EXTENDED REPORT

Effect of systemic bevacizumab therapy on retinal pigment epithelial detachment

Matthias Bolz, Stephan Michels, Wolfgang Geitzenauer, Franz Prager, Ursula Schmidt-Erfurth

Br J Ophthalmol 2007;**91**:785–789. doi: 10.1136/bjo.2006.102467

See end of article for
authors' affiliations

Correspondence to:
Stephan Michels,
Department of
Ophthalmology, Medical
University of Vienna,
Währinger Gürtel 18–20,
1090 Vienna, Austria;
Stephan.michels@
meduniwien.ac.at

Received 6 July 2006
Accepted 8 October 2006
Published Online First
18 October 2006

Background: To evaluate the effect of systemic bevacizumab (Avastin®) therapy on pigment epithelial detachment (PED) secondary to age-related macular degeneration (AMD) and to identify prognostic factors for PED regression and improvement in best corrected visual acuity (BCVA).

Study design: Prospective uncontrolled pilot study.

Methods: Nine patients (nine eyes) received three systemic bevacizumab treatments at 2 week intervals and were examined at baseline, weeks 1, 2, 4, 6 and month 3 by using optical coherence tomography (Stratus OCT™, Carl Zeiss® Meditec, Dublin, California, USA). Changes in maximum PED height and greatest linear diameter (GLD) were planimetrically analysed by using Adobe Photoshop CS and correlated with retinal morphological changes and changes in BCVA.

Results: Systemic bevacizumab therapy was well tolerated. Mean maximum PED height decreased significantly by 21% as early as 1 week ($-96\ \mu\text{m}$ (SD 48.8), $p<0.01$). At 3 months follow-up, two PEDs resolved completely, mean maximum PED height decreased significantly by 39% ($-179\ \mu\text{m}$ (SD 178), $p=0.02$) and mean PED GLD by 24% ($-714\ \mu\text{m}$ (SD 1010), $p=0.07$). Mean BCVA improved significantly by week 2 ($+8.7$ letters (SD 5.7), $p<0.01$) and at 3 months with 12.7 letters (SD 6.4) ($p<0.01$).

Conclusion: In the examined nine patients, systemic bevacizumab therapy showed evidence for an effect on PED secondary to neovascular AMD in terms of a decrease in lesion height and diameter. A high PED at baseline was found to be a negative predictive factor for visual outcome.

Age-related macular degeneration (AMD) is the leading cause of irreversible vision loss among the elderly population in Europe and North America.^{1–3} Hence, finding effective treatment strategies is of great socio-economic interest. Advances in the development of therapies inhibiting vascular endothelial growth factor (VEGF), one of the leading factors in the pathogenesis of neovascular AMD, have shown significant improvement in maintaining and improving visual function.^{4–12}

There is increasing evidence that a decrease in visual acuity secondary to AMD is not primarily due to the submacular choroidal neovascularisation (CNV) itself, but to the resulting pathomorphological retinal and subretinal changes. Accumulation of fluid with intra- and subretinal oedema or as >retinal pigment epithelial detachment (PED) is the most common pathomorphological alteration. Anti-VEGF strategies have shown that the reduction of oedema and PED rather than the destruction of the CNV itself leads to a significant improvement in best corrected visual acuity (BCVA).^{9–12} Hence, apart from treating the CNV itself, the inhibition of leakage from submacular CNV seems to become the primary focus in treating patients suffering from neovascular AMD.¹⁰

A retinal pigment epithelial detachment (PED) can be associated with several choroidal neovascular lesion types.^{13–14} Treating lesions associated with a PED was found to be particularly difficult, above all because of the risk of an retinal pigment epithelial tear and limited therapeutic benefit.^{15–19}

Optical coherence tomography (OCT) is of particular importance in evaluating effects of anti-VEGF therapies.^{20–21} It is a non-contact imaging method appropriate for identifying intra- and subretinal oedema as well identifying PED and its changes over time after therapy. However, analysis and quantification of the dimensions of a PED are still not possible in an objective, observer-independent way.

Systemic anti-VEGF therapy using 5 mg/kg or 2.5 mg/kg bevacizumab (Avastin® Genentech Inc.) in patients with CNV

secondary to AMD is a promising new treatment option, especially in those with bilateral disease and refusing intravitreal therapy or those who are not suitable for intravitreal injections. Bevacizumab is a monoclonal humanised antibody designed to bind all isoforms of VEGF. It has been approved in Europe and the USA to treat metastatic colorectal cancer. A first interventional case series showed a significant increase in BCVA within 1 week of treatment, a significant decrease in central retinal thickness and a reduction or absence of leakage from CNV as well as a beneficial effect on PED.¹⁰

The aim of this prospective study was to further investigate the effect of systemic bevacizumab therapy on PED secondary to AMD. In addition to a quantitative evaluation of PED changes after systemic anti-VEGF therapy, pathomorphological changes were correlated with changes in BCVA and potential prognostic factors were analysed.

