Verteporfin photodynamic therapy combined with intravitreal ranibizumab in neovascular age-related macular degeneration: 24-month follow-up

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Abstract

Purpose: to evaluate the efficacy and safety of combined therapy with Photodynamic Therapy with Verteporfin (PDT-V) and intravitreal ranibizumab same-day compared with monotherapy with ranibizumab (three monthly injections) for the treatment of the choroidal neovascularization (CNV) due to age-related macular degeneration (AMD).
Type of study : open-label, randomized controlled trial (RCT).
Materials and Methods: 17 eyes of 17 patients were consecutively enrolled and randomly assigned to ranibizumab intravitreal injection + PDT compared with a control group of 30 eyes of 30 patients treated with only ranibizumab 0.5mg in three monthly injections. Best corrected visual acuity (BCVA), central macular thickness (CMT) on optical coherence tomography were examined before and after treatment. Patients were followed-up for twelve months.
Results: in the combined therapy group, the mean baseline BCVA is 32.6 letters, at 24-months after treatment it's 31.4 letters with a loss of 1.2 letters. The mean central thickness at baseline is 314.6 µm. After twenty four months the mean CMT is 222.5 µm, with mean CMT reduction of 92.1µm. In the ranibizumab-alone group, the mean baseline BCVA is 29.1 letters at 24-months it's 28.6 letters with a little loss of 0.5 letters. The mean baseline CMT is 297.6 µm, at 24-months it is 235.9 µm, with mean CMT reduction of 61,7µm.
Conclusions: the two treatments showed the same efficacy from a functional and anatomic point of view with a less number of retreatments in the combined therapy group. There were no serious ocular adverse events such as retinal detachment, endophthalmitis or ocular hypertone.

Keywords: *CNV, AMD, Ranibizumab, PDT.*

Introduction

Age-related macular degeneration (AMD) is the leading cause of blindness and visual disability in patients aged 60 years and older in Europe and North America. Worldwide, after cataract and glaucoma, AMD is the third leading cause of blindness, contributing to causing 8.7% of all legal blindness [1]. Although the majority of patients with AMD have the non-neovascular form, characterized by drusen and atrophic changes in the retinal pigment epithelium, up to 90% of severe vision loss caused by AMD is attributable to the neovascular (exudative) form of the condition, which is characterized by choroidal neovascularization (CNV) [2]. With CNV, new vessels invade the retina and sub-retinal space and eventually bleed and leak serous fluid due to their altered permeability. The blood and serous fluid causes alterations in the macula, distorting images and causing

loss of visual acuity. Although the natural course of CNV secondary to AMD is highly variable, the long-term prognosis is poor [3-5].

Several therapeutic options are available. In 2000 photodynamic therapy with verteporfin (PDT-V) was approved by the United States' Food and Drug Administration for the treatment of subfoveal CNV due to AMD [6]. Recently, clinical investigations have studied a new class of drugs for subfoveal CNV: vascular endothelial growth factor (VEGF) selective inhibitors, administered via intravitreal injection [7,8]. More recently, clinicians have been offering a combined treatment, consisting of PDT followed by an intravitreal injection of an anti-VEGF drug within 24 hours. The combination of two treatments should have better results in preventing the growth of new vessels [9-12]. The purpose of our study is to compare combined therapy of PDT-V and intravitreal ranibizumab versus monotherapy with ranibizumab.

Materials and Methods

This study was conducted in compliance with the Ethics Committee of the Department of Ophthalmology of the University of Rome "La Sapienza" and in accordance with all state laws in Italy. Prior to determination of full eligibility for enrollment, all patients provided written, informed consent.

Our open-label, single-center, randomized controlled trial was designed to compare the efficacy of combined therapy, defined as intravitreal ranibizumab 0.5 mg and PDT administered on the same day, versus a group treated with ranibizumab-alone in eyes with primary classic CNV secondary to AMD.

