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Efficacy of 12-month treatment of neovascular age-related macular degeneration with intravitreal bevacizumab based on individually determined injection strategies after three consecutive monthly injections

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ABSTRACT.

Purpose: **To report the results of intravitreal treatment with bevacizumab in neovascular age-related macular degeneration (AMD) after a loading dose (LD) of three monthly injections followed by an optical coherence tomography (OCT)-guided strategy, based on best-corrected visual acuity (VA) and number of injections required over 1 year.**

Methods: **A series of consecutive cases of 149 eyes of 147 patients received three or more intravitreal injections of bevacizumab (1.25 mg) for neovascular AMD over a 1-year period. The patients underwent ophthalmological examinations: measurement of the VA, fluorescein angiography, dilated fundus examination at baseline; VA, OCT and dilated fundus examination at monthly follow-up visits. Repeated injections were given each month for the first 3 months (LD); thereafter, injections were only administered if leakage or macular oedema were present.**

Results: **Mean baseline VA was 51 ± 14 letters, which improved to 58 ± 15 letters ($p < 0.0001$; $n = 149$) at first evaluation (15 ± 2 weeks), 59 ± 15 letters ($p < 0.0001$; $n = 143$) at second evaluation (25 ± 2 weeks) and 57 ± 16 letters ($p < 0.0001$; $n = 132$) at third evaluation (51 ± 3 weeks). The baseline mean central retinal thickness (344.6 μm) and total macular volume (8.6 mm^3) decreased at first evaluation, to 219.0 μm ($p < 0.0001$) and 7.2 mm^3 ($p < 0.0001$), respectively. The mean number of injections per patient treated for 1 year was 5.1 (range 3–9). No systemic side-effects were noted.**

Conclusion: **Treatment of neovascular AMD with intravitreal bevacizumab administered in LD of three monthly injections and followed by an OCT-guided strategy provides functional and anatomical improvements for up to 1 year.**

Key words: age-related macular degeneration – anti-VEGF – Avastin® – bevacizumab – choroidal neovascularization – intravitreal injections – loading dose treatment strategy – vascular endothelial growth factor

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Introduction

Neovascular age-related macular degeneration (AMD) is one of the main causes of blindness in the industrialized world (Bressler et al. 2003), and is responsible for 80% of significant visual loss related to AMD (Ferris et al. 1984). Vascular endothelial growth factor (VEGF) stimulates angiogenesis and increases vascular permeability, and it appears to be the main mediator in the pathogenesis of neovascular AMD (Ferrara 2004; Ng & Adamis 2005). Inhibition of VEGF with an anti-VEGF drug has been demonstrated to be an effective treatment of AMD. Ranibizumab (Lucentis®; Genentech Inc., San Francisco California, USA) is a fragment of a recombinant monoclonal humanised antibody that inhibits all isoforms of VEGF. It is genetically engineered to have a greater affinity for VEGF, and is formulated for intraocular use. Ranibizumab is the first, and currently the only, US Food and Drug Administration (FDA)-approved anti-VEGF drug for the intravitreal treatment of choroidal neovascularization (CNV) that has shown improvement in visual acuity (VA) in controlled clinical trials. Bevacizumab (Avastin®; Gen-

entech) is a full-length recombinant humanised monoclonal antibody derived from the same precursor as ranibizumab, and also binds to and blocks the actions of all isoforms of VEGF. It has been approved by the FDA for the treatment of metastatic colorectal and breast cancers (Ferrara et al. 2004). However, its use in the treatment of CNV remains off-label. Systemic bevacizumab has shown encouraging results in the treatment of CNV (Moshfeghi et al. 2006); however, there are systemic side-effects. Therefore, treatment with intravitreal bevacizumab has been investigated and the results of several short-term (up to 6 months) studies have shown that it is an effective treatment for neovascular AMD (Bashshur et al. 2006; Rich et al. 2006; Spaide et al. 2006; Yoganathan et al. 2006; Aisenbrey et al. 2007; Giansanti et al. 2007; Lazic & Gabric 2007; Weigert et al. 2008). However, to date, very few studies have assessed the safety and efficacy of intravitreal bevacizumab treatment lasting more than 6 months (Arevalo et al. 2008; Bashshur et al. 2008; Cleary et al. 2008; Fong et al. 2008).

