

Treatment with Bevacizumab in Exudative Age-related Macular Degeneration

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Purpose: The aim of the study was to evaluate the preliminary results of treatment with Bevacizumab (Avastin) in the neovascular or wet form of Age-Related Macular Degeneration.

Methods: Thirty-five consecutive patients (38 eyes) received Avastin intravitreally. Every patient received 3 Avastin injections at a distance of 1 month. Each dose consisted of 2.5 mg (0.1 ml) of Avastin. The therapeutic effect has been evaluated by the value of visual acuity and the central retinal thickness before and after treatment. In order to measure the visual acuity, the classical optotype was used and the central retinal thickness was evaluated by optical coherence tomography. The follow-up period was 6 months after the last injection.

Results: A number of 28 eyes (74%) had a favorable evolution of visual acuity, 7 eyes (18%) presented a stationary evolution and 3 eyes (8%) had an unfavorable outcome. The highest values were obtained at 1 month after the last injection (control 1). The optical coherence tomography decreased in 30 eyes (79%) and increased in 8 eyes (21%).

Conclusion: The evolution of visual acuity and central retinal thickness was predominantly favorable in 74% and 79% of the cases, respectively. We observed a direct correlation between the visual acuity and morphological parameters evaluated by optical coherence tomography, in 26 eyes (68%). Most patients described an improvement in the quality of vision, even when the visual acuity remained unchanged.

Keywords: avastin, age related macular degeneration

Introduction

Vascular endothelial growth factor (VEGF) is a mediator of many pathologic conditions, including neovascular age-related macular degeneration (AMD) and serves as one of the key contributors to pathological conditions that can stimulate the formation of new blood vessels [1]. Age-related macular degeneration is a major cause of painless central vision loss and is the leading cause of blindness for people over the age of 60 years in countries of the Western world [2]. The recent special literature reveals the benefits of treating the neovascular form of AMD using antiangiogenic substances, in brief Bevacizumab (Avastin). Intravitreal injections of the antiVEGF reagents, bevacizumab (Avastin; Genentech, Inc., South San Francisco, CA) have been shown to improve mean visual acuity (VA) in the treated eyes [3]. Bevacizumab was genetically engineered from the murine monoclonal antibody against VEGF-A, the angiogenic protein considered to be the primary driver of choroidal neovascular membranes. Bevacizumab is FDA-approved (Food and Drug Administration) for the treatment of metastatic colon cancer by intravenous use [4,5]. There are two types of macular degeneration: the dry, or non-exudative form involves both atrophic and hypertrophic changes of the retinal pigment epithelium (RPE) underlying the central macula, as well as drusen deposition beneath the RPE. Non-exudative AMD can progress to the wet, or exudative form of AMD, in which pathologic choroidal neovascular membranes (CNVM) develop under the retina, leak fluid and blood, and cause a centrally blinding disciform scar over a relatively short time course if left untreated. Approximately 10–20% of patients with non-exudative AMD eventually progress to the exudative form [6].

Purpose

In this project, we proposed ourselves to evaluate the result of treatment with Bevacizumab (Avastin) in the neovascular (wet) form of AMD.

Material and method

This study is retrospective and includes 35 consecutive patients (38 eyes) diagnosed with the neovascular form of AMD. The patients were hospitalized at the Clinic of Ophthalmology from Tîrgu Mureş between December 2009 – April 2011 and received intravitreal injections of Avastin.

Inclusion criteria:

- ▶ Optical coherence tomography (OCT) – central retinal thickness (CRT) >300 µm;
- ▶ Best corrected visual acuity (BCVA) >0.001, measured with Snellen E-charts;
- ▶ No history of treatment within the previous 3 months.

Exclusion criteria:

- ▶ Systemic disease:
 - myocardial infarction;
 - cerebrovascular accident;
 - pulmonary embolus;
 - deep venous thrombosis, bleeding diathesis;
 - renal insufficiency;
 - uncontrolled systemic arterial hypertension.
- ▶ Other retinal diseases:
 - glaucomatous optic neuropathy;
 - vitreoretinal traction;
 - ischemic maculopathy.

- ▶ Diseases that prevent fundus examination:
 - clinically significant cataract;
 - corneal opacities.