Inclusion criteria were:

- Best-Corrected Visual Acuity (BCVA) letter score equal or better than 10 letters
- Classic subfoveal CNV lesions due to AMD, greatest linear dimension (GLD) of the entire lesion 5400 µm,
- At least 55 years of age
- Active CNV secondary to AMD with evidence of leakage on fluorescein angiography.

Exclusion criteria were:

- Previous treatment with bevacizumab or pegaptanib.
- Previous treatment with PDT.
- Uncontrolled diabetes, a history of coagulation disorders, cerebrovascular accidents, pulmonary embolism, deep vein thrombosis, uncontrolled systemic hypertension, chronic renal failure, myocardial infarction within the previous 6 months, major surgery within the previous 6 weeks, ocular diseases that could affect visual acuity (glaucoma, angioid streaks, trauma, choroiditis, hereditary diseases [even to fellow untreated eyes], aphakia), or previous vitreoretinal surgery.

Patients were randomized into two groups with a 1:2 ratio: group 1 patients received the combined therapy; group 2 patients, monotherapy with ranibizumab.

All patients underwent full ophthalmologic examination at baseline and during the follow-up period. BCVA of both eyes was measured by an orthoptist masked to the study using a modified Early Treatment of Diabetic Retinopathy Study (ETDRS) chart at 3 meters distance. Visual acuity improvement was defined as a gain of at least 3 ETDRS lines (15 letters), stability as a change of less than 3 ETDRS lines, and deterioration as a loss of at least 3 ETDRS lines. Central macular thickness (CMT) examinations were performed using a STRATUS OCT (V4.01 Zeiss Meditec, Dublin, CA). CMT was assessed using the high-resolution Radial Lines protocol and the Retinal Thickness Map analysis program. AMD neovascular lesions were defined by intraretinal hemorrhages and edema. From the baseline thickness, a decrease in CMT of 10% was defined as a reduction and an increase 10% was defined as an increase. Fluorescein angiography was performed by three trained unmasked photographers using a HRA2 FA (Heidelberg Engineering). The presence of CNV leakage was evaluated in the late (3-5 min) versus the early (first 1-2 min) phase. The leakage was compared between the times before and after treatment and was described as absent (CNV closure) or persistent. A relapse was defined as an evidence of leakage on FA and/or evidence of intraretinal or subretinal fluid on OCT from a previously closed lesion. OCT imaging procedures and fluorescein angiographies were evaluated by three experienced (unmasked) retinal specialists at baseline and during the follow-up, every month for 24 months. Intraocular pressure (IOP), measured by applanation tonometry, was monitored. Diastolic and systolic blood pressures were recorded at baseline and during follow-up. At baseline, the combined therapy group was treated with PDT-V and intravitreal ranibizumab administered on the same day. Monthly, additional ranibizumab injections were administered at month 1 and 2 in case of persistent activity of the neovascular lesion. Group 2 was treated with three monthly injections. Eyes underwent standard PDT-V (Visudyne; Novartis AG, Basel, Switzerland) with the following protocol: a 10-minute infusion of verterporfin (6 mg/m^2 body surface area) was followed by its activation (5 minutes later) with a 689-nm diode laser delivering an energy of 50 J/cm^2 for 83 seconds, using a spot size of a diameter 1000 µm larger than the greatest linear dimension of the lesion. Each patient was asked to wear protective sunglasses and to avoid exposure of the eyes and body surfaces to sunlight for the next 48 hours. They were given an intravitreal injection of 0.5 mg of ranibizumab on the same day.

