Augenklinik der Ludwig-Maximilians-Universität München
Direktor: Prof. Dr. Anselm Kampik

Minisymposium AAD 2006

PARABULBÄRE UND INTRAVITREALE MEDIKAMENTAPPLIKATION BEI AMD

Avastin

Anselm Kampik

AAD 2006 AUGENÄRZTLICHE AKADEMIE DEUTSCHLAND

Ätiologie der AMD

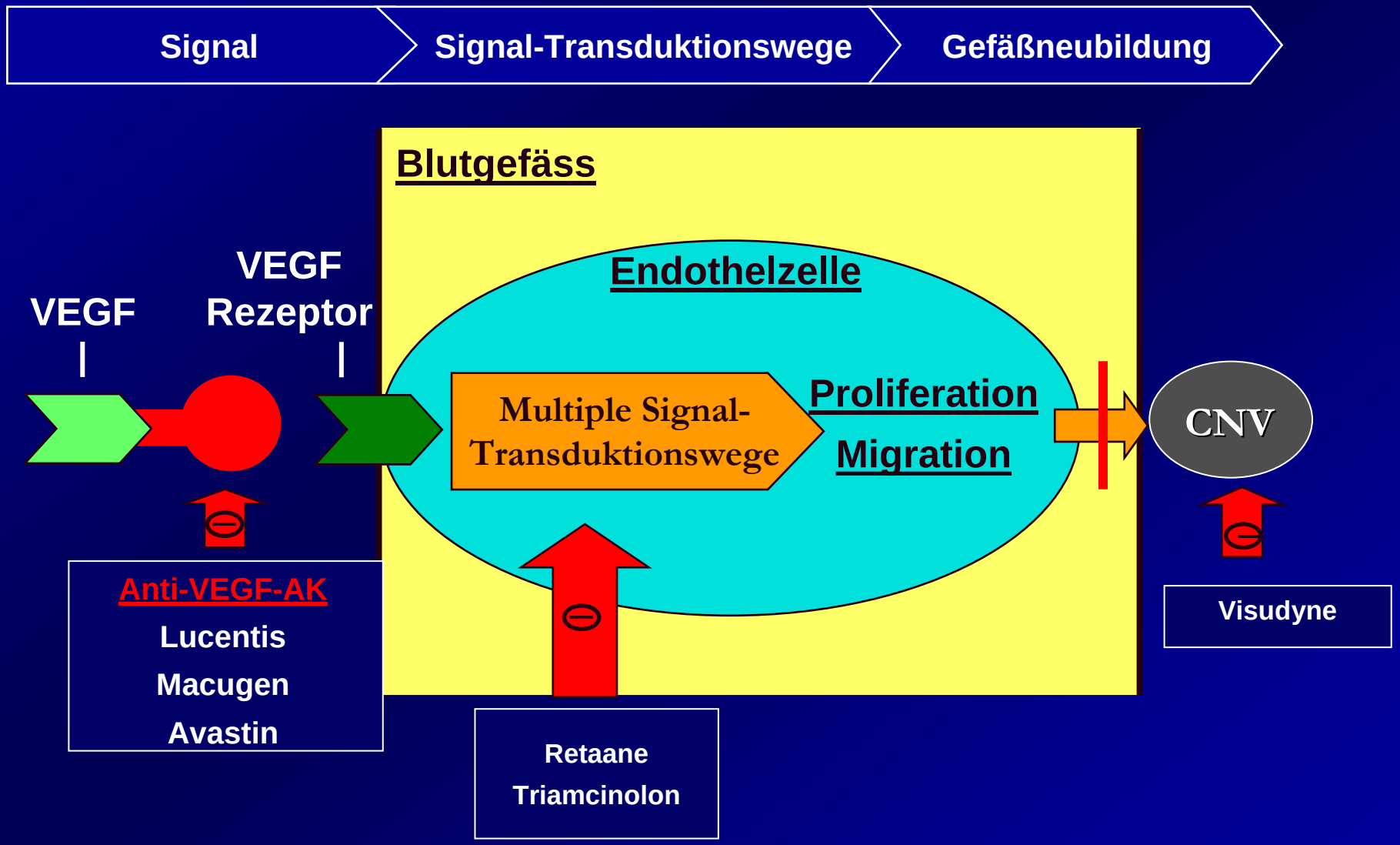
- Genetik
- Oxidativer Stress
- Bruch´sche Membran („Hydrodynamik“)
- RPE-Zellproliferation
- Choroidale Hämodynamik
- Angiogenese (**VEGF**, FGF_2, Angiopoietin ...)
- Subklinische Entzündungsreaktion

