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SYSTEMIC BEVACIZUMAB (AVASTIN®) THERAPY FOR EXUDATIVE NEOVASCULAR AGE-RELATED MACULAR DEGENERATION. THE BEAT-AMD-STUDY.

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ABSTRACT

Background:

Double-blinded, randomised, prospective, pilot-study to determine the effect of systemic bevacizumab therapy.

Methods:

Subjects with fibrovascular pigment epithelial detachment, subfoveal choroidal neovascularization extending under the geometric centre of the foveal avascular zone, and/or macular thickness of at least 300µm in both eyes were included. Sixteen eyes were included and randomised equally to receive either 3 infusions of 5mg/kg Avastin or 100ml 0.9% sodium chloride every 2 weeks. The main outcome measure was the lesion size. The follow-up time was 24 weeks.

Results:

Throughout the 24 weeks follow up the lesion size and the macular thickness decreased in the Avastin group by 0.5 ± 0.08 mm and 103.6 ± 14.9 µl respectively. In both groups visual acuity remained stable in 7 eyes and decreased in 1 eye. At the end of follow up 50% of the eyes in the Avastin group became fibrotic, 37.5% remained unchanged and 12.5% developed a subretinal bleeding. There was an treatable rise in blood pressure after Avastin treatment.

Conclusion:

We suggest offering systemic Avastin to patients with exudative age-related macular degeneration in both eyes and/or patients who refuse intravitreal injections if blood pressure is normal and there is no history of thrombosis.

Introduction

Choroidal neovascularization (CNV) in age-related macular degeneration (AMD) is one of the major causes of severe vision loss in the elderly in North America and Europe.[1] AMD threatens the distance as well as the reading acuity and it is already known that the vascular endothelial growth factor (VEGF) plays a major role in the development of CNV.[2]

When we began the present study, in June 2005, promising results were published of phase I/II clinical trials after intravitreal injections of the anti-VEGF drugs pegaptanib (Macugen®, Eyetech Pharmaceuticals),[3, 4] ranibizumab (Lucentis®, Genentech Inc.),[5] and systemic treatment with bevacizumab (Avastin®, Genentech Inc.).[6] At that time a systemic treatment, which would only need to be administered a few times within a short time, was very tempting, especially for patients with lack of quality of life due to bad visual acuity.

Photodynamic therapy (PDT), [7-9] in combination with intravitreal injection of triamcinolone acetonide, [10, 11] and subretinal surgery[12-14] were the common treatments for AMD. These methods were either very invasive or had to be repeated several times over long periods of time in order to show some effect. PDT was only performed in eyes with predominantly classic lesions and pigment epithelium detachments (PED) of maximum 50% of the lesion and there was little chance of vision improvement in these eyes. There was no treatment available for larger minimally classic and occult-only lesions or lesions including larger PED.[6]

Bevacizumab was a new anti-VEGF which showed promising results as a combination therapy with 5-fluorouracil, leucovorin, and oxaliplatin in first-line treatment of metastatic colorectal cancer[15, 16] and as systemic therapy against AMD.[6] However, only a case series for AMD treatment did exist. The rationale of the present study was to determine the effect of systemic bevacizumab therapy in subjects with fibrovascular PED, involving the geometric centre of the foveal avascular zone, in comparison to placebo treatment with sodium chloride 0.9%. The main outcome measure was the lesion size, while best corrected visual acuity (BCVA), reading visual acuity (RVA), and macular thickness were additional outcome measures. We believed that a decrease in density of the subfoveal CNV may well

lead to a decrease in macular thickness, thereby allowing a better BCVA. Systemic Avastin treatment promised to be a major effort in AMD therapy, although it is mainly administered off-label as intravitreal injection these days.[17-23]

Materials and Methods

The BEAT-AMD-Study is a prospective, double-blinded, randomised, monocentric, pilot-study, and was conducted at our clinic. The study and data accumulation were carried out with approval from the ethics committee of the city of Vienna and informed consent for research was obtained from all subjects.