In addition to differences in treatment length, the aforementioned studies also differed in the regimens and dosage of the administration of the bevacizumab injections, as well as in the inclusion and retreatment criteria. All studies concur that the initial phase of treatment is decisive, and several injection regimes have been examined for this initial phase. Furthermore, there is as yet no consensus on whether reinjection after the initial phase should be administered at regular time intervals, or whether it should be guided by clinical indications of recurrence of leakage, which can be determined by ophthalmoscopic examination, reduction of best-corrected VA, fluorescent angiography (FA) or optical coherence tomography (OCT).

Two main approaches for the administration of bevacizumab injections have been reported. One approach advocates a loading dose (LD) of three injections administered at monthly intervals in the initial 3-month phase. Studies using this approach have reported improvements during the initial 3-month phase only (Bashshur et al. 2006; Spaide et al. 2006), while improvements have also been seen during the 3-month follow-up after this initial phase either with (Weigert et al. 2008) or without (Giansanti et al. 2007; Melamud et al. 2008) additional reinjections. The second, more recent, approach recommends only one injection at baseline, followed by monthly injections administered in the presence of persistent leakage or recurrence of retinal oedema (Rich et al. 2006; Yoganathan et al. 2006; Aisenbrey et al. 2007; Lazic & Gabric 2007; Arevalo et al. 2008; Bashshur et al. 2008; Cleary et al. 2008). Determination of the need for reinjection should preferably be based on an OCT-guided treatment strategy. The first study to demonstrate the benefits of OCT-guided, variable dosing regimen was the PrONTO study (Fung et al. 2007). This study used three consecutive monthly intravitreal injections of ranibizumab (0.05 ml, 0.5 mg). Retreatment was performed if one or more of the following criteria were present: vision loss (≥ 5 letters) associated with fluid detected by OCT, increase in central retinal thickness (CRT) (≥ 100 μm), new onset haemorrhage, new classic CNV and persistent fluid following last injection. Compared with the results of the MARINA and ANCHOR studies, which administered ranibizumab at monthly intervals, the PrONTO study indicated that comparable VA results over 1 year could be achieved with fewer injections.

The present study is a 1-year review of a series of consecutive cases of eyes with treatment-naive neovascular AMD (i.e. no previous treatment for AMD) that received an LD of monthly intravitreal injections of bevacizumab for 3 months followed by individually determined reinjections for up to 12 months based on the PrONTO strategy for retreatment. The aim of the study was to determine the efficacy of this treatment strategy regarding VA and the number of bevacizumab injections required over 1 year.

Materials and Methods

We reviewed a series of consecutive cases of 149 eyes of 147 patients with CNV secondary to AMD who were offered treatment with intravitreal bevacizumab. The inclusion criteria were age ≥ 50 years, active leakage documented by FA, subfoveal lesion, VA ≥ 20 letters [measured using a standardized Early Treatment Diabetic Retinopathy Study (ETDRS) chart], no previous treatment and completion of the initial LD treatment with three intravitreal bevacizumab injections. All angiographic lesion types were included, regardless of size or proportion of fibrosis. The off-label use of bevacizumab and its potential risks were discussed in detail with all of the patients, and informed consent was obtained. All of the patients underwent ophthalmological examination, including VA measurement, slit-lamp examination, tonometry, dilated fundus examination, FA (ImageNet 2000; Topcon, Tokyo, Japan) and OCT (3D OCT-1000; Topcon). Intravitreal bevacizumab 1.25 mg was injected via the pars plana under sterile conditions in accordance with the recommendations of Aiello et al. (2004). All of the patients received the initial LD of three bevacizumab injections separated by 4–6 weeks. Thereafter, patients were followed at monthly intervals. At each visit, the patient underwent an ophthalmological examination, including VA (measured using a standard ETDRS chart), slit-lamp examination, tonomtery, dilated fundus examination and OCT. FA was performed only in the event that clinical examination and OCT could not confirm whether the lesion was still active. The decision to retreat with subsequent injection was based on the recommendations proposed by the PrONTO study (Fung et al. 2007). Patients were retreated when either the presence or recurrence of fluid in the macula (intra- or subretinal) was observed with OCT. Retreatment criteria were also loss of vision of more than five letters associated with fluid detected, new haemorrhage, new CNV and/or an increase in CRT of more than 100 μm. All retreatment criteria were based on comparison with the results of the previous visit. The study was approved by the National Medical Ethics Committee (Republic of Slovenia).

