One-Year Outcomes Using Bevacizumab for Neovascular Age-Related Macular Degeneration

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Purpose: To report the 12-month anatomic and Early Treatment Diabetic Retinopathy Study (ETDRS) best-corrected visual acuity (VA) response after primary intravitreal bevacizumab (Avastin, Genentech Inc., San Francisco, CA – 2.5 mg) in patients with choroidal neovascularization secondary to age-related macular degeneration.
Methods: One-hundred seventy-two eyes of 164 consecutive patients with choroidal neovascularization secondary to age-related macular degeneration, a mean age of 74.7 years and a minimum of 12 months of follow-up participated in this interventional prospective case series. Patients were treated with at least 3 intravitreal injection of 2.5 mg of bevacizumab. Patients underwent Early Treatment Diabetic Retinopathy Study BCVA testing, ophthalmoscopic examination, optical coherence tomography, and fluorescein angiography at baseline and follow-up visits.
Results: Mean baseline VA was 0.17±0.17 (172 eyes), and mean final VA was 0.15±0.18 (40 eyes) at 12 months. Central macular thickness at baseline by optical coherence tomography had a mean of 386.1±135.8 μm which was significantly reduced to a mean of 281.5±100.3 μm, 313.8±103.3 μm, 296.5±129.6 μm, and 276.8±95.69 μm at 1, 3, 6, and 12 months after initial treatment, respectively ($p < 0.0001$). No systemic adverse events were observed.
Conclusions: Primary intravitreal bevacizumab at doses of 2.5 mg seems to provide stability or improvement in VA, optical coherence tomography, and fluorescein angiography in subfoveal choroidal neovascularization secondary to age-related macular degeneration at 12 months.

Keywords: age related macular degeneration, intravitreal bevacizumab, best corrected visual acuity, retinal macular thickness

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Introduction

Age related macular degeneration (AMD) is the leading cause of irreversible blindness in patients over the age of 50 [1–3], with an incidence that rises from 0.2% in those aged 55–64 to 13% after the age of 85 [4].

The neovascular form of AMD, characterised by choroidal neovascularisation (CNV) and proliferation of fibrous tissue, represents only 10–15% of cases but is responsible for more than 80% of AMD-related severe visual loss or blindness [5].

"Wet" AMD, also known as neovascular AMD, is preceded by "dry" AMD and is characterized by choroidal neovascularization. CNV is the formation of abnormal blood vessels from existing vessel networks, which grow from the choroid to develop in or under the retina. These blood vessels may bleed into the subretinal space resulting in oedema and damage [6]. Vascular endothelial growth factor (VEGF) is a diffusible cytokine that stimulates angiogenesis and vascular permeability and has been found to be a potent inducer of CNV [6,7].

A new therapeutic era emerged, utilizing VEGF blockade for the management of chorioretinal diseases characterized by vascular hyperpermeability and/or neovascularization. Intravitreal injection of biological agents such as bevacizumab (IVB) (an off-label use of this agent) has proved safe and effective against choroidal neovascularization in AMD patients.

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Bevacizumab (Avastin, Genentech, South San Francisco, CA) is a full-length monoclonal antibody, first derived from a murine source and prepared for intravenous administration, which binds to and inhibits all isoforms of VEGF [8,9].

Patients with neovascular AMD usually report a sudden deterioration in vision that may be associated with distortion of the image.

Anti-VEGF factors have helped preserve and even improve vision in patients with "wet" type AMD.

Purpose

This study will provide preliminary data on the dose and dose interval related effects of intravitreally administered bevacizumab on retinal thickness and visual acuity in subjects with Age Related Macular Degeneration.

Material and methods

This prospective, interventional case series study was conducted in the Ophthalmology Clinic of Tîrgu Mureș from December 2007 to September 2012.

In this prospective pilot study 172 eyes of 164 patients with age related macular degeneration were given off-label intravitreal bevacizumab.

Each patient underwent best corrected visual acuity (VA) measurement with early treatment diabetic retinopathy study (ETDRS) chart and ophthalmic assessment including slit-lamp biomicroscopy. All the patients underwent anterior segment examination, biomicroscopic evaluation with fundus non contact +90D lens. Central macular thickness

Table I. Characteristics of patient groups

	Female	Male	Total	p value
Affected eye				
Right eye	41	26	67 (40.9%)	0.50
Left eye	53	44	97 (59.1%)	
Both eyes	8			
Total	94 (57.3%)	70 (42.7%)	164	
Age groups (mean age, yrs)				
48–64 (59.8)	9	7	16 (9.8%)	0.06
65–74 (70.2)	27	24	51 (31.1%)	
75–84 (78.6)	49	39	88 (53.7%)	
>85 (88.8)	9	0	9 (5.5%)	
Total	94 (57.3%)	70 (42.7%)	164	

Table II. The moments of injections and reinjections

	A1	A2	A3	C1	C3	C6	C12	Total
Eyes	172	159	138	129	98	77	40	172
Injections	172	159	138					469
Reinjections				2	4	6	8	20

was measured with optical coherence tomography (OCT III, Stratus OCT, Carl Zeiss, Germany).Three vertical and horizontal manually assisted OCT scans were obtained to locate the fovea and foveal thickness. The study parameters were evaluated one month, three months, six months and twelve months after the third intravitreal injection.

