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Pegaptanib: choroidal neovascularization in patients with age-related macular degeneration and previous arterial thromboembolic events

Maurizio Battaglia Parodi[1], Emanuele Di Bartolo[2], Claudia Brue[3], Ezio Cappello[4], Claudio Furino[5], Sebastiano Giuffrida[6], Manuela Imparato[7], Michele Reibaldi[8]

[1] Department of Ophthalmology, Ospedale San Raffaele, Milan - Italy
[2] Department of Ophthalmology, Azienda Ospedaliero-Universitaria Pisana, Pisa - Italy
[3] Department of Ophthalmology, Polytechnic University of Marche, Ancona - Italy
[4] Department of Ophthalmology, Ospedale San Bassiano, Bassano del Grappa - Italy
[5] Department of Ophthalmology, University of Bari, Bari - Italy
[6] Bausch and Lomb Iom SpA, Vimodrone, Milan - Italy
[7] Department of Ophthalmology, Fondazione IRCCS Policlinico San Matteo, Pavia - Italy
[8] Department of Ophthalmology, University of Catania, Catania - Italy

ABSTRACT

Purpose: To evaluate the efficacy and the rate of side effects of the pegylated aptamer pegaptanib in the treatment of patients with choroidal neovascularization (CNV) secondary to age-related macular degeneration (AMD) and a history of previous arterial thromboembolic events (ATEs).

Methods: Twenty-three eyes of 23 patients with subfoveal CNV due to AMD and cerebrovascular accidents (n = 12) and myocardial infarction (n = 11) in the previous 6 months received intravitreal pegaptanib 0.3 mg according to a pro re nata regimen and were followed for 12 months. The paired Student t test was used to evaluate mean changes in best-corrected visual acuity (BCVA; primary outcome measure) and central foveal thickness (CFT).

Results: The mean patient age was 71.5 ± 4.6 years; there were 14 women and 9 men. The CNV was type 1, 2, and 3 in 18, 3, and 2 eyes, respectively. The mean BCVA improved from 0.67 ± 0.23 logMAR at baseline to 0.52 ± 0.31 logMAR at the end of 12-month follow-up (p = 0.044). Thirty-five percent of patients achieved ≥3 Early Treatment Diabetic Retinopathy Study lines improvement at 12 months. Mean CFT at baseline (381 ± 111 µm) decreased to 304 ± 82 µm at 12 months (p = 0.008). Patients received a mean of 4.3 ± 1.3 (range 3-7) injections. No systemic or ocular side effects occurred; no patient experienced further ATEs.

Conclusions: Intravitreal pegaptanib can be considered a viable treatment option for patients with AMD-related CNV who are at high risk of ATEs.

Keywords: Age-related macular degeneration, Choroidal neovascularization, Pegaptanib, Thromboembolism

Introduction

The introduction of intravitreal injection of anti-vascular endothelial growth factor (anti-VEGF) drugs has completely transformed the management of patients with choroidal neovascularization (CNV) secondary to age-related macular degeneration (AMD). Many randomized controlled trials have demonstrated the efficacy of anti-VEGF molecules, with encouraging results reported (1-7). However, data on the systemic effects of chronic intravitreal anti-VEGF exposure in patients with AMD, especially regarding the occurrence of arterial thromboembolic events (ATEs), are limited (8-10).

Pegaptanib (Macugen®; Bausch & Lomb) is a pegylated aptamer that targets the $VEGF_{165}$ isoform and has been shown to inhibit the endothelial mitogen activity of VEGF-A and its vascular permeability effects (1). Pegaptanib was specifically approved for the treatment of CNV secondary to AMD, and no systemic effects were attributed to the drug to date. Therefore, this molecule may be appropriate for the treatment of patients with a positive history of ATEs who need anti-VEGF therapy to arrest the progression of AMD-related CNV. However, until now, no study has specifically focused on the management of this subset of patients.

Therefore, the aim of the present study was to describe the outcomes of patients with CNV secondary to AMD with a positive history of ATEs who were treated with pegaptanib over a 12-month follow-up.

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Corresponding author:
Maurizio Battaglia Parodi
Ospedale San Raffaele
Via Olgettina 60
20132 Milan, Italy
battagliaparodi.maurizio@hsr.it

Methods

This retrospective, multicenter study was conducted across 6 Italian ophthalmology departments. Medical records for consecutive patients with an angiographic subtype of subfoveal CNV secondary to AMD treated with 0.3 mg pegaptanib were retrieved. The retrospective protocol was approved by the Comitato Etico Area Pavia, IRCCS Regione Lombardia (P-20170004133; 13/02/2017), and the study was conducted in accordance with the ethical principles set forth in the Declaration of Helsinki. As the study was retrospective and patients received treatment in routine clinical ophthalmology practice settings, additional informed consent was not required. All patient data were anonymized.