METHODS

The study was performed at the Department of Ophthalmology, Medical University of Vienna. All the research and measurements followed the tenets of the Helsinki Agreement. The study was approved by the local ethics committee, and informed consent was obtained from all individuals after explanation of the nature and possible consequences of the study.

A total of nine eyes from nine patients with PED secondary to AMD were evaluated. In addition to PED identified by OCT in all eyes, all eyes demonstrated a CNV with leakage as demonstrated by fluorescein angiography. Most of the eyes were graded as retinal angiomatous proliferation (RAP) (8/9). The study included patients with neovascular AMD who were

Abbreviations: AMD, age-related macular degeneration; BCVA, best corrected visual acuity; CNV, choroidal neovascularisation; ETDRS, early treatment diabetic retinopathy study; GLD, greatest linear diameter; PED, pigment epithelial detachment; VEGF, vascular endothelial growth factor; OCT, optical coherence tomography.

Figure 1 Relative change in mean pigment epithelial detachment (PED) height in micrometres assessed at baseline, weeks 1, 2, 4, 6 and month 3. Boxes indicate mean values, error bars indicate SD.

not eligible for photodynamic therapy with verteporfin or who strictly refused photodynamic therapy. According to protocol, BCVA using early treatment diabetic retinopathy study (ETDRS) charts had to be 20/40–20/400 (Snellen equivalent) in the study eye. If both eyes were eligible, they were assessed in the study. Because of the potential risk of systemic adverse events, as reported in patients with metastatic colorectal cancer receiving continuous bevacizumab therapy in addition to chemotherapy, patients with a history of thrombo-embolic events, kidney dysfunction, history of bleeding, uncontrolled hypertension and recent or planned surgery were excluded from the study.^{22–24} All patients were routinely seen by an internist.

Five individuals received three 5 mg/kg and four individuals received three 2.5 mg/kg bevacizumab (Avastin®, Genentech Inc.) infusions at 2 week intervals. The patients were included in a consecutive fashion; a lower dose of systemic bevacizumab was administered to reduce possible systemic adverse events. Despite the small group size, no significant differences were found between patients treated with 2.5 and 5 mg/kg at baseline and follow-up.

For the assessment of changes in PED diameter and height, optical coherence tomography (Stratus OCT™, Carl Zeiss® Meditec, Dublin, California, USA) was performed at baseline and at weeks 1, 2, 4 and 6 and month 3. Two high-resolution slow scans showing maximum PED extension were selected at baseline. At all follow-up evaluations, identical angle OCT scans were used for comparison. Each PED was evaluated planimetrically using Adobe Photoshop CS software. At each visit, the PED GLD and PED height were measured for both scans and the mean value was determined. All OCT readings were performed by a masked observer.

Planimetric results were correlated with changes in BCVA assessed by using the ETDRS protocol. In addition, intra- or subretinal oedema graded by OCT at baseline was evaluated as prognostic factor.

The paired *t*-test was used for statistic analysis of changes in PED height and GLD compared with baseline. A value of $p \leq 0.05$ was considered statistically significant.

RESULTS

The intravenous infusion of bevacizumab was well tolerated by all patients. There were no significant changes in systemic blood pressure in the nine treated individuals.

Figure 2 Relative change in mean PED greatest linear diameter (GLD) in micrometres assessed at baseline, weeks 1, 2, 4, 6 and month 3. Boxes indicate mean values, error bars indicate SD.

At baseline, all nine PED lesions were classified by fluorescein angiography. Eight PEDs secondary to RAP and one notch PED were identified. Mean (SD) PED height was 461.15 µm (99.83); mean PED GLD was 3008.38 µm (650.94); mean BCVA at baseline was 54.0 letters (13.3).

The mean change in maximum PED height over time is shown in fig 1. One week after the first drug administration mean maximum height was decreased significantly by 21% (–96 µm (SD 49), $p < 0.01$), after 2 weeks by 32% (–149 µm (SD 134), $p = 0.01$), after 4 weeks by 45% (–208 µm (SD 122), $p < 0.01$), after 6 weeks by 46% (–211 µm (SD 143), $p < 0.01$) and after 3 months by 39% (–179 µm (SD 178), $p = 0.02$), respectively compared with baseline values. Two PEDs resolved completely within the 3 months after initiation of treatment.