The intravitreal dosage of bevacizumab was 2.5 mg/0.1 ml. A standard protocol for intravitreal injections was followed, including the operative room, the use of topical 5% povidone-iodine, eyelid speculum, and postoperative topical antibiotic drops for seven days postinjection. They were asked to return the following day for assessment of intraocular pressure and signs of intraocular inflammation or infection. Whenever intraocular pressure exceeded 24 mmHg, patients were given topical medication to reduce the pressure. Patients received a loading phase of three consecutive monthly injections of bevacizumab.

At each visit, VA was measured along with the slit lamp examination of the anterior segment, intraocular pressure measurement and dilated fundus examination.

Indications for retreatment by IVB were defined as persistent subretinal and/or intraretinal fluid on OCT. No repeat treatment was performed if cessation of dye leakage from the CNV was revealed in fluorescein angiography (FA), as well as total resolution of the subretinal fluid on OCT. The off-label use of the drug and its potential risks and benefits were discussed extensively with all patients. All patients signed a comprehensive consent form before administration of bevacizumab.

Study parameters included ETDRS visual acuity and central macular thickness as measured by OCT.

Inclusion criteria:

– exudative AMD (confirmed by clinical and OCT examination);
– a best-corrected visual acuity using Early Treatment Diabetic Research Study (ETDRS) charts VA > 0.01.

Exclusion criteria:

– patients with untreated glaucoma;
– uncontrolled hypertension;
– history of thromboembolic events.

In neovascular AMD, the signs of disease activity include:

1. deterioration in visual acuity;
2. evidence of CNV leakage on fluorescein angiography;
3. abnormal retinal thickness on OCT, with evidence of intraretinal, subretinal, or sub-retinal pigment epitelium fluid;
4. presence/recurrence of intraretinal or subretinal haemorrhage.

Results

One-hundred seventy-two eyes of 164 patients with choroidal neovascularization due to AMD were treated with intravitreal injection of bevacizumab at baseline. The characteristics of the patients are presented in Table I.

Patients received a loading phase of three consecutive monthly injections of bevacizumab, then they were followed-up at 1, 3, 6 and 12 months after the last injection. Visual acuity testing and repeat fundus biomicroscopy were performed at each visit. OCT performed at baseline and month 1, 3, 6 and 12 were compared. The number of patients, injections and reinjections belonging to the each phase of the study is presented in Table II.

After the loading phase, bevacizumab retreatment was performed, in large part, based on OCT criteria: a loss of five letters of visual acuity in conjunction with intraretinal fluid on OCT or an increase of OCT central retinal thickness of at least 100 μm, being indications for retreatment. Other criteria used to trigger retreatment consisted of new-onset haemorrhage or new "classic" CNV (although, for the latter, fluorescein angiography was only required at follow-up in cases of significant or unexplained visual loss).

Changes in visual acuity values at different phases are presented in Table III. VA measurements are presented as absolute values (mean ± standard deviation [SD]), as a mean change from baseline to month 12, and in terms of the number of patients with (i) a gain of ≥15 letters or 3 lines, (ii) a change of <15 letters or 3 lines (stable), or (iii) a loss of ≥15 letters or 3 lines. At control 1 there was a statistically significant difference between baseline and control 1 ($p<0.05$), at control 3 there was a statistically significant difference between baseline and control 1 ($p<0.05$) and baseline and control 3 ($p<0.05$). At control 6 there was no statistically significant difference in the VA improvement between groups ($p=0.08$). There was a statistically significant difference between baseline and control 1 ($p<0.05$) at one year of follow-up.

Mean central retinal thickness changes are presented in Table IV. At baseline, the mean central retinal thickness was 386.1 μm. At 12 months follow-up the mean central retinal thickness was 276.8 μm. The central retinal thickness

Table III. Change in visual acuity values at different control times

	Stable	Gained ≥ 15 letters	Lost ≥ 15 letters
Control 1 (n=129)			
VA2–VA1	97.60%	27.10%	2.40%
VA3–VA1	96.10%	40.30%	3.90%
VA C1–VA1	96.90%	41.80%	3.10%
Control 3 (n=98)			
VA2–VA1	96.90%	26.50%	3.10%
VA3–VA1	95.90%	39.70%	4.10%
VA C1–VA1	96.90%	39.80%	3.10%
VA C3–VA1	94.90%	40.80%	5.10%
Control 6 (n=77)			
VA2–VA1	96.10%	26.00%	3.90%
VA3–VA1	94.80%	38.90%	5.20%
VA C1–VA1	96.10%	30.90%	3.90%
VA C3–VA1	94.80%	64.90%	5.20%
VA C6–VA1	84.40%	35%	15.69%
Control 12 (n=40)			
VA2–VA1	97.50%	35.00%	2.50%
VA3–VA1	97.50%	50.00%	2.50%
VA C1–VA1	100.0%	50%	0%
VA C3–VA1	95%	45%	5%
VA C6–VA1	82.50%	45%	17.50%
VA C12–VA1	87.50%	40%	12.50%

reduction began to appear after the first month of follow-up. Statistical significant difference were between baseline and control 1 and baseline and control 12 ($p<0.05$).