We analysed the changes in VA during the first year of patient treatment at three time-points: first evaluation, 4 weeks after the third LD injection of bevacizumab; second evaluation, 6 months after the first LD injection; and third evaluation, 1 year after the

first LD injection. The main outcome measures were changes between baseline and follow-up visits for VA, CRT (in μm, defined as the mean thickness of the neurosensory retina in a central 1-mm-diameter area) and total macular volume (TMV, in mm^3, defined as the total volume of the scanned neurosensory retina) as measured by the OCT software.

For a subgroup analysis the neovascular lesions were classified by FA as occult with no classic, minimally classic and predominantly classic (Macular Photocoagulation Study Group 1991), and retinal angiomatous proliferation (RAP) (Yannuzzi et al. 2001). Changes of VA were compared before treatment and 1 year after the first LD injections. The visual outcome of patients with subfoveal fibrosis was compared with that of patients who had no subfoveal fibrosis in their lesion. Subfoveal fibrosis was defined as the presence of fibrous tissue or a disciform scar in the foveal region observed by biomicroscopy and late staining with FA.

Statistical analyses were performed using graphpad prism 5 software for Windows (GraphPad Software, San Diego, California, USA). For statistical analysis purposes, patients' ETDRS VA was converted to a standard logarithm of the minimum angle of resolution scale (LogMAR). The paired *t*-test was used to compare the changes in VA and OCT parameters (CRT and TMV). The Pearson test was adopted to assess whether there were correlations between VA and OCT parameters. For the comparison of VA and the total number of injections between different CNV lesion types and the presence of fibrosis, an analysis of variance (Anova) and unpaired *t*-test were used, respectively. Statistical significance was defined as $p < 0.05$.

Results

One hundred and forty-nine patients with a mean age (range) of 76.2 (50–96) years participated in the study (93 female, 56 male). Two of these patients received treatment in both eyes. Follow-up ranged from 12 to 58 weeks, with a mean of 48 weeks.

Of the 149 patients who were included in the study, 132 completed 1 year of treatment. By the second evaluation, six patients had dropped out: four for unknown reasons and two for medical reasons (one developed uveitis, the other preretinal bleeding). By the third evaluation, an additional 11 patients had dropped out: 10 for unknown reasons and one because of the development of a macular hole.

The mean VA at baseline was 51 ± 14 letters [mean ± standard deviation (SD)]. At first evaluation (15 ± 2 weeks), VA improved to 58 ± 15 letters ($p < 0.0001$; $n = 149$); at second evaluation (25 ± 2 weeks), to 59 ± 15 letters ($p < 0.0001$; $n = 143$); and at third evaluation (51 ± 3 weeks), to 57 ± 16 letters ($p < 0.0001$; $n = 132$). The changes in VA in patients who were treated with intravitreal bevacizumab for 1 year are illustrated in Fig. 1. The scatterplots of baseline VA versus VA at all three evaluations are shown in Fig. 2. Table 1 shows the proportion of patients with improved or worsened VA at all three evaluations.

The changes in VA in patients who were treated with intravitreal bevacizumab for 1 year are illustrated in Fig. 2. The comparison of VA at baseline and the third evaluation by lesion type and presence of subfoveal fibrosis in these patients is shown in Table 2.

The mean CRT decreased from 344.6 ± 152.0 μm at baseline to 219.0 ± 126.1 μm ($p < 0.0001$; $n = 62$) at first evaluation. The mean TMV decreased from 8.6 ± 1.4 mm^3 at baseline to 7.2 ± 1.0 mm^3 ($p < 0.0001$; $n = 60$) at first evaluation. The scatterplots of baseline CRT and TMV versus CRT and TMV at first evaluation are shown in Fig. 3. There was no correlation between final VA and baseline CRT ($p > 0.05$). The changes in CRT and TMV did not show any correlations with the change in VA ($p > 0.05$).

The mean number of injections given per patient at the first evaluation was 3.0. After the initial treatment phase, 57% of patients required a mean of 1.5 reinjections before the second evaluation, with the remaining 43% stable without further treatment. Between the second and third evaluations, 65% of patients required a mean of 1.8 reinjections, whereas the remaining 35% remained stable without further treatment. The mean number of injections per patient was 4.9 (range 3–9). The mean number of injections per patient who were treated for 1 year was 5.1 (range 3–9). The number of injections for subgroups by lesion type is shown in Table 2.