The mean change in PED GLD over time is shown in fig 2. The decrease in PED height preceded the reduction of PED diameter in all cases. During the first 3 months after onset of therapy, a distinct and close to significant decrease in maximum diameter was found. After 1 week it decreased by 2% (–54 µm (SD 192), $p = 0.42$), after 2 weeks by 16% (–539 µm (SD 978), $p = 0.16$), after 4 weeks by 14% (–500 µm (SD 929), $p = 0.11$) and after 6 weeks by 17% (–521 µm (SD 1146), $p = 0.21$). Three months after the first drug administration, GLD was decreased by 24% (–714 µm (SD 1010), $p = 0.07$). Figure 3 shows a PED regression in its characteristic pattern after systemic bevacizumab therapy.

Mean BCVA assessed as ETDRS score was 54 letters (SD 13.3) at baseline, 63 (SD 12.2) ($p = 0.16$) at week 1, 62.7 (SD 11.5) ($p < 0.01$) at week 2, 65.3 (SD 12.3) ($p < 0.01$) at week 4, 66.3 (SD 12.8) ($p < 0.01$) at week 6 and 66.7 (SD 14.1) ($p < 0.01$) at month 3 (fig 4). Hence, after three months BCVA improved by 12.7 letters (SD 6.4) ($p = 0.25$; analysis of variance). A statistically significant difference was found as early as 2 weeks after initiation of therapy.

There was a significant correlation between the decrease in PED height and the mean change in BCVA ($r^2 = 0.00$; Pearson: -0.30 ; $p = 0.02$). Figure 5 shows these correlations for all nine eyes for all visits. Correlation of relative change in PED GLD and relative change in BCVA was significant also ($r^2 = 0.05$; Pearson: -0.4 ; $p = 0.01$; data not shown). Most important as a predictive factor was PED height at baseline. The higher the PED was at baseline, the less improvement in BCVA could be observed at month 3 ($r^2 = 0.51$; Pearson: -0.72 ; $p = 0.03$; fig 6).

Furthermore, there was a significant correlation ($r^2 = 0.16$; Pearson: -0.4 ; $p = 0.01$) between the decrease in the central

Figure 3 PED performance assessed with optical coherence tomography (OCT) at baseline (a), week 1 (b), week 2 (c), week 4 (d), week 6 (e) and month 3 (f). The horizontal scan is shown left, the vertical scan to the right.

retinal thickness assessed by OCT and the relative change in BCVA during therapy (fig 7). After 1 week retinal thickness decreased by 23% ($282.6 \mu\text{m}$ (SD 79.4); $p = 0.08$), after 2 weeks by 35% ($239.6 \mu\text{m}$ (SD 66.6); $p < 0.01$), after 4 weeks by 44% ($207.7 \mu\text{m}$ (SD 33.7); $p < 0.01$), after 6 weeks by 48% ($192.3 \mu\text{m}$ (SD 33.3); $p < 0.01$) and after 3 months by 45% ($201.8 \mu\text{m}$ (SD 51.7); $p < 0.01$) compared with baseline values respectively.

No statistically significant correlation was found between the presence of pre-existing intra- or subretinal oedema and the change in PED height or diameter.

Patients receiving 5 mg/kg Avastin were found to have an improvement in BCVA of 14.8 (SD 3.6) letters, and patients receiving 2.5 mg/kg an improvement of 10.8 (SD 8.8)

($p = 0.30$). In the first group (5 mg/kg), the relative change in PED height at month 3 was $131.8 \mu\text{m}$ (SD 193.2), in the second (2.5 mg/kg) it was $238.7 \mu\text{m}$ (SD 161.7) ($p = 0.41$). Thus, no statistically significant differences were found that could be attributed to the difference in dosage, or for changes in functionality or morphology. Nevertheless, in evaluating these significant values, the small number of patients has to be considered.

DISCUSSION

In the present study, systemic bevacizumab therapy appeared effective in decreasing PED secondary to AMD in height and diameter. Regression of PED was slower than regression of

Figure 4 Relative change in best corrected visual acuity (BCVA) assessed by the early treatment diabetic retinopathy study (ETDRS) protocol at weeks 1, 2, 4, 6 and month 3. Boxes indicate mean values, error bars indicate standard error of the mean.

intra- or subretinal oedema.¹⁰ Significant reduction in PED height preceded in all cases the reduction of PED extension. Significant changes in lesion height could be observed and measured planimetrically and were associated with improvement in BCVA. A significant correlation of improvement in BCVA and reduction in central retinal thickness – regression of intra- and subretinal oedema – was demonstrated as well.

