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PLENARY LECTURES

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Successful pharmacological treatment for ocular neovascularization (age-related macular degeneration and corneal neovessels)

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Introduction For many years, ophthalmologists have been trying to solve the problem of ocular neovascularization. Development of pathologic vessels in eye tissues, as a result of different pathological processes, had caused irreversible blindness and no treatment was available.

Exudative age-related macular degeneration (AMD) with development of choroidal neovascular membrane (CNV) is the most common cause of severe vision loss in persons over 55 years of age in developed countries, affecting millions of people and their number is expected to increase because of population growth and aging. The treatment of CNV is based on the interrupting of angiogenic cascade involved in the growth of new blood vessels.

Vascular endothelial growth factor (VEGF) plays a major role in ocular neovascularization and the pathogenesis of AMD. VEGF - a homodimeric glycoprotein - has been shown to be an endothelial cell specific mitogen *in vitro* and an angiogenic inducer in a variety of *in vivo* models. It increases vascular permeability, induces vascular endothelial cell proliferation, and promotes endothelial cell survival. It also serves as a chemotactic factor for leukocytes (1). VEGF is up-regulated by hypoxia. Inhibition of VEGF and, thereby, inhibition of angiogenesis and vascular permeability can be an effective treatment for a variety of ocular diseases including neovascular AMD (2) and corneal opacification with neovessels.

Bevacizumab (Avastin®; Roche) is a full-length humanized antibody that binds to all subtypes of VEGF and is successfully used in tumour therapy as a systemic drug.

In July 2005 at the ASCRS meeting Rosenfeld and colleagues reported favorable visual acuity responses to systemic Bevacizumab (3), and disclosed that they had administered intravitreal Bevacizumab in a small number of patients with no serious adverse events and good visual responses (4). The favorable short-term clinical efficacy was so apparent that use of intravitreal Bevacizumab spread rapidly among the retina community.

Uncontrolled prospective and retrospective case series studies including large number of patients in different countries have shown the short-term success of anti-vascular endothelial growth factor (VEGF) therapy with intravitreal Bevacizumab for choroidal neovascular membrane regression and visual acuity improvement in patients with neovascular AMD (5, 6) and other pathological processes (7–11). Recently subconjunctival application of Avastin has been discussed as efficient approach to reduce corneal neovascularisation (12).

Meanwhile other anti-VEGF drugs have been introduced for selective AMD treatment. Even though Bevacizumab is still used as an off-label therapy, the significant cost difference between it and the other pharmacological treatments for neovascular AMD (Pegaptanib, Verteporfin and Ranibizumab) is an important advantage and motivation for its wide acceptance (13).

Purpose The purpose of this study was to investigate the therapeutic effect of Bevacizumab in patients with neovascular AMD with classic and occult CNV as well as in cases with corneal neovascularization–eyes with penetrating keratoplasty and recurrent pterygium.

Methods For the period of 29 months (December 2006–April 2009), 115 patients were included in prospective interventional clinical study for evaluation of the efficacy of treatment with intravitreal and subconjunctival Avastin depending on indication. The study was approved by the Institutional Review Board. Examination of AMD patients included: visual acuity testing, intraocular pressure (IOP)

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measurement, bio microscopy, ophthalmoscopy, Amsler grid, fluorescein angiography (FA), macular perimetry testing with the Humphrey Automated Perimeter, B-scan and OCT with Stratus OCT (Carl Zeiss Meditec) in selected cases.

In patients with corneal neovascularization, full eye exam included anterior segment photo documentation for monitoring the morphologic changes of corneal vessels.

All patients have signed informed consent for the off-label use of Bevacizumab after discussing the risks, benefits, and the possible alternatives for treatment.

Intravitreal and subconjunctival Bevacizumab injections were performed in the operating theatre under strict aseptic technique using topical anaesthesia.

