Acta Ophthalmologica

Microperimetric changes after intravitreal bevacizumab injection for exudative age-related macular degeneration

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ABSTRACT.

Purpose: **To evaluate the effect of intravitreal bevacizumab on macular function in the cases of exudative age-related macular degeneration (AMD).**

Methods: **A total of 21 eyes of 21 patients with exudative AMD were included in this study. In each eye, at baseline and 1, 3 and 6 months after intravitreal bevacizumab injection, logMAR visual acuity, central 4° macular sensitivity, absolute scotoma size, fixation stability and fixation location by MP-1 microperimetry and optical coherence tomography (OCT) foveal morphologic changes were assessed. After the initial treatment phase which included three consecutive injections, the decision to re-treat was based on OCT and clinical findings. Subsequent injections could be administered at least 1 month after the previous injection period according to the OCT-guided treatment regimen.**

Results: **Mean retinal sensitivity within central 4° (12 points) area had increased from 3.69 ± 3.44 dB at baseline to 7.16 ± 3.27 dB at month 6. In all controls after the treatment, there was significant increase in logMAR visual acuity ($p < 0.001$) and MP-1 retinal sensitivity ($p < 0.001$). Mean absolute scotoma in test point location had decreased significantly from 12 of the 76 applied test point locations measured at baseline to five test point locations (−7 test point locations; $p < 0.001$) at month 6 showing statistical significance. Fixation properties had preserved in all patients 6 months after intravitreal bevacizumab treatment.**

Conclusion: **Intravitreal bevacizumab therapy induced a significant increase in mean retinal sensitivity and significant decrease in mean absolute scotoma size during 6 months. The MP1 microperimetry proved to be a valuable tool in the evaluation of functional benefit of exudative AMD therapy with intravitreal bevacizumab.**

Key words: exudative age-related macular degeneration – intravitreal bevacizumab – microperimetry – retinal sensitivity.

Acta Ophthalmol. 2012: 90: 71–75

doi: 10.1111/j.1755-3768.2009.01838.x

Introduction

Exudative age-related macular degeneration (AMD) is responsible for 80% of significant visual disability related to AMD (Ferris et al. 1984). Loss of visual acuity typically results from choroidal neovascularization (CNV) beneath the macula. Vascular endothelial growth factor (VEGF), a central mediator of angiogenesis and a potent permeability factor, seems to be a major stimulus for CNV in AMD. Most of the new treatment modalities for exudative AMD are drugs that act against active forms of VEGF (Eyetech Study Group 2003; Ng & Adamis 2005).

Bevacizumab (Avastin; Genentech, Inc., South San Francisco, CA, USA) is a full-length humanized monoclonal antibody to VEGF-A that neutralizes all VEGF-A isoforms. It is approved by the Food and Drug Administration for the treatment of metastatic colorectal cancer (Ferrara et al. 2004). The Systemic Avastin for Neovascular AMD (SANA) study was the first trial to evaluate bevacizumab in ophthalmology (Michels et al. 2005; Moshfeghi et al. 2006). Twelve-week and 24-week study results showed improvement in visual acuity, and optical coherence tomography (OCT) and angiography outcomes after systemic anti-VEGF therapy with bevacizumab for patients with exudative AMD.

However, there was a concern about systemic side-effects, namely elevated arterial blood pressure. Rosenfeld et al. (2005) published the first case report about the intravitreal use of bevacizumab for CNV. Since then, several reports have shown that intravitreal bevacizumab appears to be an effective treatment for exudative AMD (Algvere et al. 2008; Pedersen et al. 2008; Furino et al. 2009). In these studies, visual acuity was the standard way of measuring visual performance, but it poorly described the functional impact in patients with compromised central visual fields because of AMD. Perimetry examines the light differential threshold, which is different than the minimal angle of spatial resolution (also termed as visual acuity). The latter markedly depends on the clearness of the optic media, while the light differential threshold mainly depends on the intactness of the photoreceptors. So the evaluation of retinal sensitivity and central retinal field function using microperimetry, that is one of the functional evaluation techniques, is more informative than only visual acuity testing (Varano & Scassa 1998). For exudative AMD, the value of testing macular function by central microperimetry has been shown extensively (Schneider et al. 1996; Tezel et al. 1996; Midena et al. 2004). MP-1 microperimetry allows automated functional analysis of the macula associated with real-time correction of eye movements. The procedure localizes the tested region on the retina exactly, even in patients with unstable fixation. Microperimetry is also a valuable tool in evaluating the safety of new therapeutic strategies. Improved or stable retinal sensitivity and visual fields are important indicators of the absence of treatment-induced toxic effects.

