB injections, whereas the eyes with recurrence received a mean of 3.2 (Group 1) vs 2.2 (Group 2) IVB injections. At the end of follow-up such difference between the two Groups was

statistically significant ($P = 0.03$, ANOVA test). We did not find any correlation between VA and the number of injections performed in both Groups.

PDT is an established modality for the treatment of neovascular AMD, although the release of a wide variety of potent mediators, including vasoactive substances, components of the complement and clotting cascades, acute phase proteins, proteases, peroxidases, radicals, leukocyte chemoattractants, cytokines, growth factors, and other immunoregulators has been documented after its use[18-20]. All these compounds, together with the PDT induced hypoxia, increase VEGF-A levels, as suggested by Schmidt-Erfurth et al.[9] Therefore, IVB plus PDT treatment would both ablate established vessels (PDT) and inhibit re-growth due to increased expression of VEGF-A (bevacizumab).

The overall improvement in vision with a good efficacy on fluorescein leakage from CNV and less IVB re-injections rate throughout the study suggest that a possible synergistic effect may arise from the combination of intravitreal bevacizumab with low fluence PDT for the treatment of classic or predominantly classic neovascular AMD.

These present findings are promising**;** in fact, the vessel regression effects observed in the present study suggest that the combined use of IVB plus PDT may provide a beneficial option for any ocular disease in which CNV plays a major role. However, the mode, dosage, and timing of administration of these agents in combination may have to be considered to ensure optimal efficacy, as recently pointed out by Ju and coworkers, [18] who have found that pre-treatment with anti VEGF before PDT resulted in reduced efficacy of PDT, due to the influence of anti VEGF agents both on the inflammatory component of PDT, and on the delivery of verteporfin to the sites of CNV, hence reducing the effective concentration of the photoactive and thereby the efficacy of the

treatment.

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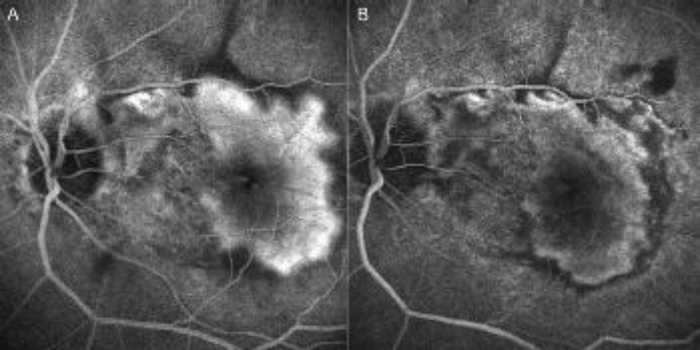
Legend:

Figure 1: Predominantly classic CNV lesion treated with 4 intravitreal bevacizumab injections during the 12mo follow-up. The angiogram shows a regression of choroidal neovascular activity from baseline (A) to 12-mo follow-up (B).

Figure 2: Classic CNV lesion treated with low fluence PDT and 2 intravitreal bevacizumab injections. The angiogram shows a regression of choroidal neovascular activity from baseline (A) to 12-mo follow-up (B).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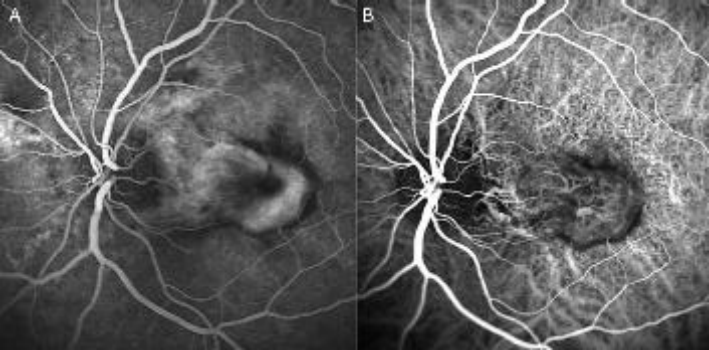
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