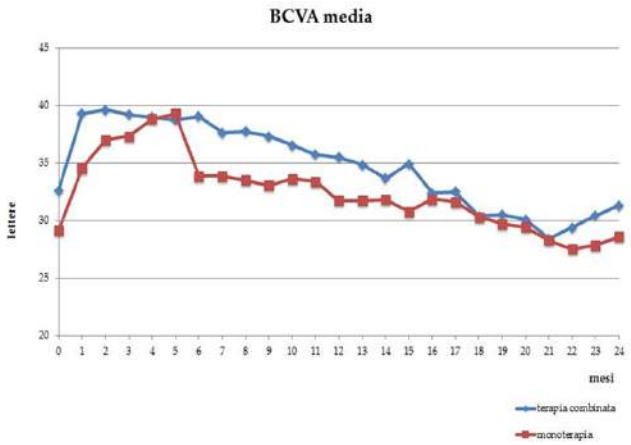

Fig 1. Best-corrected visual acuity from baseline to months 12 Combined therapy versus Monotherapy for AMD CNV.

Follow-up consisted of monthly examinations for a period of 24 months. Patients received complete ocular examinations; additionally, BVCA, OCT, FA, IOP, and blood pressure were recorded. Indications for retreatment after the first 3 months were evidence of visual deterioration of at least 5 ETDRS letters together with evidence of persistent or recurrent leakage on FA and/or evidence of intraretinal or subretinal fluid on OCT. Patients with persistence of leakage on OCT/FA but with stable vision, were treated however with additional intravitreal injection of ranibizumab.

Group 1 patients requiring further treatment received a second session of PDT combined with intravitreal ranibizumab; Group 2 patients received additional monthly injections. We performed a t test to compare the data at T0 and T24 and to determine whether retreatments depended on treatment protocol. The significance level was defined as $P < 0.05$.

Results

A total of 47 eyes of 47 patients were consecutively enrolled and randomly assigned to group 1 (n = 17) or group 2 (n = 30). There were no significant differences in age, pretreatment BCVA, or initial CMT between the groups. All the patients completed the 24-month follow-up.

In group 1, the mean baseline BCVA was 32.6 letters. Twenty four months after treatment, the mean BCVA was 31.4 letters, with a loss of 1.2 letters. In group 2, the mean baseline BCVA was 29.1 letters. Twenty four months after treatment, the mean BCVA was 28.6 letters with a little loss of 0.5 letters. In both groups there isn't a statistically significant improvement in visual acuity ($p>0.05$). There was no statistically significant difference in the BCVA improvement between groups 1 and 2 Fig. 1.

In group 1, the mean central thickness at baseline was 315 µm. At 24 months follow-up the mean CMT was 222.5 µm with mean CMT reduction of 92.1µm.

In group 2, the mean CMT before treatment was of 306 µm. At 24 months follow-up the mean CMT was 235.9 µm, with mean CMT reduction of 61,7 µm. In both groups CMT reduction began to appear after the first month of follow-up. In both groups CMT reduction was statistically significant ($p<0.05$). There was no statistically significant difference in the CMT reduction between groups Fig. 2.

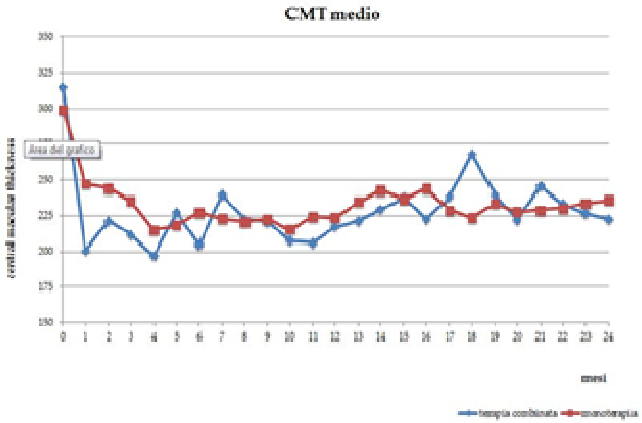

Fig. 2. CMT: baseline to months 12 Combined therapy versus Monotherapy for AMD CNV.