Patients who were treated with intravitreal application of the medication received 2 to 6 consecutive 1.25 mg/0.05 ml Bevacizumab injections in 30 to 45 days interval. Indirect ophthalmoscopy and tonometry were performed after the procedure in all cases. Topical antibiotic for 7 days was prescribed to all patients. Strict instructions for immediate report on possible complications were given to patients and in many cases to their relatives also. The follow-up visits were arranged on the 7th and 30th day after the injection and then every month. In cases with visual acuity deterioration due to active disease (based on FA and/or OCT), another intravitreal injection was performed.

Patients with corneal neovascularization received 2.5 mg/0.1 ml of Bevacizumab per affected quadrant at the site of neovascularization at the time of operation (penetrating keratoplasty or excision of the recurrent pterygium with limbal stem cell auto transplantation) or at follow-up visits. Indication for re-treatment was the presence of new vessels on the corneal graft or corneal neovascularization after the operation for recurrent pterygium. Effect on vascularization was accessed based on photo documentation and the number, size and centricity of neovessels.

Results Patients were divided into two groups according to the way of application of the medication as shown in Table 1.

Table 1 Indication for treatment with Bevacizumab (Avastin), way of application and patient population

	Group 1	Group 2
Indication	No (%) of patients with ivt. Bevacizumab	No (%) of patients with s.c Bevacizumab
Neovascular AMD	95, (82.6%)	
Corneal neovasculaization in PKP		15, (13.1%)
Corneal neovasculaization in recurrent pterygium		5, (4.3%)

Ivt. = intravitreal; s.c. = subconjunctival; PKP = penetrating keratoplasty.

A total of 95 patients with a mean age of 73 years (range 50–85) were included in the intravitreal Bevacizumab study-group. Occult CNV associated with AMD was the most frequent indication.

Preoperative visual acuity in the intravitreal Bevacizumab study-group varied from 0.05 to 0.6. Improvement in visual acuity by one, two or more lines was achieved in 65 patients (68.4%) of group 1. Twenty patients (21%) had no change and in five cases (10.6%) visual acuity deteriorated despite treatment.

Very encouraging results in terms of visual acuity improvement were obtained in patients with neovascular AMD up to 65 years of age. An example of angiographic changes in a patient with neovascular AMD is shown in Figure 1. The patient is 64-years-old and his visual acuity has increased from 0.3 to 0.7 after two intravitreal injections of 1.25 mg/0.05 ml of Bevacizumab.

Micro-perimetry test (performed on selected patients) showed slight deterioration of central visual field despite visual acuity improvement (Figure 2).

CNV documented on FA and OCT demonstrated minor changes following first Avastin application in contrast with rapid and dramatic improvement of visual acuity (Figure 3).

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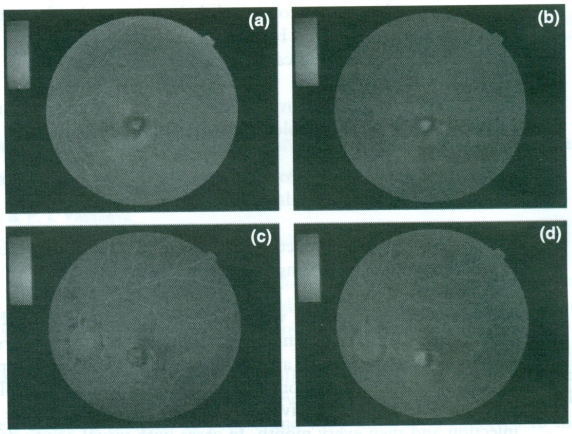

Figure 1 (a) Pre-treatment early-phase fluorescein angiogram showing a classic subfoveal CNV with (b) intense leakage in the late phase. Early phase (c) and late phase (d) fluorescein angiograms showing staining of the CNV with no evidence of leakage after treatment.