Eligible patients were ≥50 years of age with subfoveal CNV with any type of angiographic lesion composition due to AMD, best-corrected visual acuity (BCVA) in the study eye of 20/25 to 20/320, and previous ATEs such as cerebrovascular accidents (CVA) and myocardial infarction (MI) within 6 months.

Exclusion criteria were defined as follows: previous treatments including laser photocoagulation, photodynamic therapy, or intravitreal anti-VEGF injection; intraocular surgery within 6 months of the day of injection; any other ocular disease that could compromise vision in the study eye; ocular hypertension or glaucoma; or uncontrolled systemic hypertension.

At baseline, a complete ophthalmologic examination of each patient was carried out, including BCVA assessment on standard Early Treatment Diabetic Retinopathy Study (ETDRS) logMAR charts at 4 meters, slit-lamp examination, tonometry, dilated fundus examination, fluorescein angiography (FA), indocyanine green angiography (ICGA), and spectral-domain optical coherence tomography (SD-OCT) examination (Spectralis OCT, Heidelberg Engineering). Fluorescein angiography and ICGA were performed using scanning laser ophthalmoscopy (Heidelberg Retina Angiograph). Spectral-domain OCT was performed on all patients using a scan line pattern. Central foveal thickness (CFT) was calculated manually, measuring the distance between Bruch membrane and the internal limiting membrane on the fovea. The patients were evaluated every 6 weeks and received 0.3 mg of intravitreal pegaptanib according to a pro re nata (PRN) regimen, after an initial loading phase of 2-3 injections. Retreatment was performed in case of CNV activity as shown by intraretinal/subretinal fluid on OCT examination, and/or leakage on FA, and/or new hemorrhages on biomicroscopy. At each visit, the patients were carefully questioned about the occurrence of ATEs.

The primary outcome measure was the mean change in BCVA over 1 year of follow-up. Secondary outcome measures included changes in the CFT, the proportion of eyes improving in BCVA by >3 lines at the 12-month examination, and the assessment of side effects. The paired Student t test was used to evaluate mean changes in the BCVA and CFT. All tests were 2-tailed and the level of significance was set at $p<0.05$.

Results

All files of patients with AMD-related CNV at the 6 study sites over the period January 2015 to January 2016 were reviewed (n = 1,723). Overall, 23 patients (23 eyes) fulfilled the inclusion and exclusion criteria, and were recruited for the study (Tab. I); 8 patients were recruited in Pavia, 6 in Milan, 3 in Ancona, 2 in Catania, 2 in Bari, and 2 in Bassano.

TABLE I - Demographics and clinical characteristics of study participants at baseline

Characteristics	Values
Patients, n	23
Age, y, mean ± SD	71.5 ± 4.6
Sex, n (%)	
Female	14 (68.9)
Male	9 (39.1)
Previous arterial thromboembolic event, n (%)	
Cerebrovascular accident	12 (52.2)
Myocardial infarction	11 (47.8)
Best-corrected visual acuity, logMAR, mean ± SD	0.67 ± 0.23
Choroidal neovascularization type, n (%)	
1	18 (78.3)
2	3 (13.0)
3	2 (8.7)
Central foveal thickness, µm, mean ± SD	381 ± 111

Mean patient age was 71.5 ± 4.6 years and the majority (61%) were female (Tab. I). History of CVA and MI was present in in 12 and 11 patients, respectively (Tab. I). All patients were carefully examined by an internist, who was responsible for prescription of clinically indicated systemic therapy, including antihypertensive agents, anticoagulants, and cardiac medications. Choroidal neovascularization had a subfoveal location in all cases, and was type 1 in the majority of eyes (n = 18; 78%) (Tab. I).

Mean BCVA improved from 0.67 ± 0.23 logMAR at baseline (approximately corresponding to 20/100 Snellen equivalent) to 0.52 ± 0.31 logMAR at the end of follow-up (approximately corresponding to 20/40 Snellen equivalent) ($p = 0.044$) (Fig. 1). A functional improvement of at least 3 ETDRS lines was obtained in 8 eyes (35%) at the 12-month examination. Eleven eyes (48%) had stable BCVA, whereas 4 eyes (17%) experienced a 3-line decrease. Mean CFT at baseline was 381 ± 111 µm, and decreased significantly to 304 ± 82 µm at the 12-month examination ($p = 0.008$) (Fig. 2). The mean number of injections over the follow-up was 4.3 ± 1.3 (range 3-7).