Discussion

Early treatment of wet AMD may limit the CNV-induced damage to the photoreceptors on the retinal pigment epithelium, leading to a better visual acuity outcome and prevention of vision loss.

Between december 2009 and september 2012 164 patients (172 eyes) were enrolled and randomly assigned to study treatment. At 12 months in the study remained 40 eyes. All patients were treated with 2.5 mg (0.1 ml) bevacizumab at first three months, then when they need for relaps (“as needed” treatment).

At baseline (before the first injection) all the 172 eyes had received 172 intravitreal injections. The baseline characteristics included a mean VA 0.17 (SD 0.17) and mean central macular thickness of 386.1 μm (156 patients). The best improvement was seen at first month following administration of three bevacizumab injections, when mean VA peaked at 0.30 (SD 0.27) (129 eyes).

At three month after the third injection (control 3), the mean VA progressively declined to 0.26 (SD 0.26).

At six month after the third injection (control 6) the mean VA was 0.21 (SD 0.24) from fewer number of eyes (77 eyes), and at one year (control 12) the mean VA declined to 0.15 (SD 0.18) from only 40 eyes.

Visual acuity improved by 15 or more letters at 41.86% and mean increases in visual acuity were 12.1 letters at control one.

The majority of patients (96.9%) showed a stable score at control one after the third injection, defined as a change of <15 letters/3 lines, while 3.1% of patients had lost ≥15 letters/3 lines.

Table IV. Central retinal thickness at baseline and different control times

	B CRT	C1 CRT	C3 CRT	C6 CRT	C12 CRT
Eyes	156	112	14	12	9
CRT (μm)	386.1	281.5	313.8	296.5	276.8
SD	135.8	100.3	103.3	129.6	95.69

In our report, at 3 months, visual improvement occurred in 40.8% of eyes at least by three lines with mean gain of 10.1 letters; stabilisation occurred in 94.9%.

At control 6, gained in VA with 3 lines or more was found at 35% of patients, stable VA (gaine or lost of 1-3 lines) at 84.4%, and lost of more then 3 lines at 15.6% of patients. At 12 months, visual improvement occurred in 40% of eyes (16 eyes) at least by three lines, with mean gain of 7.85 letters; stabilisation occurred in 87.5% (35/40 eyes).

These findings compare well with other series in the literature. Ehrlich et al. and Galbinur et al. report similar results, respectively, at 27 weeks and 3, 6, 9 months followup; here, we demonstrate that visual improvement can last 6 and even 12 months after treatment [10,11].

The improvement in VA at the end of our study was somewhat lower than that observed in PrONTO study (10 letters at 12 month).

Another nonrandomised prospective study, in which patients received a mean of 5.1 bevacizumab injections over 12 months, reported a mean VA improvement of 7.2 letters at month 12 [12].

Other recent studies have demonstrated a higher response as the number of injections increases [13,14].

The most conclusive evidence comes from the recent CATT trial, a large randomised study in which ranibizumab given monthly or "as needed" was compared to bevacizumab, again administered monthly or "as needed" on the basis of monthly evaluations [15].

Results showed that the efficacy of bevacizumab at one year ("as needed" injections), as measured by improvement in VA, was lower then our results (28% vs 40%). The mean gain in VA was 5.9 letters at one year.

The ABC study which is a multicentre, randomised, double masked study shows that the mean visual acuity improved by 7 letters in the bevacizumab group, 32% of patients gained 15 or more letters from baseline. In addition the proportion of patients who lost fewer than 15 letters of visual acuity from baseline was 91% [16].

In our study, the mean central retinal thickness was significantly reduced from 386.1 μm to 267.80 μm at 12 months. Significant decrease in central retinal thickness was reported by Ehrlich et al. [10] measuring at baseline 324±121 μm to 264±65 μm at final examination. We assumed that a decrease in the leakage and absorption of the subretinal and intraretinal fluid would improve the function of the remaining viable photoreceptors.

Conclusions

1. Our data indicate that intravitreal bevacizumab injection results in a significant improvement in functional and anatomic outcomes from the first month after injection, maintained at 12 months.
2. The lack of our study is no acquisition of OCT data at each follow up visit.
3. Limitation of this study includes lack of a control group after treatment
4. The strength of our study is use of standardized ETDRS protocol visual acuity data.
5. Our results suggest that intravitreal bevacizumab is well tolerated and may increase the chance of visual acuity gain in neovascular age-related macular degeneration even in cases with initial low vision.
6. The results of this study provided evidence that "as required" retreatment regimens could be a viable approach when administering bevacizumab in the treatment of neovascular AMD.

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