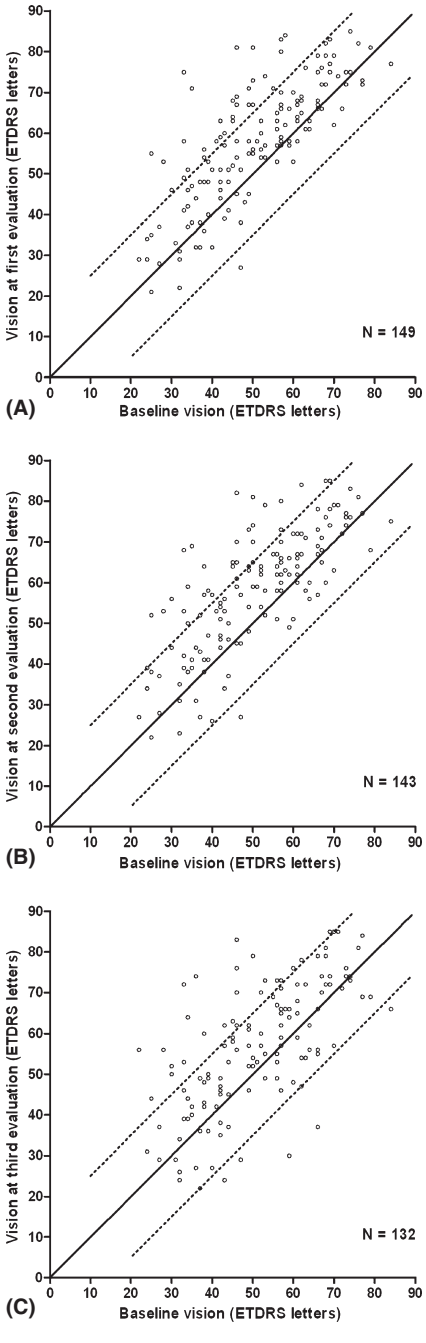

Fig. 1. Scatterplots of baseline best-corrected visual acuity (VA) versus VA at first evaluation (15 ± 2 weeks) (A), second evaluation (25 ± 2 weeks) (B) and third evaluation (51 ± 3 weeks) (C). All points above the solid line imply improvements in VA. Points above the upper/below lower dotted lines represent a gain/loss, respectively, of more than 15 letters.

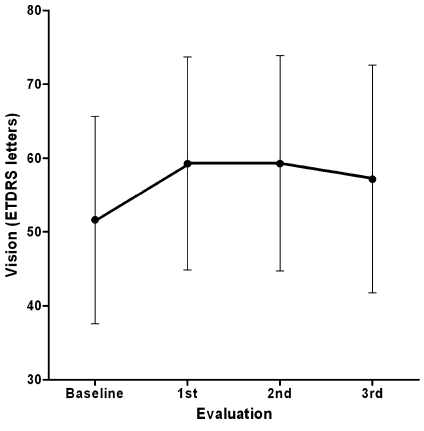

Fig. 2. Mean visual acuity [± standard deviation (SD); derived from Early Treatment Diabetic Retinopathy Study (ETDRS) letters] at baseline, and at the first (15 ± 2 weeks), second (26 ± 2 weeks) and third (51 ± 3 weeks) evaluations over 1 year of intravitreal bevacizumab treatment (n = 132, mean number of injections per patient = 5.1).

Table 2. Comparison of visual acuity at baseline and third (51 ± 3 weeks) evaluation with the number of injections (mean ± standard deviation) by lesion type and presence of subfoveal fibrosis in patients who were treated with intravitreal bevacizumab for 1 year.

	n (%)	Baseline evaluation (letters)	Third evaluation (letters)	Paired t-test	Total number of injections
All	132 (100)	51 ± 14	57 ± 16	p < 0.0001	5.1 ± 1.5
Occult with no classic	52 (39)	54 ± 13	59 ± 16	p = 0.02	5.3 ± 1.7
Minimally classic	29 (22)	51 ± 13	54 ± 17	p = 0.1	5.0 ± 1.2
Predominantly classic	40 (30)	48 ± 17	56 ± 16	p = 0.0003	4.9 ± 1.6
RAP	11 (8)	51 ± 10	60 ± 12	p = 0.002	5.0 ± 1.5
anova		p = 0.2	p = 0.8		p = 0.8
Without fibrosis	110 (83)	53 ± 14	60 ± 15	p < 0.0001	4.8 ± 1.6
Subfoveal fibrosis	22 (17)	43 ± 12	44 ± 13	p = 0.7	4.9 ± 1.6
Unpaired t-test		p = 0.001	p < 0.0001		p = 0.96

anova, analysis of variance; RAP, retinal angiomatous proliferation.