Each patient underwent a complete eye examination:

- ▶ best corrected visual acuity, measured with Snellen E-charts;
- ▶ slit-lamp examination;
- ▶ Intraocular pressure (IOP) measurement;
- ▶ stereoscopic microscopy of the retina using a 90-diopter lens;
- ▶ retinal thickness measurement by optical coherence tomography (Stratus OCT model 3000, Carl Zeiss Meditec Inc.);
- ▶ fluorescein angiography and fundus photography for some of the patients.

The patients were injected with three shots of Avastin at one month interval. The injected doses were 0.1 ml Avastin (2.5 mg/shot). The following parameters were recorded: sex and age of the patients, the evolution of visual acuity, central retinal thickness.

BCVA was evaluated with the help of the classic optotype, and retinal thickness was measured by optical coherence tomography (Stratus OCT model 3000, Carl Zeiss Meditec Inc.)

Surgical technique

- ▶ dilatation of the pupil;
- ▶ topical anaesthesia (Benoxi) and an antibiotic (Floaxal) were applied to the affected eye;
- ▶ the surrounding eyelashes, caruncle, and the upper and lower eyelids were swabbed with povidone-iodine 10%, followed by a drape over the face and the insertion of a lid speculum;
- ▶ a flush of 10 ml 5% bethadine solution was placed in conjunctival cul-de-sac, avoiding the cornea, for a minimum of 30 seconds and the excess was removed with a cotton applicator;
- ▶ the proper injection site was located at 6–7 o'clock of the right eye or at 5–6 o'clock of the left eye;
- ▶ the surgeon donned sterile gloves;
- ▶ a sterile caliper was inspected to make sure the tips were not bent and the exact injection site was located. The patient was given a fixation target superonasally;
- ▶ the needle was uncapped, and the tip was kept away from the mouth of the surgeon, nurse and patient. In pseudophakic or aphakic patients, the injection site was 3.0–3.5 mm posterior to the limbus, inferotem-

porally, and the needle was directed toward the center of the vitreous cavity to a depth of 4–6 mm. In phakic patients, the injection site was 3.5–4.0 mm posterior to the limbus, inferotemporally, and the needle was directed more obliquely half way between the center of the vitreous cavity and the direction of the optic nerve, to a depth of 4 mm;

- ▶ injection of the substance intravitreally, with a 30 gauge needle (no contact with the eyelashes and free palpebral margins) over 0.5–2.0 seconds;
- ▶ the injection site was tamponated with a cotton tip, to avoid the reflux of the substance;
- ▶ one drop of 5% bethadine solution was inserted in conjunctival cul-de-sac;
- ▶ after that the needle was immediately withdrawn, the surgeon checked for retinal perfusion by indirect ophthalmoscopy and ensured that each patient could see light and count fingers;
- ▶ an antibiotic (Floaxal) was instilled immediately post procedure;
- ▶ in addition, Floxal ointment was applied to the affected eye, and the eye was patched;
- ▶ each patient was given or prescribed an antibiotic (Floaxal or Tobrex) to instill at home, 4 times a day for 7 days;
- ▶ each patient received written post-operative instructions and was warned of the symptoms of retinal detachment (RD) and endophthalmitis.

The off-label use of antiVEGF treatment and its potential risks and benefits were discussed extensively with all patients. From all patients we obtained a written informed consent. Patients were followed for the development of complications for 6 months after the last injection. The statistical analysis of the collected data was made using Microsoft Excel and Graph Pad In Stat 3.

Results

In our study group 22 from 35 patients were females (63%) and 13 were males (37%). The mean age was 73.6 years. Avastin treatment was applied to both eyes for 3 patients (8%) and to only one eye for 32 patients (92%). The mean BCVA at baseline and after 1, 3 and 6 months after the third injection, measured with Snellen E-charts, showed the highest level 1 month after the third injection (Control 1), increasing from 0.1375 to 0.2805 (Figure 1), ($p=0.0004$).