In this study, we evaluated changes in macular perimetry obtained by the MP-1 microperimeter for patients with exudative AMD during a 6-month follow-up of intravitreal bevacizumab therapy.

Methods

Twenty-one eyes of 21 patients with exudative AMD met the eligibility criteria summarized in Table 1 and were enrolled in the study. Patients with predominantly classic, minimally classic and pure occult CNV were eligible, while those with retinal angiomatous proliferation (RAP) were excluded, because it was thought these lesions might respond to treatment differently from non-RAP lesions. Patients with a history of a cardiovascular, cerebrovascular or peripheral vascular events <6 months before enrolment were excluded under the assumption that they might be at higher risk of developing another event and would have to withdraw before completion of the study. The procedure and the treatment options were explained thoroughly to patients, who then signed a consent form. Patients were informed of the off-label use of intravitreal bevacizumab.

Table 1. Inclusion and exclusion criteria for the treatment of exudative age-related macular degeneration (AMD) with intravitreal bevacizumab.

Inclusion criteria
1. Age 50 years and older
2. Subfoveal CNV attributable to AMD diagnosis by fluorescein angiography
3. Presence of subretinal fluid, cystic maculopathy or central retinal thickness >250 μm on OCT
4. Best corrected vision, using ETDRS charts, between 20/40 and 20/400 (Snellen equivalent)
5. CNV <5400 μm in greatest linear dimension
6. Ability to understand and sign consent form
Exclusion criteria
1. Prior treatment for CNV
2. Submacular haemorrhage involving the fovea
3. Submacular scarring involving the fovea
4. Retinal angiomatous proliferation
5. Corneal, lenticular or vitreous opacification that prevents good quality angiograms or OCT
6. History of uveitis
7. History of vitrectomy
8. Diabetic retinopathy
9. Other ocular conditions that affect vision
10. Cardiovascular, cerebrovascular or peripheral vascular events <6 months prior to enrollment

CNV, choroidal neovascularization; ETDRS, early treatment diabetic retinopathy study; OCT, optical coherence tomography.

Baseline work-up included best corrected visual acuity (BCVA), slit-lamp examination of the anterior chamber, dilated fundus examination, fluorescein angiography, OCT and MP-1 microperimetry (Nidek, Vigonza-Italy). BCVA was measured with Early Treatment Diabetic Retinopathy Study (ETDRS) charts at 4 metres and expressed as logMAR.

Before the injection of bevacizumab, topical proparacaine hydrochloride was applied to the ocular surface followed by preparation with 5% povidone iodine. A cotton-tipped applicator soaked in proparacaine hydrochloride was then applied to the injection site 4 mm posterior to the limbus. Commercially available bevacizumab (0.1 ml at 25 mg/ml) was prepared for each patient and was placed in a tuberculin syringe by a compounding pharmacist using aseptic techniques. The eye was observed until the optic nerve head was adequately perfused, and the intraocular pressure was less than 25 mmHg. Patients were instructed to use topical ciprofloxacin four times a day for 5 days and then were examined 1 week after injection and every month for 6 months. BCVA was measured at each visit along with slit-lamp examination of the anterior segment and dilated fundus examination. OCT and MP-1 microperimetry were repeated every month.

After the initial treatment phase, which included three consecutive injections, the decision to re-treat was based on OCT and clinical findings. Subsequent injections could be administered at least 1 month after the previous injection period according to the OCT-guided treatment regimen.

The response to treatment was monitored functionally by visual acuity and macular perimetry assessment after injection. Any potential bevacizumab-induced and injection-related complications were also noted.

Macular sensitivity was evaluated by MP-1 microperimetry. The MP-1 provides a 45° non-mydriatic view of

the fundus with an automated correction for eye movements. Goldmann III stimuli and a 4-2 staircase strategy were used, and a circular test grid with 74 stimulus locations covering an area of 20° was applied. The stimuli were projected on a white background with background illumination set to 1.27 cd/m^2 and a stimulus presentation time of 200 ms. The perimetric strategy of the current software version of the MP-1 starts at an initially defined threshold level for each stimulus. A 4-2 staircase strategy is then carried out. To assess the central macular retinal sensitivity, differential light threshold values were compared by calculating the mean of the central 4° (12 test points), which was averaged automatically by the MP-1 microperimetry software program of mean sensitivity in a polygon. Absolute scotoma is present if no threshold can be seen. Absolute scotoma points within all 74 test points (20°) were counted at each examination.