→ Multifaktorielles Geschehen

VEGF

- Bindet selektiv an Gefäßendothelzellen (VEGF-Rezeptoren)
- Gefäßneubildung, Permeabilität und Entzündung
- 4 Isoformen auf: $VEGF_{121}$, $VEGF_{165}$, $VEGF_{189}$ und $VEGF_{206}$
- **VEGF ist der wichtigste angiogenetische Wachstumsfaktor bei der Pathogenese der feuchten AMD**

Angiogenese - Hemmer - Überblick



Anti-angiogenetische Therapie

- Pegaptanib (Macugen®)
- Anecortave-Acetat (Retaane®)
- Ranibizumab (Lucentis®)
- **Bevacizumab (Avastin®)**

Bevacizumab (Avastin®) in der Tumorbehandlung

- Monoklonaler Antikörper gegen VEGF
- Erstes Anti-VEGF Medikament

  (metastatisches kolorektales Karzinom)
- Intravenöse Applikation (5mg/kg/KG) alle 2 Wochen
- Komplikationen: Hypertensive Krisen, thromboembolische Vorfälle 4.4%
- Keine Heilung aber gesteigerte Lebenserwartung

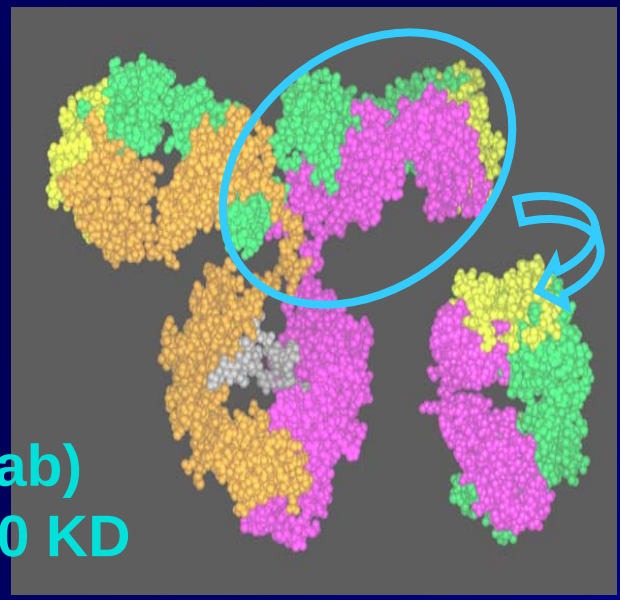
→ Therapieoption bei Augenerkrankungen (AMD, Diabetes etc) ?

→ Ranibizumab (Lucentis®)

Ranibizumab, rhuFab V2 (Lucentis®)

- “Tochtermolekül” des Avastin
- Niedermolekularer Anti-VEGF AK

- rekombinant hergestellt
- humanized
- Fab Fragment
- V2 – Version 2



IgG (Mab)
MW 150 KD

Fab
MW 48 KD

Penetriert die Retina

Intravitreale Injektion von Bevacizumab (Avastin®)

Contra:

- Experimentell am Affen aber nicht am Menschen

  (Adamis AP et al. Arch Ophthalmol 1996)

- Hinweise auf fehlende Penetration der Retina (150 KD)

  (Mordenti J et al. Toxicol Pathol 1999) → Ranibizumab (Lucentis®)

Pro:

- Wirkung nach i.v. Gabe erwiesen
- Niedrige Kosten (ca. 4 €/Injektion)
- Dosis 1 – 1.25 mg entspricht 0.04 – 0.05 ml des erhältlichen Avastin (keine Additiva)
- Längere intravitreale HWZ als Ranibizumab (Lucentis®) ?