The BCVA values before the treatment with Avastin were divided in three categories: 8 eyes (21%) had BCVA

Table I. Distribution of mean BCVA values before and after treatment, at 1, 3 and 6 months after the third injection

BCVA	No. of eyes before treatment	%	Mean BCVA before the first injection	Mean BCVA at 1 month after the last injection	Mean BCVA at 3 months after the last injection	Mean BCVA at 6 months after the last injection
<0.02	8	21%	0.011	0.009	0.008	0.008
0.02–0.1	19	50%	0.072	0.075	0.066	0.067
>0.1	11	29%	0.341	0.562	0.485	0.476

Table II. The ratio between mean best corrected visual acuity before and after treatment for different grades of vision

BCVA	Mean before/after 1 month	Mean before/after 3 months	Mean before/after 6 months
<0.02	1:0.81	1:0.72	1:0.72
0.02–0.1	1:1.04	1:0.91	1:0.93
>0.1	1:1.64	1:1.42	1:1.39

<0.02; 19 eyes (50%) had BCVA 0.02–0.1 and 11 eyes (29%) had BCVA >0.1 (Table I).

From the total of 38 treated eyes, at the 1 month control 28 eyes (74%) had a favorable evolution of the BCVA, 7 eyes (18%) presented a stationary evolution (BCVA remained the same after treatment), and 3 eyes (8%) had an unfavorable evolution (BCVA after treatment decreased since the beginning of the treatment). At 3 months after the last injection, only 5 eyes were in a stationary status (compared with 7 after 1 month), but 5 patients presented an unfavorable status of BCVA (compared with 3 after 1 month). The evolution of BCVA at 6 months was favorable for 23 eyes (61%), 3 eyes were stationary (9%) and 12 eyes had an unfavorable evolution (30%) (Figure 2).

For eyes with BCVA between 0.02 and 0.1, the BCVA was greater with 1.04 than the baseline, and in the next

Table III. Correlation between central retinal thickness and best corrected visual acuity at control 1

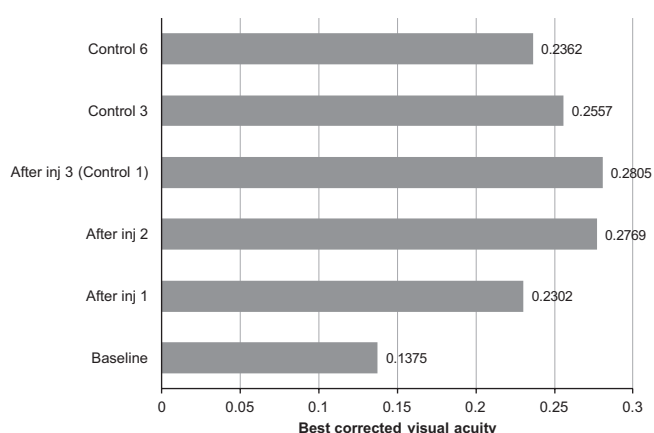
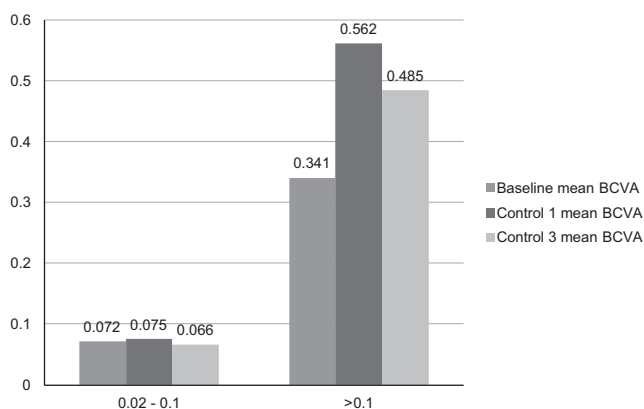
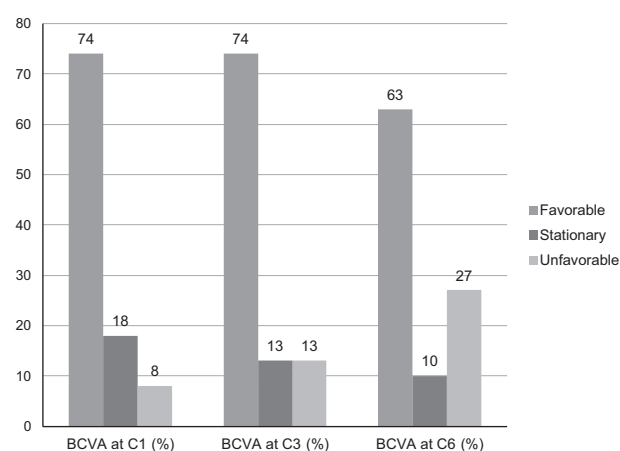
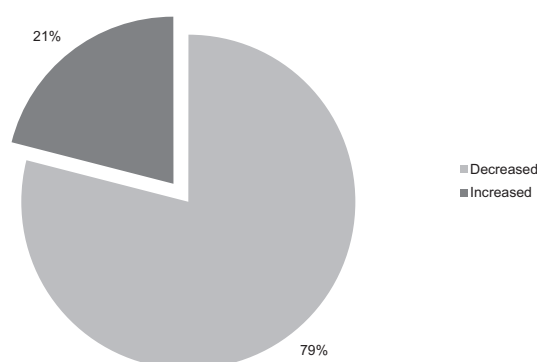
CRT/BCVA evolution	Favorable	Unfavorable	Total
Favorable	25	3	28
Stationary	3	4	7
Unfavorable	2	1	3
Total	30	8	38