Data were analysed statistically with the Friedman test (non-parametric repeated ANOVA), in absolute scotoma point numbers within 20° and the mean differential light threshold within the central 4°. For assessment of fixation, the fundus movements were tracked during examination while the patient gazed at the fixation target. A 2° red cross was chosen as fixation target; however, the size was enlarged if the patient was not able to fixate. The autotracking system calculated horizontal and vertical shifts relative to a reference frame and drew a map of the patient's eye movements during the examination. The recorded fixation points were classified into three categories for fixation stability analysis (stable, relatively unstable, and unstable). Fixation is regarded as 'stable' if more than 75% of the fixation points are inside the 2° diameter circle, as 'relatively unstable' if >75% are inside the 2° diameter circle but more than 75% inside the 4° diameter circle, and as 'unstable' if less than 75% of the fixation points are inside the 4° diameter circle. To assess the fixation location, a standard, circular, central fixation area 2° in diameter (approximately 700 μm) centred on the fovea was defined. Eyes with more than 50% of the preferred fixation points located within the central area were classified as having predominantly central fixation. Eyes with more than 25% but <50% of preferred fixation points located within the central area were classified as having poor central fixation. Eyes with <25% of the preferred fixation points located within the central area were classified as having predominantly eccentric fixation. Fixation locations were classified automatically by the MP-1 MICROPERIMETRY software after a landmark had been positioned in the centre of the foveal avascular zone. For statistical analysis, fixation stability was graded as: stable = 3, relatively stable = 2, unstable = 1; and fixation location was graded as: predominantly central = 3, poor central = 2, predominantly eccentric = 1.

Results

A total of 21 eyes of 21 patients with exudative AMD were included in this study. Patients' ages ranged from 60 to 77 years (mean ± SD, 67 ± 5 years). The right eye was involved in 10 cases (48%), and the left eye in 11 (52%). After the initial treatment phase, 11 eyes (52%) were re-treated, and the mean number of injections at month 6 was 3.57 times (one patient had 5 injections and 10 had 4 injections). During follow-up, no cataract progression, endophthalmitis or injection-related complications were encountered. At 1, 3 and 6 months after intravitreal bevacizumab injection, mean retinal sensitivity within the central 4° area had increased from 3.69 ± 3.44 dB to 6.09 ± 3.37 dB, to 6.95 ± 3.43 dB and to 7.16 ± 3.27 dB, respectively (Fig. 1). At 1, 3 and 6 months after injection, the mean visual acuity had increased from 0.59 ± 0.25 logMAR to 0.36 ± 0.18 logMAR, to 0.32 ± 0.19 logMAR and to 0.34 ± 0.17 logMAR, respectively (Fig. 2). There were significant increases in logMAR visual acuity and MP-1 retinal sensitivity at 1, 3 and 6 months after injection [all ($p < 0.001$)].

One month after intravitreal bevacizumab injection, the mean absolute scotoma in test point locations had decreased significantly from 12 of the 76 test point locations measured at baseline to seven test point locations (−5 test point locations; $p < 0.001$). Mean scotoma decreased further to five test point locations (−7 test point locations; $p < 0.001$) at month 3. At month 6, the mean absolute scotoma had stabilized at five test point locations (−7 test point locations; $p < 0.001$) (Fig. 3). Figure 4 shows changes in retinal sensitivity for a 69-year-old man, 6 months after receiving intravitreal bevacizumab injection.

Fixation stability had increased at months 1, 3 and 6 from 2.42 ± 1.0 to 2.57 ± 0.5, to 2.66 ± 0.48 and to 2.66 ± 0.48, respectively, moderate but not significant improvements. Fixation location increased from 2.61 ± 0.49 to 2.66 ± 0.48, to 2.66 ± 0.48 and to 2.71 ± 0.46, respectively, again moderate but not significant improvements (Table 2).

Discussion

Patients with exudative AMD complain about a reduction in their quality of life. This impairment is caused by the early development of an abso-

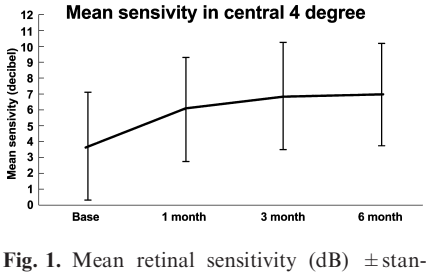

Fig. 1. Mean retinal sensitivity (dB) ± standard deviation within the central 4° (12 points) area.