Eight subjects with fibrovascular PED, subfoveal CNV extending under the geometric centre of the foveal avascular zone, and/or a macular thickness of at least 300µm in both eyes were included. Exclusion criteria were proteinuria or renal impairment, hepatic dysfunction, vision threatening ophthalmic diseases other than AMD, or a history of arterial thromboembolic diseases or cancer.

Examinations were performed before start of infusion therapy, on a weekly basis for the first 6 weeks, every second week for the following 6 weeks, then every 4 weeks for the next 12 weeks. The follow-up time was 24 weeks.

Measurement of BCVA, RVA, intraocular pressure (IOP), macular thickness, and complete slit lamp examination were performed at every visit, while fluorescein angiography (FA), and indocyanine green angiography (ICGA) were performed before infusion therapy and after 12 and 24 weeks.

BCVA was determined using the ETDRS charts according to the guidelines of the Treatment of Age-related Macular Degeneration with Photodynamic Therapy (TAP) study.[7] It was performed at a test distance of 4 meters, with letter-by-letter scoring and a chart luminance of 100 candelas (cd)/m². A loss or gain of up to 2 lines (10 letters) was considered as stable BCVA, a loss of 3 lines (15 letters) was considered as decrease in BCVA.

RVA was examined using a standardised, German-language reading test (Radner® reading charts).[24] The measurements were performed monocularly with the patient's optimal refractive correction at working-distance.

The macular thickness was measured using the Stratus OCT 3 (Carl Zeiss Meditec Inc.). Using the macular thickness program, 6 radial lines through the centre of the foveal avascular zone were performed. An internal fixation light was used to maintain the fixation throughout the examination, where possible.

FA was performed with the Heidelberg Retina Angiograph (Heidelberg Engineering GmbH, Heidelberg, Germany). 6-8 pictures were taken in the early phase after injection of fluorescein, then every 15 seconds, after 1 minute, 2, 5, and 10 minutes. Distances in the angiograms were measured in mm with the help of the Heidelberg software. ICGA was also performed, including late frames after 20-30 minutes.

Subjects were looked after by an internal medical doctor (oncologist) throughout the entire study. Internal medical examinations including blood pressure, blood sampling, urine sampling, electrocardiogram, and weight measurement were performed throughout the first 6 weeks and after 24 weeks, in order to avoid any additional risk related to the administration of Avastin.

Subjects were randomised to receive either bevacizumab (Avastin®, Genentech Inc.) intravenous infusions, 3 times 5 mg/kg every 2 weeks (Avastin group) or sodium chloride 0.9% intravenous infusions, 3 times 100 ml every 2 weeks (NaCl group). Randomisation was performed by the oncologist, by picking an envelope. As the present study is double-blinded, the oncologist and the pharmacist, who prepared the infusion, were the only ones informed about the treatment group the subject was randomised in to. The subject and the examining ophthalmologists were not informed about the randomisation result.

Data was collected and calculated using SPSS (Version 11.0). Statistical analysis was not performed due to the small number of subjects included. Data are presented

as mean \pm SDM, percentage, and difference between measurements at different time points.

Results

Four subjects received Avastin systemic therapy and four subjects received NaCl infusions. 4 women and 4 men were included. Two women and two men received Avastin and the others received NaCl. The mean age was 79 \pm 4 (73-82 years) in the Avastin group and 74 \pm 9 (65-83 years) in the NaCl group. All eyes were phakic.

Before treatment the BCVA in the Avastin and in the NaCl group was 0.33 \pm 0.4 and 0.56 \pm 0.33 respectively, while the RVA was 0.6 \pm 0.5logRAD and 0.5 \pm 0.4logRAD respectively. At that time the macular thickness and the lesion size were 375.9 \pm 76.6 μ m and 5.42 \pm 2.15mm respectively in the Avastin group (Figures 1 and 2) and 263.2 \pm 81.2 μ m and 3.72 \pm 1.88mm in the NaCl group (Figures 3 and 4). The mean blood pressure was 140/80mmHg in both groups. The IOP was 16 \pm 1mmHg in the Avastin group and 16 \pm 4mmHg in the NaCl group.