The following ocular adverse affects were observed: uveitis (one patient), preretinal bleeding (one patient), macular hole (one patient), cataract (one patient) and subfoveal pigment epithelium tear (one patient). No systemic adverse events, permanently raised intraocular pressure or ocular toxicity were noted.

Discussion

This 1-year study demonstrates that intravitreal bevacizumab is a safe treatment for neovascular AMD that provides functional and anatomical improvement. Significant improvements in mean VA were noted after the initial LD treatment with three injections of bevacizumab, and these improvements were maintained over the whole study period. This functional improvement in VA was associated with an anatomical improvement of the macula, as noted by OCT (reduction in intraretinal and subretinal fluid).

Similar results have been reported in a number of short-term studies (Avery et al. 2006; Rich et al. 2006; Spaide et al. 2006; Yoganathan et al. 2006; Aisenbrey et al. 2007; Giansanti et al. 2007; Lazic & Gabric 2007; Madhusudhana et al. 2007; Weigert et al. 2008). However, to date, only four other studies have reported 9-month and 12-month follow-up results (Arevalo et al. 2008; Bashshur et al. 2008; Cleary et al. 2008; Fong et al. 2008). Our results are in agreement with the findings of these longer-term follow-up studies: there was a significant preservation of visual improvement with continued treatment, despite differences in the treatment protocols. Arias et al. (2008) demonstrated that patients with CNV secondary to AMD treated with a loading-phase protocol had better outcomes than patients treated with a *pro re nata* (as needed) protocol with intravitreal bevacizumab administered as required after the first injection. Therefore, the results of this 6-month follow-up, non-randomized study suggest that treatment with an initial loading phase (three monthly injections; thereafter as required) currently provides the best management of AMD. As in the study of Fong et al. (2008), all patients in the present study received an LD of three injections in the initial treatment phase, whereas the previously reported longer-term follow-up studies used individually determined reinjection requirements after the first injection in the initial treatment phase, based on the presence of persistent leakage and retinal oedema (Arevalo et al. 2008; Bashshur et al. 2008; Cleary et al. 2008).

In the present study, we adopted the PrONTO study strategy (Fung et al. 2007): after three consecutive monthly injections of anti-VEGF, further retreatment was based on the criteria proposed by the PrONTO study. Instead of ranibizumab we used bevacizumab, because it was the only anti-VEGF available in Slovenia at that time. Intravitreal bevacizumab proved to be an effective treatment for wet AMD: its use prevented moderate vision loss (as defined by a loss of > 15 letters) in 95.5% of patients at 12 months, which is similar to the results of the PrONTO study (Table 3). In the present study, after LD the majority of patients (72.4%)

Table 1. Proportion of patients with improved or worsened best-corrected visual acuity at first (15 ± 2 weeks), second (26 ± 2 weeks) and third (51 ± 3 weeks) evaluations.

	First evaluation (n = 149)	Second evaluation (n = 143)	Third evaluation (n = 132)
Letters gained (%)			
≥ 0	79	82	73
≥ 5	58	62	55
≥ 15	21	23	20
Letters lost (%)			
≥ 1	21	18	27
≥ 5	6	12	18
≥ 15	1	1	5

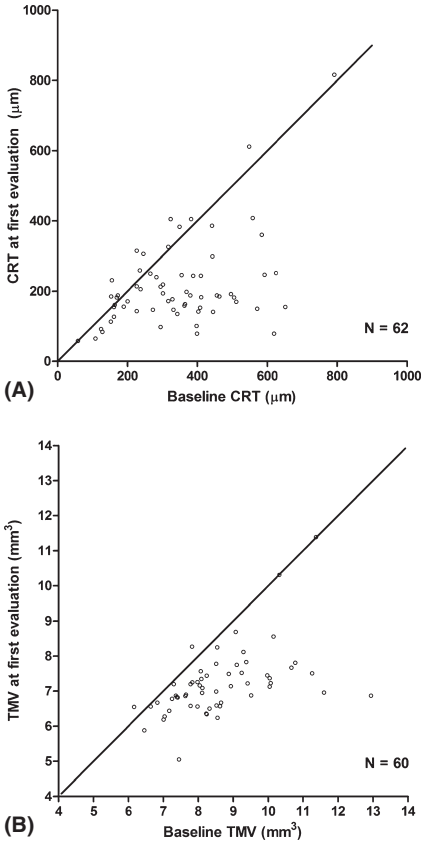

Fig. 3. Scatter plots of baseline central retinal thickness (CRT) (A) and total macular volume (TMV) (B) versus CRT and TMV, respectively, at first evaluation (15 ± 2 weeks). All points below the solid lines imply decreases in CRT or TMV.