interval (BCVA >0.1) with 1.64 greater than the baseline value, at control 1. The BCVA values decreased at the next controls (Table II).

The mean BCVA values showed the most remarkable increase at control 1, especially where BCVA was higher than 0.1 (Figure 3).

From the total of 38 treated eyes with Avastin, 30 eyes (79%) had a favorable evolution of CRT (lower after the treatment), and 8 eyes (21%) had an unfavorable evolution (CRT was higher/stationary after treatment) ($p=0.0001$) (Figure 4).

We have correlated the evolutions of BCVA and CRT after Avastin treatment at control 1. There was a direct correlation as both parameters presented the same type of evolution: favorable for 25 eyes, unfavorable for 1 eye, representing 68% from the 38 eyes (Table III.)

**Fig. 1.** Mean best corrected visual acuity values at baseline and different control times**Fig. 3.** Mean best corrected visual acuity values on two intervals at different control times**Fig. 2.** Best corrected visual acuity evolution at different control times**Fig. 4.** Central retinal thickness evolution after treatment at control 1

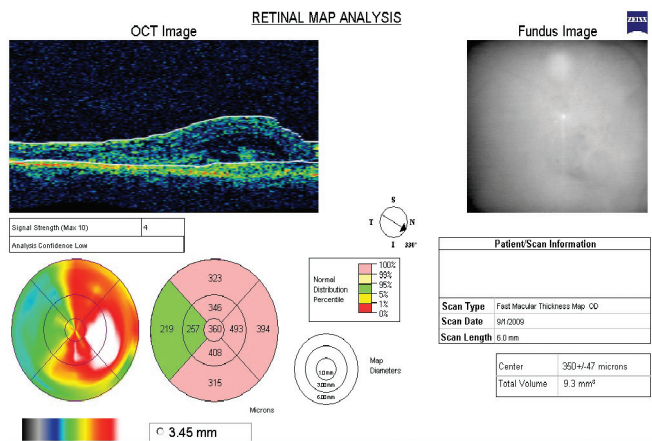


Fig. 5. Serous retinal detachment before the injection with Avastin, in wet AMD

There were no complications of myocardial infarction, stroke, endophthalmitis, toxic reactions, traumatic cataracts, RD, or vitreous hemorrhage. Figures 5 and 6 present the evolution of CRT after 3 injections with the complete resolution of subretinal fluid in a case with wet form AMD (Figure 5 and 6).