At the last examination visit, 5 eyes showed the presence of intraretinal cysts on SD-OCT associated with fluorescein leakage, requiring further retreatment. No systemic or ocular side effects were recorded over the follow-up. Specifically, no patient experienced further ATEs.

Discussion

Pegaptanib is a selective $VEGF_{165a}$ inhibitor, which can be of benefit in the management of CNV secondary to AMD. The phase III VEGF Inhibition Study in Ocular Neovascularization (VISION) demonstrated the safety and efficacy of 6-weekly pegaptanib administration in eyes affected by all CNV subtypes related to AMD (1). Subsequently, a post hoc subgroup analysis of the VISION data showed that pegaptanib therapy

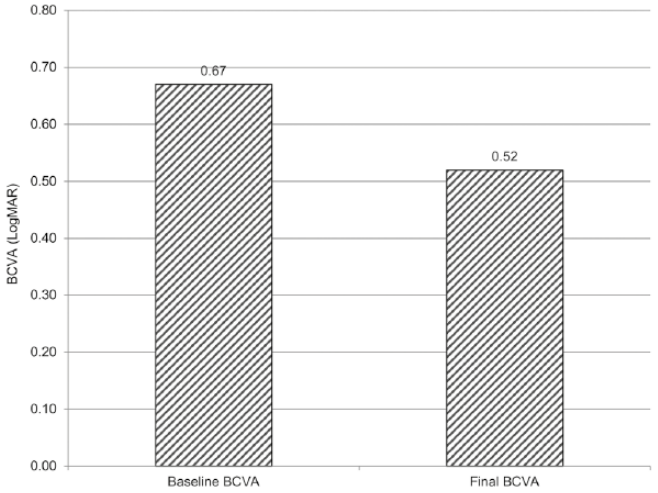

Fig. 1 - Changes in mean best-corrected visual acuity (BCVA) over the follow-up. Best-corrected visual acuity measured on standard Early Treatment Diabetic Retinopathy Study logMAR charts at 4 meters.

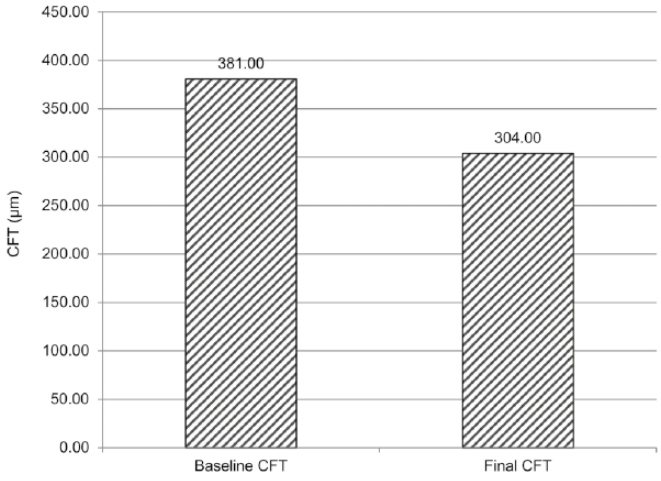

Fig. 2 - Changes in mean central foveal thickness (CFT) over the 12-month follow-up.

was more effective in eyes characterized by treatment-naive CNV, and also in patients with earlier disease with smaller lesion size and better baseline BCVA (11). A real-world, retrospective European study, scheduling pegaptanib administration following a PRN regimen, achieved good results, showing that more than 90% of patients lost fewer than 3 ETDRS lines from baseline, whereas a BCVA gain of more 3 lines was achieved by 4.8% of patients at the 12-month examination (12).