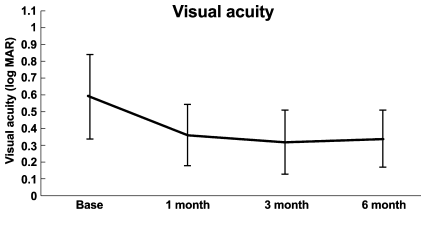

Fig. 2. Visual acuity (logMAR) ± standard deviation.

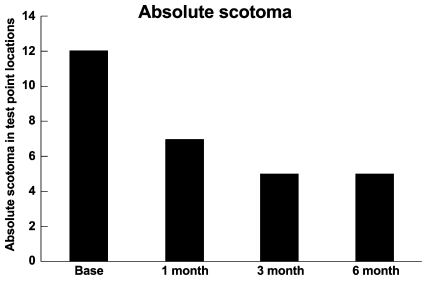

Fig. 3. Mean absolute scotoma at test point locations.

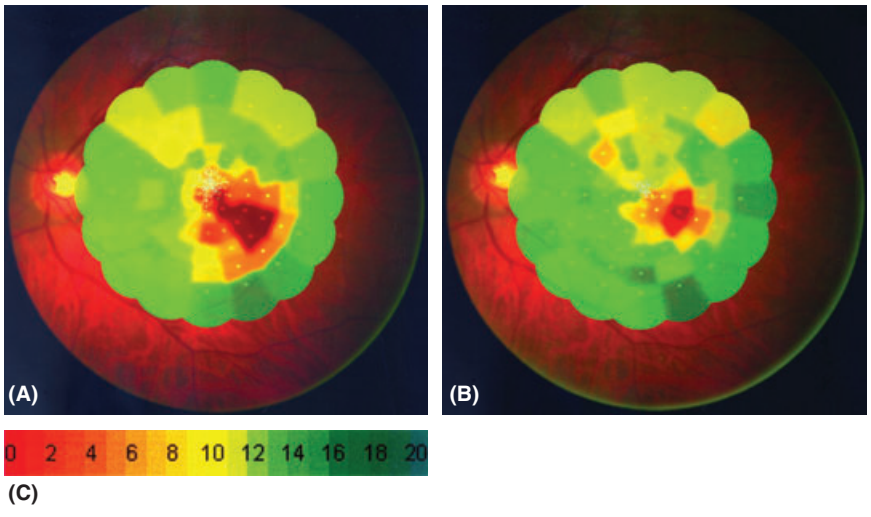

Fig. 4. Changes in retinal sensitivity for a 69-year-old man after receiving intravitreal bevacizumab injection: (A) Baseline, (B) 6 months, (C) colour coded, numeric scale shows the threshold in 2 dB steps from 0 to 20 dB.

Table 2. Fixation properties before and after intravitreal bevacizumab injection in eyes with exudative age-related macular degeneration.

	Baseline	1 month	3 month	6 month
Fixation stability*	2.42 ± 1.0	2.57 ± 0.5 NS	2.66 ± 0.48 NS	2.66 ± 0.48 NS
Stable [*n*(%)]	9 (43)	12 (57)	14 (67)	14 (67)
Relative unstable [*n*(%)]	12 (57)	9 (43)	7 (33)	7 (33)
Unstable [*n*(%)]	0 (0)	0 (0)	0 (0)	0 (0)
Fixation location	2.61 ± 0.49	2.66 ± 0.48 NS	2.66 ± 0.48 NS	2.71 ± 0.46 NS
Central [*n*(%)]	13 (62)	14 (67)	14 (67)	15 (71)
Poor central [*n*(%)]	8 (38)	7 (33)	7 (33)	6 (29)
Predominantly eccentric [*n*(%)]	0 (0)	0 (0)	0 (0)	0 (0)

* Fixation properties: stable = 3; relative unstable = 2; unstable = 1; central = 3; poor central = 2; predominantly eccentric = 1.
NS = Not significant.

lute central scotoma, owing to the generally subfoveal location of the lesion. The scotoma affects spatial perception, dark adaptation and the ability to recognize faces and details (McClure et al. 2000). The size of the scotoma correlates significantly with reading capacity and reading speed in exudative AMD (Ergun et al. 2003). It is known that the preservation of the central visual field is most important to the ability to use magnification aids (Ergun et al. 2003).

MP-1 microperimetry is a developed instrument that combines digital fundus imaging with automated perimetry (Springer et al. 2005). During the test, the autotracking function corrects for shifts in the measurement position caused by small, involuntary movements. The procedure localizes the tested region on the retina exactly, even in patients with unstable fixation. It also allows evaluation of function not only in the fovea, but also in the central macular area. This may be a more comprehensive approach for quantifying macular function in exudative AMD than visual acuity measurement alone. Therefore, in any therapy for exudative AMD, the aim must also be the preservation of central retinal function.