In the group 1, 11 of 17 eyes (64.7%) showed active signs of the membrane (evidence of persistent or recurrent leakage on FA and/or evidence of intraretinal or subretinal fluid on OCT), needing a further cycle of combined therapy, whereas the remaining 6 (35.3%) needed no further treatments. The mean number of intravitreal injections was 3.6 Fig.3 and 4.

In group 2, of 30 eyes, 24 (80%) needed a further cycle of intravitreal injections. The mean number of intravitreal injections per eye was 5.9. There were no serious ocular adverse events such as retinal detachment, endophthalmitis or ocular hypertension Fig. 5 and 6.

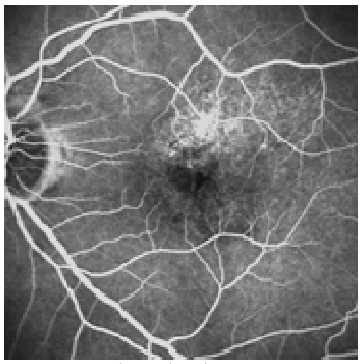

Fig.3 Combined Therapy: A. FA Pre (TO) and B. Post (T24) treatment.

Discussion

PDT combines the intravenous injection of a photosensitizer drug with an activating low-power laser beam. PDT has shown good results on classic and

predominantly classic subfoveal lesions but has been less effective on occult lesions. PDT-V alone has been shown in a large number of cases to require retreatments every 3 months [13].

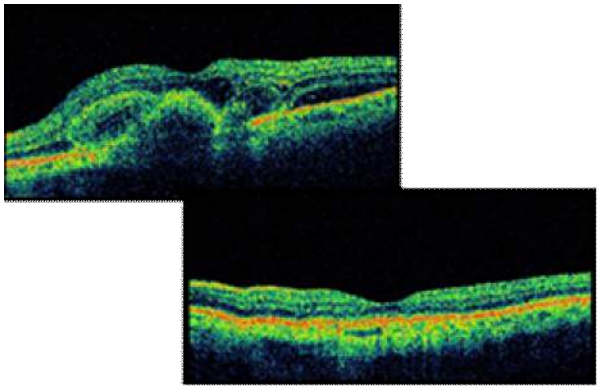

Fig 4. Central macular thickness: A. anatomical benefits of combination therapy from baseline to B. 12 months.

Recently, VEGF selective inhibitors have been investigated for treatment of exudative AMD. The "on label" agents used are pegaptanib sodium and ranibizumab [14]. Ranibizumab is a humanized antibody fragment with low molecular weight (48-kDa) that targets all isoforms of VEGF-A, including VEGF-110, VEGF-121, and VEGF-165 [15,16]. Although anti-VEGF treatments have been effective, some experimental models have shown that it becomes less effective in preventing the neovascularization and promoting its regression [17,18].

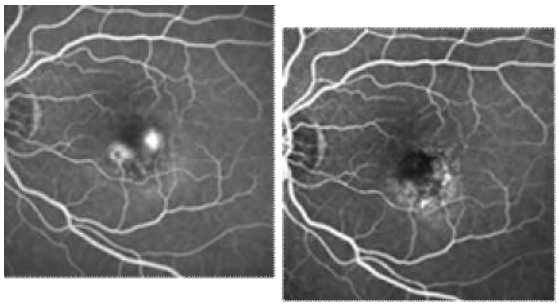

Fig 5. Monotherapy: A. FA Pre (TO) and B. Post (T24) treatment.

An alternative treatment option is the combined treatment we used for our group 1 patients. This treatment protocol gives PDT-V a new role, in which it may complement anti-VEGF drugs [19] Combined therapy allows treatment of neovascularization by targeting several key points of the physiopathological processes that are involved in its progression. PDT-V causes the ablation of the already present neovascularization with a phototoxic selective process that destroys endothelial cells and exposes basal membrane [20].

Ranibizumab may block neovascularization relapse with an anti-angiogenetic action toward VEGF-A. A recent study that evaluated VEGF levels in aqueous humor before and one month after combined therapy showed a significant decrease, positively correlated with CMT [21].