The aim of this study was not only to investigate resolution of PED after systemic bevacizumab therapy, but also to find possible prognostic factors for vision outcomes in patients with PED. A possible negative prognostic factor could be the height of a PED before onset of therapy. There was a weak correlation between the PED height at baseline and the relative change in height after 3 months. Higher PED lesions seemed to show a faster decrease in height. However, the higher a PED lesion was at baseline, the less the improvement in BCVA at month 3. This is most likely due to a corresponding amount of destruction of retinal structures caused by the lesion itself, which again may be dependent on the duration of the pathology. However, even if BCVA did not correlate linearly, PED lesion size could be

Figure 5 Correlation between relative change in mean PED height in micrometres and the relative change in BCVA assessed using the ETDRS protocol at all visits ($r^2=0.00$; Pearson: -0.30 ; $p=0.02$).

Figure 6 Correlation between absolute PED height at baseline measurements and the relative change in BCVA (ETDRS) at month 3 in letters ($r^2=0.51$; Pearson: -0.72 ; $p=0.03$).

reduced effectively in all patients treated with systemic bevacizumab.

The relative change in PED height correlated with the relative change in BCVA at each follow-up visit (fig 5). In most cases, a distinct improvement in BCVA was found when there was only a small decrease in PED height (fig 5). Furthermore, a strong correlation was found evaluating BCVA and CRT, which is in good agreement with the result of other studies.¹⁰ This indicates that resolution of intraretinal and subretinal oedema and the decrease of PED height and GLD are relevant for visual recovery. Apart from that, morphological retinal improvement preceded the functional, which compares favourably with results of other studies investigating effects of anti-VEGF therapies.^{9–12} Nevertheless, after 3 months, mean BCVA was improved by 12.7 letters (SD 6.4) and statistically significant differences were already found at week 2.

In this study, OCT proved to be an appropriate device for the imaging of PED. Stratus OCTTM provided good resolution necessary for assessing PED, but its retinal imaging is limited to six radial scans. New technological advances such as spectral domain OCT will allow more linear scans because of a higher scanning speed and a complete optic biopsy based on raster scanning of the central macula. A further disadvantage of the

Figure 7 Correlation between relative change in retinal thickness in micrometres and the relative change in BCVA assessed using the ETDRS protocol at all visits ($r^2=0.16$; Pearson: -0.4 ; $p=0.01$).

current OCT system is the lack of an appropriate algorithm to analyse a PED volume quantitatively. Additional fast and observer-independent software for volumetric data analysis should be developed.

Nevertheless, further cross-sectional, double-blinded studies including more patients and assessing therapeutically induced long-term effects are necessary to validate the outcomes of this uncontrolled short-term study. The study was neither large enough, nor designed to show a difference between the two-dose regimen.

The results of this study show that systemic bevacizumab therapy is a well-tolerated treatment option for neovascular AMD with PED for carefully selected patients. Additionally, the long half-life time of systemic bevacizumab might be an important advantage compared with intravitreal delivery. The higher a PED, the smaller the improvement in BCVA that can be expected from therapy, most likely because of a more advanced destruction of the overlying photoreceptor layer. OCT is a helpful tool in evaluating the effect of anti-VEGF therapy on PED and intraretinal and subretinal oedema, but also for predicting functional benefits from anti-VEGF therapy.

Authors' affiliations

Matthias Bolz, Stephan Michels, Wolfgang Geitzenauer, Franz Prager, Ursula Schmidt-Erfurth, Department of Ophthalmology, Medical University of Vienna, Vienna, Austria

Funding: this study was supported financially by the Austrian National Bank (Jubilaeumsfonds: project number 11857) and by the "Buergermeisterfond" of Vienna (project number 2445).

Competing interests: None.