At the end of follow up, after 24 weeks, the BCVA and RVA were 0.33 \pm 0.44 and 0.3 \pm 0.4logRAD respectively in the Avastin group and 0.53 \pm 0.42 and 0.5 \pm 0.4logRAD in the NaCl group. The macular thickness and lesion sizes were 272.3 \pm 91.5 μ m and 4.86 \pm 1.92mm respectively in the Avastin group (Figures 1 and 2), 290.8 \pm 78.2 μ m and 3.93 \pm 1.93mm in the NaCl group (Figures 3 and 4). The mean blood pressure remained 140/80mmHg in the NaCl group, while the systolic pressure increased to 150 \pm 12mmHg and the diastolic pressure increased to 90 \pm 12mmHg in the Avastin group. The IOP was 15 \pm 1mmHg in the Avastin group and 17 \pm 2mmHg in the NaCl group.

After 10 weeks the BCVA in the Avastin group dropped to 0.39 \pm 0.46, which was a difference of 0.07 \pm 0.06 compared to BCVA in the same group before start of therapy. There were no differences in BCVA in the NaCl group and no differences in RVA in either group.

Throughout the 24 weeks the macular thickness decreased in the Avastin group by 103.6 \pm 14.9 μ m, while there was an increase of 22.1 \pm 8.4 μ m in the NaCl group

(Table1). In the NaCl group the highest increase in macular thickness was found after 10 weeks, which was an increase of $133.7 \pm 20.4 \mu\text{m}$. In the Avastin group, the thinnest macular thickness was measured at 5 weeks, with a difference of $138 \pm 2.6 \mu\text{m}$.

Table 1: Macular thickness in both groups throughout the study. (Pre= before infusion therapy)

	Avastin Group	NaCl Group
	Macular Thickness (μm)	Macular Thickness (μm)
Pre	375.9 ± 76.6	263.2 ± 81.2
Week 1	306.9 ± 144.8	295.8 ± 99.6
Week 2	275.2 ± 81.1	292.3 ± 119.8
Week 3	271.9 ± 94.7	282.3 ± 96.9
Week 4	303.4 ± 164.0	326.5 ± 39.5
Week 5	237.9 ± 79.2	367.0 ± 39.6
Week 6	259.1 ± 116.2	339.3 ± 95.0
Week 8	258.3 ± 116.7	374.0 ± 75.9
Week 10	251.3 ± 81.9	400.8 ± 44.3
Week 12	279.4 ± 145.9	314.8 ± 104.4
Week 16	235.2 ± 69.0	333.8 ± 89.4
Week 20	239.9 ± 58.9	339.8 ± 46.6
Week 24	272.3 ± 91.5	290.8 ± 78.2

The lesion size decreased in the Avastin group from $6.1 \pm 2.2 \text{mm}$ before treatment, to $5.1 \pm 1.9 \text{mm}$ at week 12, and $5.6 \pm 2.1 \text{mm}$ after 24 weeks. In the NaCl group the lesion size increased from $3.7 \pm 1.9 \text{mm}$ prior to treatment, to $3.8 \pm 2.0 \text{mm}$ after 12 weeks, and 3.9 ± 1.9 at the end of follow up.

In both the Avastin and the NaCl group 5 eyes remained stable with the BCVA being ± 5 letters throughout the 24 weeks, 2 remained stable with ± 10 letters, and 1 showed a decrease with -15 letters.

In the FA all 8 eyes in the NaCl group showed to remain exudative, while in the Avastin group 4 (50%) eyes became quiet and fibrotic, 3 (37.5%) eyes remained exudative and 1 (12.5%) eye had a subretinal bleeding. The subretinal bleeding began in week 10, while the other eye turned fibrotic.

Discussion

When Michels and co-authors published the idea of systemic Avastin treatment against AMD,[6] the idea of systemic anti-VEGF treatment against AMD was implicated. The idea of treating both eyes at the same time was also very tempting, since it has been proven that patients with occult CNV with serous PED in the first eye have a significantly higher risk of visual loss in the second eye.[25] A systemic treatment with initial 3 infusion therapies over 6 weeks seemed very promising. Lesions too big for PDT had no treatment option, since intravitreal anti-VEGFs were not yet available and they were thought to be very invasive bearing the risk of endophthalmitis. Subretinal surgery[12-14] was too invasive for those eyes too.