either retained their initial VA or improved VA by < 15 letters. In contrast, in the PrONTO study the majority of patients (77.5%) gained 15–30 letters after LD. As can be seen from Table 3, these proportions remained after 12 months. The better results reported for ranibizumab may be due, in part, to the stricter inclusion criteria of the PrONTO study. In our study, we included patients with all subtypes of lesion, including lesions with subfoveal fibrosis. The latter, for example, was one of the exclusion criteria in the PrONTO study. A subgroup analysis of our patients revealed no improvement of VA in patients with subfoveal fibrosis. The possibility that the better results observed with ranibizumab might be caused by a greater affinity of ranibizumab for VEGF cannot be excluded. The effect of bevacizumab on VA observed in the present study is similar to the results observed by Fong et al. (2008), who also treated patients with bevacizumab according to the PrONTO strategy. The distribution of VA changes presented in Table 3 indicates that 61.5% of their patients either retained their initial VA or gained < 15 letters after 6 months, compared with 65.1% in the present study. In contrast to the PrONTO study, which reported results of 40 eyes at 3- and 12-month follow-ups, and the study of Fong et al. (2008) – which reported results of 109 eyes at 3- and 6-month follow-ups, but only 41 eyes at the 12-month follow-up – the present study reports results of 149, 143 and 132 eyes at 3-, 6- and 12-month follow-ups, respectively (Table 3). Fong et al. (2008) reported a mean VA increase of 5.4 letters at 12 months (40 eyes), whereas in the present study the mean VA increase was 6.2 letters at 12 months (132 eyes). This difference may be partly because of the fact that the mean baseline VA was 45.6 letters in the study of Fong et al. (2008), and 50.5 letters in the present study. On the basis of the results of the present study and those of the PrONTO and Fong et al. studies (Table 3), it may be speculated that by using the PrONTO strategy of anti-VEGF administration, both ranibizumab and bevacizumab prevent the loss of vision to the same degree.

The average number of bevacizumab injections over 12 months was 5.1 (range 3–9) in the present study, compared with 5.6 ranibizumab injections in the PrONTO study. This slight difference may be a consequence of a longer half-life of bevacizumab, and a greater affinity for VEGF of ranibizumab (Bakri et al. 2007).

Because of the well-documented vastly improved outcomes gained using VEGF-inhibition therapies, the use of placebo groups for evaluating treatment efficacy in future studies raises concern regarding the medical ethics of such an experimental design. A meta-analysis conducted by Wong et al. (2008) on the natural history and progression of visual loss in eyes with untreated neovascular AMD demonstrated a mean loss in all of the patients of 2.7 lines (13.5 letters) after 1 year. In contrast, the results of the present study demonstrate that only 5% of 132 patients who received intravitreal bevacizumab treatment had a loss of 15 letters or more.

In the present study, of the patients with a loss of 15 letters or more after 1 year of treatment (n = 7) three had persistent serous detachment of the retina, of whom two developed

Table 3. Distribution of visual acuity changes in eyes with neovascular age-related macular degeneration after three doses of ranibizumab (PrONTO study by Fung et al. 2007) or bevacizumab (this study and Fong et al. 2008) at month 3 and after a variable-dosing regimen at 6 and at 12 months (where applicable).