Several multicenter studies are evaluating the effects of the combination of PDT-V with anti-VEGF in patients with subretinal neovascularization. The FOCUS study compared the results of ranibizumab therapy combined with PDT-V and PDT-V alone in patients with subfoveal, predominantly classic CNV, not larger than 5400 μm [9]. In this study, one group of patients had PDT-V and a monthly sham injection and the other PDT-V with a monthly ranibizumab 0.5 mg injection for 24 months.

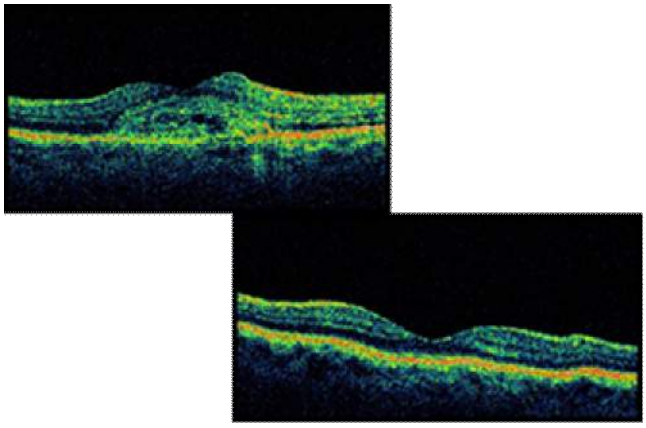

Fig 6. Monotherapy: A. OCT Pre (TO) and B. Post (T24) treatment.

After 24 months, 88% of patients treated with combined therapy and 75% of controls lost fewer than 15 letters. The percentage of patients that has repeated PDT-V was significantly less in the group treated with ranibizumab. The PROTECT study evaluated the efficacy of the combination of a single PDT-V application with a single ranibizumab intravitreal injection administered on the same day and followed by two more injections in 3 months, in eyes with CNV due to AMD. After 9 months of follow-up, 70% (22/33) of eyes had only the scheduled 3 ranibizumab injections and a PDT, whereas 21.8% had an additional PDT treatment with verteporfin [11]. The CAM study showed that the optimal timing for ranibizumab administration is within the 24 hours after PDT [22].

Kumar et al evaluated the results of combined therapy of a single PDT-V treatment and ranibizumab 0.5 mg received on the same day by 17 patients with CNV due to AMD. Visual acuity was stable (gain/loss <2 lines) 82.2% of cases, whereas it improved (gain 2 lines) in 17.6% of cases [10].

Our combined therapy protocol differs from others in

that it provides only one injection at baseline and additional ranibizumab injections at 1 and 2 months to address any persistent activity of the neovascular lesion. In our study, there was no statistically significant difference ($p>0.05$) between groups. In group 1, the CMT mean reduction was 10% in 11 eyes (64.7%). In group 2, the CMT mean reduction was 10% in 25 eyes (83.3%). Statistical analysis showed a considerable efficacy of both treatments in reducing CMT (and intraretinal edema) but did not indicate significant advantage in using one or the other ($p>0.05$) although fewer intravitreal injections were required in group 1 high compliance by the patients, which has to be strictly monitored to avoid serious ocular complications, such as than in group 2.

This finding has important ethical and economic implications. Intravitreal injections require a endophthalmitis and retinal detachment. Risk is directly proportional to the number of injections, thus monotherapy carries a greater risk than the combined therapy. The risk for patients undergoing the combined therapy is reduced due to the limited number of injections. The combination treatment appeared to be useful for regressing the choroidal neovascularization (CNV) lesions in AMD on indocyanine green angiography and in reducing their recurrence. The patients thus have an improved quality of life and psychophysical wellness. In addition, combined therapy reduces the costs of intravitreal injections [23-25].

"The authors declare that they have no competing interests''.

All authors read and approved the final manuscript.

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