The advantage of our BEAT-AMD-Study, compared to the SANA-Study,[6] is that our study is randomised, double-blinded, and placebo controlled. Neither the patient, nor the investigating ophthalmologist knew which treatment arm the patient was randomised into. We began our study in August 2005 and recruited until January 2008. However, recruitment showed to become more difficult, after the idea of the off-label use of Avastin intravitreal injections has worked itself out.[17, 18] Those intravitreal injections of anti-VEGFs[3, 5] showed not to be as invasive as assumed,[18] only few patients develop exudative AMD on both eyes, and of these most have some internal medical problem, which did not allow inclusion into the BEAT-AMD-Study. Due to those reasons we decided to discontinue recruitment and publish our data.

Our main outcome measure was lesion size and we were able to show a decrease of 0.5 ± 0.08 mm in the Avastin group throughout the 24 weeks. Macular thickness and visual acuity were additional outcome measures, whereby we found decreases in macular thickness in the Avastin group already within the first two weeks, with a difference of 100.7 ± 4.5 μ m lasting until week 24. However, neither the BCVA, nor the RVA, showed improvement in this group. Unfortunately, there was a decrease in

BCVA in week 10 by 0.07 ± 0.06 , which may be due to the development of the subretinal bleeding in one eye of a patient in week 10. Furthermore, there was a slight rise in blood pressure in this group, which began with 140/80mmHg and ended with the systolic pressure being 150 ± 12 mmHg and the diastolic pressure being 90 ± 12 mmHg. The rise in blood pressure was controlled and treated by the specialist for internal medicine and did not exceed 160/100mmHg in any patient.

In the placebo control group there was an increase in lesion size throughout the 24 weeks. BCVA and RVA remained stable. Although, after 24 weeks, macular thickness was comparative to the thickness before treatment, a big increase was found at week 10, which showed a difference of $133.7 \pm 20.4 \mu\text{m}$ compared to prior treatment. Blood pressure remained stable.

When defining the BCVA by loss of lines, both groups had the same outcome. In both groups only one eye showed a loss of 3 lines (15 letters), while the other eyes remained stable. However, the FA in week 24 showed that 50% of the eyes turned quiet and fibrotic, 37.5% remained unchanged and 12.5% developed a subretinal bleeding in the Avastin group, while all 8 eyes remained exudative in the NaCl group. IOP remained unchanged in both groups.

Even though the macular thickness got smaller in the Avastin group, the BCVA did not get better. In the NaCl group the BCVA and the macular thickness remained stable. This might be due to the fibrovascular reaction of the macula in the Avastin group, developing a fibrotic scar, with low BCVA, while a PED with a greater macular thickness still seems to have an equivalent BCVA.

Concluding we can say, that the lesion size and the macular thickness decreased in the Avastin group. The OCT and FA showed that the macula turns quiet and fibrotic under Avastin systemic treatment. Development of BCVA and RVA are comparable in both groups and did not show any difference. Avastin has systemic side effects such as arterial hypertension and thrombosis. Due to its systemic side effects, expensive costs and comparable results with intravitreal injections we suggest offering this systemic therapy to selected patients. After careful selection, according to thrombosis anamnesis, patients with exudative AMD in both eyes, patients who

refuse an intravitreal injection, and patients who have had previous vitrectomy should be considered for this treatment option.

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Appendices

Figures 1 and 2: Displaying the FA and OCT from both eyes of one patient who received systemic treatment with Avastin. The FA and OCT pictures were taken before treatment (top), after 12 weeks (middle), and after 24 weeks (bottom).

Figures 3 and 4: Displaying the FA and OCT from both eyes of one patient who received NaCl. The FA and OCT pictures were taken before infusion (top), after 12 weeks (middle), and after 24 weeks (bottom).