	Month 3			Month 6			Month 12		
	This study (n = 149) eyes (%)	Fung et al. (n = 40) eyes (%)	Fong et al. (n = 109) eyes (%)	This study (n = 143) eyes (%)	Fung et al. (n = 40) eyes (%)	Fong et al. (n = 109) eyes (%)	This study (n = 132) eyes (%)	Fung et al. (n = 40) eyes (%)	Fong et al. (n = 41) eyes (%)
Letters gained									
≥ 30	4 (2.7)	2 (5)	2 (1.8)	4 (2. 8)	–	1 (0.9)	6 (4.6)	3 (7.5)	–
≥ 15 to < 30	28 (18.8)	11 (27.5)	18 (16.5)	29 (20.3)	–	19 (17.4)	20 (15.2)	11 (27.5)	–
≥ 5 to < 15	55 (36.9)	20 (50)	35 (32.2)	56 (39.2)	–	35 (32.1)	40 (30.3)	16 (40)	–
No change	53 (35.5)	5 (12.5)	33 (30.3)	37 (25.9)	–	32 (29.4)	48 (36.4)	5 (12.5)	–
Letters lost									
≥ 5 to < 15	8 (5.3)	1 (2.5)	21 (19.3)	16 (11.2)	–	22 (20.2)	12 (9.1)	3 (7.5)	–
≥ 15	1 (0.7)	1 (2.5)	0	1 (0.7)	–	0	6 (4.5)	2 (5)	–

epiretinal membrane and two had CNV that responded well to the treatment anatomically, although their VA decreased despite the cessation of leakage from the CNV. The reduction in vision of the sixth patient was because of the development of a cataract; cataract surgery was thus performed subsequent to the third evaluation, 14 months after the initial treatment. After this surgery, the VA of the patient improved substantially. In the seventh patient, there was a pigment epithelium detachment tear beneath the fovea.

One year after treatment, 20% of patients (n = 26) gained more than 15 letters compared with the pre-treatment baseline values. In all of these patients, deterioration of VA began less than 6 months before the onset of treatment, and none had submacular haemorrhage involving the fovea. FA revealed that of these 26 patients, 13 showed classic or predominantly classical CNV, three showed minimally classical and 10 showed pure occult CNV. Twelve also had CNV with very significant leakage. None of the CNV lesions that reacted positively to the treatment exhibited prior subfoveal fibrosis. This is in accordance with the findings of the studies by Krebs et al. (2009) and Algvere et al. (2008). Both studies compared the effect of bevacizumab in the treatment of early and advanced AMD and observed a statistically significant improvement in the early lesions only.

As indicated here and as seen previously, there were no correlations between the changes in VA and CRT or TMV (Bashshur et al. 2006, 2008; Spaide et al. 2006). Because the reduction in macular thickness was not always associated with visual improvement, this can probably be attributed to permanent photoreceptor damage.

Neovascular AMD tends to be a chronic, progressive condition. Fibrosis in the lesion is a sign of longer duration of neovascular AMD that can affect photoreceptors irreversibly. The average ± SD VA (44 ± 12 letters) in the subgroup of patients whose lesion included subfoveal fibrosis was significantly lower (nine letters; $p = 0.003$) than that in the subgroup of patients without fibrosis in the lesion (53 ± 14 letters). The subgroup of patients with subfoveal fibrosis had no significant gain (one letter; $p = 0.7$) in VA at final evaluation. In contrast, the gain in VA over 1 year in the group of patients without subfoveal fibrosis was highly significant (seven letters; $p < 0.0001$). Therefore, the final outcome appears to be influenced by the duration and stage of CNV, the presence of macular scarring and retinal atrophy and the duration of the disease prior to treatment.

As observed in Fig. 2, in the group of patients treated for 1 year, the mean VA at the final (third) evaluation remained significantly higher compared with baseline values ($p < 0.0001$), despite a gradual and significant decline ($p = 0.019$) in VA from 58 ± 15 letters at first evaluation (4 weeks after the third LD injection) to 57 ± 16 letters at final evaluation (12 months after the first LD injection). This can be attributed to the natural progression of AMD.

Although there was an overall significant improvement in VA in the total patient group, when the patients were subdivided into FA-determined lesion-type subgroups, all but the minimally classic lesions exhibited significant improvement in VA at the third evaluation (Table 2). The results of this retrospective subgroup analysis should be interpreted with some caution, because of the small sample size. It is possible that the potential benefits of the treatment are influenced by the duration of the disease prior to treatment. Unfortunately, we cannot confirm this because we could not obtain precise information regarding the duration of the disease prior to drop in VA for all patients.

As in other studies, no serious drug-related ocular or systemic adverse effects were noted (Fung et al. 2006; Rich et al. 2006; Fong et al. 2008; Wu et al. 2008).

Although the present study reviews a series of consecutive cases that included a wide range of patients with various types and stages of CNV caused by AMD, the results demonstrate that intravitreal bevacizumab treatment provided long-lasting functional and anatomical improvement in the majority of patients. Intravitreal treatment was well tolerated over 1 year and further follow-up is in progress.

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