REFERENCES

- Bressler NM, Bressler SB, Congdon NG, *et al.* Potential public health impact of Age-Related Eye Disease Study results: AREDS report no. 11. *Arch Ophthalmol* 2003;**121**:1621–4.
- Klein R, Peto T, Bird A, *et al.* The epidemiology of age-related macular degeneration. *Am J Ophthalmol* 2004;**137**:486–95.
- Gohdes DM, Balamurugan A, Larsen BA, *et al.* Age-related eye diseases: an emerging challenge for public health professionals. *Prev Chronic Dis* 2005;**2**:A17.
- Ferrara N. Vascular endothelial growth factor: basic science and clinical progress. *Endocr Rev* 2004;**25**:581–611.
- Lopez PF, Sippy BD, Lambert HM, *et al.* Transdifferentiated retinal pigment epithelial cells are immunoreactive for vascular endothelial growth factor in surgically excised age-related macular degeneration-related choroidal neovascular membranes. *Invest Ophthalmol Vis Sci* 1996;**37**:855–68.
- Kvanta A, Algvere PV, Berglin L, *et al.* Subfoveal fibrovascular membranes in age-related macular degeneration express vascular endothelial growth factor. *Invest Ophthalmol Vis Sci* 1996;**37**:1929–34.
- Kliffen M, Sharma HS, Mooy CM, *et al.* Increased expression of angiogenic growth factors in age-related maculopathy. *Br J Ophthalmol* 1997;**81**:154–62.
- Otani A, Takagi H, Oh H, *et al.* Vascular endothelial growth factor family and receptor expression in human choroidal neovascular membranes. *Microvasc Res* 2002;**64**:162–9.
- Heier JS, Antoszyk AN, Pavan PR, *et al.* Ranibizumab for treatment of neovascular age-related macular degeneration: a phase I/II multicenter, controlled, multidose study. *Ophthalmology* 2006;**113**: 642 e1–4.
- Michels S, Rosenfeld PJ, Puliafito CA, *et al.* Systemic bevacizumab (Avastin) therapy for neovascular age-related macular degeneration twelve-week results of an uncontrolled open-label clinical study. *Ophthalmology* 2005;**112**:1035–47.
- Spaide RF, Laud K, Fine HF, *et al.* Intravitreal bevacizumab treatment of choroidal neovascularization secondary to age-related macular degeneration. *Retina* 2006;**26**:383–90.
- Avery RL, Pieramici DJ, Rabena MD, *et al.* Intravitreal bevacizumab (Avastin) for neovascular age-related macular degeneration. *Ophthalmology* 2006;**113**:363–72.
- Pauleikhoff D, Loffert D, Spital G, *et al.* Pigment epithelial detachment in the elderly. Clinical differentiation, natural course and pathogenetic implications. *Graefes Arch Clin Exp Ophthalmol* 2002;**240**:533–8.
- Baumal CR, Reichel E, Duker JS, *et al.* Indocyanine green hyperfluorescence associated with serous retinal pigment epithelial detachment in age-related macular degeneration. *Ophthalmology* 1997;**104**:761–9.
- Lim JJ, Aaberg TM, Capone A Jr, *et al.* Indocyanine green angiography-guided photocoagulation of choroidal neovascularization associated with retinal pigment epithelial detachment. *Am J Ophthalmol* 1997;**123**:524–32.
- Gross-Jendroska M, Flaxel CJ, Schwartz SD, *et al.* Treatment of pigment epithelial detachments due to age-related macular degeneration with intra-ocular C3F8 injection. *Aust N Z J Ophthalmol* 1998;**26**(4):311–7.
- Axer-Siegel R, Ehrlich R, Rosenblatt I, *et al.* Photodynamic therapy for occult choroidal neovascularization with pigment epithelium detachment in age-related macular degeneration. *Arch Ophthalmol* 2004;**122**:453–9.
- Nicolo M, Ghigione D, Lai S, *et al.* Intravitreal triamcinolone in the treatment of serous pigment epithelial detachment and occult choroidal neovascularization secondary to age-related macular degeneration. *Eur J Ophthalmol* 2005;**15**:415–9.
- Dhalla MS, Blinder KJ, Tewari A, *et al.* Retinal pigment epithelial tear following intravitreal pegaptanib sodium. *Am J Ophthalmol* 2006;**141**:752–4.
- Rosenfeld PJ, Moshfeghi AA, Puliafito CA. Optical coherence tomography findings after an intravitreal injection of bevacizumab (Avastin) for neovascular age-related macular degeneration. *Ophthalmic Surg Lasers Imaging* 2005;**36**:331–5.
- Hee MR, Baumal CR, Puliafito CA, *et al.* Optical coherence tomography of age-related macular degeneration and choroidal neovascularization. *Ophthalmology* 1996;**103**:1260–70.
- US FDA. AVASTIN (bevacizumab). http://www.fda.gov/medwatch/SAFETY/2005/Jan_PI/Avastin_PI.pdf 03-14-, 2005.
- Kabbinavar F, Hurwitz H, Fehrenbacher L, *et al.* Phase II, randomized trial comparing bevacizumab plus fluorouracil (FU)/leucovorin (LV) with FU/LV alone in patients with metastatic colorectal cancer. *J Clin Oncol* 2003;**21**:60–5.
- Hurwitz H, Fehrenbacher L, Novotny W, *et al.* Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med* 2004;**350**:2335–42.