Photodynamic therapy with verteporfin, which is one of the treatment options for exudative AMD, reduces the loss of central visual field function, but has not been able to improve central visual field sensitivity (Schmidt-Erfurth et al. 2004).

For the treatment of exudative AMD, ranibizumab is administered as an intravitreal injection and received FDA approval in 2006. Parravano et al. (2009) assessed functional and structural retinal changes in 18 patients with exudative AMD treated with intravitreal ranibizumab 0.5 mg in their retrospective 24-week follow-up study. They found that mean retinal sensitivity measured with microperimetry significantly improved from 3.89 ± 3 dB at baseline to 6.61 ± 3.4 dB at 24 weeks ($p = 0.04$). An improvement of fixation stability from baseline was observed in 33.3% of patients. They concluded that although visual acuity and retinal thickness changes seemed to be almost maximum at 4 weeks after intravitreal ranibizumab 0.5 mg, retinal sensitivity as measured by microperimetry showed a trend of progressive improvement till 24 weeks. Bolz et al. (2009) also analysed that morphological and functional changes of loading regimen with intravitreal ranibizumab in 29 patients (29 eyes) with exudative AMD. They found that the initial administration of intravitreal ranibizumab in exudative AMD induces a significant effect on intraretinal and subretinal fluid and visual function but subsequent injections have a less pronounced effect.

Prager et al. (2008) showed that systemic bevacizumab therapy induced a significant increase in mean retinal sensitivity and a significant decrease in mean absolute scotoma size. In this study, the mean absolute scotoma size decreased from 33% to 22% at month 3 and to 23% at month 6. Mean differential light thresholds increased significantly throughout the observation period from 3.8 dB at baseline to 5.5 dB at month 6. To date, no information has been available on central visual field function after intravitreal bevacizumab injection in exudative AMD. In our study, intravitreal bevacizumab therapy induced a significant increase in mean retinal sensitivity and a significant decrease in mean absolute scotoma size. At all follow-up visits, 1, 3 and 6 months after intravitreal bevacizumab injection, the mean retinal sensitivity within the central 4° area had improved significantly. One month after injection, the mean absolute scotoma in test point locations had decreased significantly from 76 applied test point locations measured at baseline to seven test point locations, showing statistical significance. Mean absolute scotoma decreased further to five test point locations at month 3 and to five test point locations at month 6. Fixation analysis showed a moderate, but not significant, improvement of fixation up to month 6.

These results are superior to those of currently approved verteporfin therapy, which only slows down the loss of central macular function (Schmidt-Erfurth et al. 2004), and are consistent with those of systemic bevacizumab therapy (Prager et al. 2008). The results for increase in mean retinal sensitivity and decrease in mean absolute scotoma size by intravitreal bevacizumab injection also support many investigation outcomes obtained for distance visual acuity (Algvere et al. 2008; Pedersen et al. 2008; Furino et al. 2009). Scotoma may reflect photoreceptor dysfunction because of intraretinal and subretinal fluid and fibrotic components of membrane, and photoreceptor cell loss itself. When extensive leakage was resolved, which means a decrease in intraretinal and subretinal fluid, the area of scotoma was decreased. These beneficial effects were obtained even 1 month after intravitreal bevacizumab injection. With multiple additional injections, enlargement of the functional defect was not seen. Therefore, these results at least show that multiple intravitreal bevacizumab injections did not damage the retinal pigment epithelium secondary to choriocapillaris damage, as in photodynamic therapy (Schmidt-Erfurth et al. 2004). Improvement of retinal sensitivity and fixation properties offers evidence of safety. At least in follow-up, significant toxic effects on the retina, retinal pigment epithelium and choroid were not detected.

In addition to anatomical restoration and increase in visual acuity, intravitreal bevacizumab injection also improved the central macular function. Although 6 months of follow-up are insufficient to draw conclusions on any treatment, use of MP-1 microperimetry enabled us to evaluate accurately the retinal sensitivity and scotoma size in eyes with exudative AMD that had received intravitreal bevacizumab injection. In addition to visual acuity, measurement of retinal sensitivity would be a great help in the evaluation of the effectiveness of intravitreal bevacizumab injection in eyes with exudative AMD. Because this study consisted of a small number of patients, with a short follow-up period, further prospective studies are necessary to determine the effectiveness of intravitreal bevacizumab injection on retinal sensitivity.

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Received on September 16th, 2009.
Accepted on November 27th, 2009.

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