Overall, the effectiveness of pegaptanib in maintaining visual acuity in eyes affected by AMD-related CNV has been confirmed, even though other anti-VEGF molecules can produce a larger functional improvement (13). In fact, even though pan-VEGF agents rapidly and efficaciously block ocular CNV, long-term inhibition of all VEGF isoforms may result in the loss of the physiologic effects applied by $VEGF_{121}$ and $VEGF_{165b}$. VEGF is produced by several retinal cells, such as vascular endothelial cells, retinal pigment epithelium, pericytes, retinal neurons, and astrocytes, confirming the hypothesis that VEGF has a key ocular homeostatic role (14). The $VEGF_{165a}$ blockade stoppage mediated by pegaptanib may be enough by itself to inhibit CNV growth. Considering that the amount of $VEGF_{165}$ is significantly greater than other VEGF isoforms, including $VEGF_{121}$, the first isoform is thought to have a relevant role in angiogenesis. Preclinical data indicate that VEGF plays a significant neuroprotective action in conditions of ischemia. The sparing of the $VEGF_{121}$ by pegaptanib leads to preservation of the retinal ganglion cells with a consequent neuroprotective role of pegaptanib (15). Vascular endothelial growth factor also has a protective action on the choriocapillaris, as suggested by the induced loss of choriocapillaris fenestrations and by the occlusion of the choriocapillaris lumen by intravitreal injections of bevacizumab (16).

As well as a favorable ocular safety profile, pegaptanib has also been shown to be associated with a low rate of ATEs (10, 13, 15). All intraocular injected anti-VEGF agents can bypass the blood-retinal barrier and reach the systemic circulation, reducing VEGF plasma levels to varying degrees. Plasma VEGF protects vascular integrity and upregulates nitric oxide; reduced basal nitric oxide synthesis and action can result in vasoconstriction, increased blood pressure, and thrombus formation (17). Increased cardiovascular risk is a particularly relevant concern because the AMD population is already at higher risk. Vascular endothelial growth factor plays a complex role in atherosclerosis (18). In fact, VEGF upregulates the synthesis of tissue factor, the initiator of the coagulation cascade, and inhibition of VEGF could result in antithrombotic effects. However, VEGF is an endothelial cell survival factor, so that inhibition could promote apoptosis of endothelial cells, resulting in a procoagulant action. In addition to the aforementioned upregulation of nitric oxide, a potent anticoagulant, by VEGF, VEGF also has the ability to destabilize cholesterol plaques, probably by the blocking the formation of immature surface blood vessels (19). Some studies have reported a higher incidence of nonocular hemorrhage (20) and CVA (21) in subjects injected with a nonselective anti-VEGF treatment compared with sham injection. Overall, although concerns regarding the long-term systemic impact of anti-VEGF administration have been raised, it is important to note that the trials were not designed to detect ATEs and would in fact be underpowered for this purpose. In addition, all the trials excluded patients with recent positive history of ATEs. The current lack of data in this patient group prompted us to assess the effectiveness and the safety of pegaptanib in this retrospective study. The results are of interest because they show that even in this subgroup of patients, about one-third achieved a visual acuity improvement of at least 3 lines, with a functional stabilization in about half of all patients. The results are consistent with previously reported data from a study in patients without a history of ATEs (1, 12). In addition, the number of injections over the 12-month follow-up was very similar to that reported in the cohort of patients treated with pegaptanib in clinical ophthalmology practices across Europe (12). It is also interesting that, in our case series, the most frequent CNV subtype was type 1, which seems to respond well to pegaptanib, as shown previously (1, 12, 22).

TABLE II - Adverse events registered over the 12-month follow-up

	Patients (n = 23), n (%)
Nausea	0
Vomiting	0
Blood pressure increased	0
Transient ischemic attack	0
Cerebrovascular accident	0
Myocardial infarction	0
Death	0
Eye pain	2 (0.8)
Visual impairment	0
Intraocular pressure increased	0
Vitritis	0
Retinal detachment	0
Vitreous hemorrhage	0
Drug hypersensitivity	0

The current results suggest that pegaptanib intravitreal injections did not precipitate any recurrent ATEs (Tab. II). However, it is not possible to say whether this fully reflects the safety profile of pegaptanib or whether concomitant anticoagulant and cardiac medications contributed to the lack of ATEs seen in this at-risk patient population.

We acknowledge that the present study has several limitations, especially regarding the relatively small number of patients (likely due to the rarity of the association between active CNV and thromboembolic events), and follow-up of only 1 year. In addition, the study has a retrospective design, and therefore other factors such as selection bias and individualized clinical management may have contributed to the study findings. Nevertheless, this is the first study specifically focused on the management of patients with a history of ATEs who were therefore at particular risk if treated with anti-VEGF therapy.

In conclusion, our results suggest that intravitreal pegaptanib can be considered a viable treatment option for patients with AMD-related CNV who are at high risk of ATEs. We encourage further research in larger patient groups to confirm and extend these findings.

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