Discussions

In the according literature, it was shown that women have a slightly higher risk to develop neovascular AMD than men, especially in the group of patients over 75 years [6]. A possible explanation could be the longer hope of life of women, and the fact that women take advantage of medical services more frequently than men. Also, most specialized studies report a lower ratio of genders, e.g. the Blue Mountains Eye study reports a double prevalence of the neovascular form in women, compared with men [6]. Intravitreal bevacizumab has been used worldwide during the last year for the treatment of VEGF-related diseases, namely choroidal neovascularisation (CNV) secondary to AMD. Two papers have explored the administration of three initial injections at 1 month intervals in a fixed protocol, but with no control group [7,8]. Bashshur et al. gave an intravitreal injection of Avastin (2.5 mg/0.1 ml) at baseline, followed by two additional injections at 4-week intervals to 17 eyes with subfoveal CNV due to AMD. Mean BCVA significantly improved from 20/252 at baseline to 20/76 at 12 weeks. Seventy-six per cent of eyes had total resolution of subretinal fluid and 24% of eyes had BCVA better than 20/50 [7]. Giansanti et al. treated 27 patients with CNV secondary to AMD with three monthly injections of Avastin (1.25 mg). At the 6-month follow-up, the treatment showed stabilisation of visual acuity and CNV activity [8]. In the evaluation of the functional results after Avastin treatment, the evolution of visual acuity was taken into consideration. In the studied group, the evolution was favorable in 74% of the treated eyes. The obtained results are in consense with the results from special literature, which carry a prevailing evolution of visual acuity [9]. Most of the patients had a very low

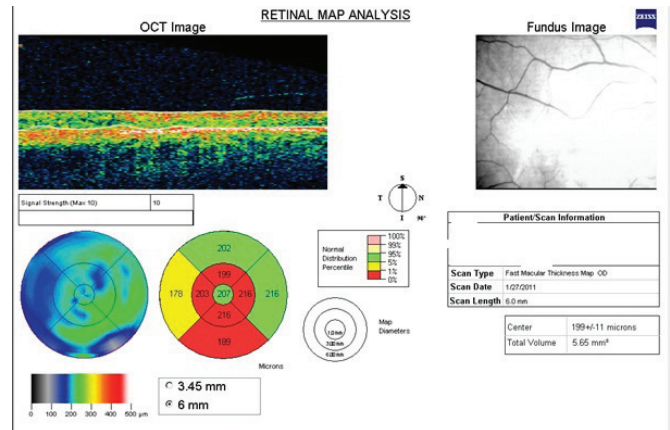


Fig. 6. Complete resolution of fluid after three injections of Avastin at the same patient

BCVA before treatment: only 29% had presented BCVA higher then 0.1. For the eyes with BCVA >0.1, the average of visual acuity after treatment was higher 1.64 times at 1 month, 1.42 times at 3 month, and 1.39 at 6 month. The Avastin treatment offered good functional results, as the BCVA was less affected by the disease, signaling the importance of precocious treatment in wet AMD. Some services do not treat advanced forms of AMD, considering them irreversible. For the evaluation of structural results from retinian level after Avastin treatment, we examined the evolutions of CRT, obtained through Stratus exam. In the studied group, CRT had good evolutions in 79% of the cases. The results are in correlation with data from the literature [9]. Statistically, the difference between CRT values before and after treatment at 1 month after the last injection, are significant ($p=0.0001$). Regarding the correlations between the functional modifications, visual acuity and structural, quantisized through CRT, we observed that they are not always parallel. The modifications of CRT correlate directly with BCVA modifications, in 68.42% of the cases. Statistically the difference between values of BCVA at baseline and at 1 month after the last injection are significant ($p=0.0004$). The most significant difference is between BCVA at baseline and BCVA at 3 months ($p=0.0021$). There were no relevant ocular or systemic side effects. Although randomised clinical trials with Avastin have not been carried out yet, there is clinical evidence that it has a good safety profile [10,11].

Conclusions

1. Quantitative evolution of visual acuity was favorable in 74% of treated eyes at 1 month, when the highest levels were obtained. Most of the patients described an amelioration of the quality of eyesight, even if, quantitatively, it was unmodified.
2. Avastin treatment offered good functional results, as the BCVA was less affected by the disease, which shows us the importance of precocious treatment in wet AMD.
3. Central retinal thickness decreased after Avastin treatment in 79% of cases.

4. The above results were maintained at 3 months from the first shot with Avastin. There was a direct correlation between BCVA evolution and morphological dates, evaluated through OCT, in at 68.42% of the treated eyes.
5. No significant ocular or systemic side effects were observed. More studies are required, to evaluate the long term effects of Avastin treatment in AMD.

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