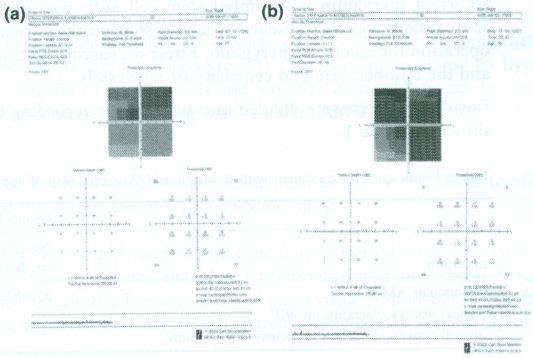

Figure 2 (a) Macular perimetry testing with the Humphrey Automated Perimeter before intravitreal administration of Bevacizumab and (b) two months later.

None of the patients in the intraocular Bevacizumab study group experienced systemic complications associated with the treatment. Transient intraocular pressure (IOP) elevations were detected in 16 patients (24.6%) in group 1 and this was the most common ocular complication. Other complications included subconjunctival hemorrhage, foreign body sensation, and tearing.

Fifteen patients with penetrating keratoplasty with a mean age of 63 years (range 30–83) and five with recurrent pterygium with a mean age of 46.8 (range 32–55) have received subconjunctival injection of Bevacizumab because of corneal neovascularization (group 2). Figure 4 demonstrates one of the patients in this group. Decrease and even disappearance of the new vessels were observed in 14 patients (82.4%) from subconjunctival Bevacizumab study-group. Adverse reactions included redness, tearing, and foreign body sensation.

Discussion Studies based on psychophysical (visual fields, colour vision) and electrophysiological (ERG/EOG) tests have approved Avastin as safe and well-tolerated treatment option (14, 15). Major local complications of intravitreal application of Bevacizumab include: endophthalmitis, tears of the retinal pigment epithelium, retinal detachment, traumatic lens injury, and immune reaction to repetitive doses.

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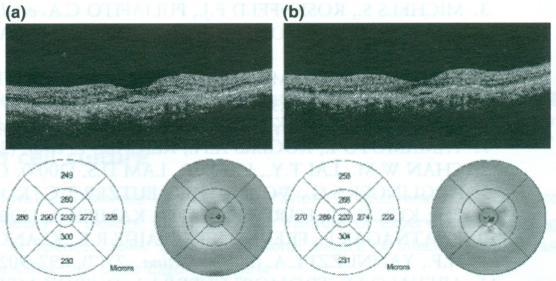

Figure 3 OCT image before (a) and 15 days after (b) intravitreal Bevacizumab.

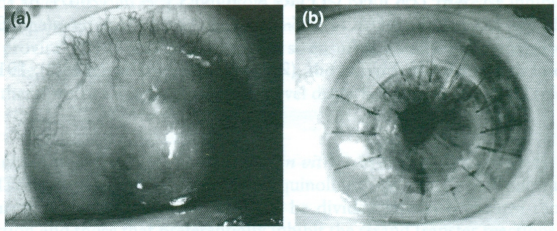

Figure 4 Patient before (a) and 8 months after (b) after corneal transplantation and subconjunctival Bevacizumab application.

Systemic complications reported in literature include: hypertension, myocardial infarction, and stroke. None of our patients has experienced significant ocular or systemic complications from this treatment.

There is no consensus yet about the optimal number of intravitreal injections needed for stabilization of results concerning visual acuity, central retinal thickness and fluorescein angiography changes. Many studies recently discuss the synergic effect of two or more medications and conclude that combined therapy increases the effectiveness of treatment and delays the necessity of new intravitreal injection of anti-VEGF drugs.

The main limitations of this study are the lack of control groups and the short follow-up period. Lack of central visual field improvement may be associated with another aspect of the VEGF- neuroprotective effect. Despite these, our results show that Bevacizumab is effective and safe treatment option for AMD and a number of ocular diseases associated with CNV and VEGF overproduction: pathologic myopia, angioid streaks, central or branch retinal vein occlusion, proliferative diabetic retinopathy with or without macular oedema.

Positive effect on corneal neovascularization has also been observed in the majority of patients with subconjunctival application of the medication.

Conclusions Our results show favourable effect of intravitreal Bevacizumab in properly selected patients' with wet form of AMD. Subconjunctival Avastin may be used as additional treatment option in cases with corneal neovascularization.

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