Systemic Avastin for Neovascular AMD (SANA-Study)

- AMD Patienten ohne PDT-Indikation
- Visus 0.5 bis 0.05
- Macugen noch nicht erhältlich

- Behandlung: 3x i.v. Gabe (5mg/kg/KG) alle 2 Wochen
- Ergebnisse nach 12 Wochen :
  - Visus: Gewinn von 12 Zeichen (p = 0.008)
  - Netzhautdicke (OCT): Abnahme 177 µm (p = 0.001)
  - Abnahme der Exsudation (FLA/ICG)
  - Neben-Wirkung: Arterielle Hypertonie

Michels S et al. Ophthalmology 2005

Intravitreale Injektion von Bevacizumab (Avastin®)

Erste klinische Berichte

- Netzhautdicke (OCT) ↓
- Leckage in FLA / ICG ↓
- Visus stabil über 4 Wochen

(Rosenfeld PJ et al. Ophthalmic Surg Lasers Imaging 2005)

- Positive Ergebnisse sind reproduzierbar
- Extrem rasche Aufnahme in der retinalen „Community“

→ **„Off label use“ !**

Indikation: AMD Patienten, die nicht für PDT geeignet sind oder die auf etablierte Therapie nicht ansprechen.

Intravitreale Injektion von Bevacizumab (Avastin®)

Academy seeks reimbursement guidance on use of Avastin

The Academy has received numerous inquiries regarding the off-label use of Avastin in the treatment of AMD.
It is currently involved in discussions with …, the FDA, Genetech, malpractice carriers, and members of the retinal community regarding coverage for off-label use of this drug. The Academy will keep you apprised of any developments on this issue in the near future.

Washington Report Express August 25, 2005

Intravitreale Injektion von Bevacizumab (Avastin®)

OCULAR SURGERY NEWS 3/1/2006

RIO GRANDE, Puerto Rico – After the annual meeting of the American Society of Retina Specialists in August 2005, a majority of physicians said they began using intravitreal bevacizumab to treat age-related macular degeneration and other retinal diseases. At that time, some physicians were calling Genentech's Avastin (bevacizumab) a "wonder drug" for AMD treatment. At the 2006 Masters of the American Society of Retina Specialists meeting, a select group of about 50 physicians gathered to share their experiences with the drug and to discuss other surgical techniques and pharmaceutical treatments and methods for AMD and complications of diabetes.

Intravitreale Injektion von Bevacizumab (Avastin®)

EyeNet's March 2006 issue

Clinical Update: Retina

Considering Avastin?
AMD Treatment Information Emerging

Although its use is off-label, Avastin is advancing as a treatment for AMD.

Intravitreale Injektion von Bevacizumab (Avastin®)

EyeNet's March 2006 issue

"It became a global phenomenon within six months," said Philip J. Rosenfeld, MD, PhD, associate professor of ophthalmology at the University of Miami. "But it just goes to show that when patients are losing vision despite receiving approved therapies, there is a tremendous unmet need. And when a potential therapy is introduced that seems rational, based on science and our clinical experience with related drugs, and it’s inexpensive, our profession understands that there is an ethical obligation to at least inform our patients that such a treatment is available, even if all the risks have yet to be identified."

Intravitreale Injektion von Bevacizumab (Avastin®)

TESTING INTRAVITREAL TOXICITY OF BEVACIZUMAB (AVASTIN)

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Purpose: To evaluate the retinal toxicity of varying doses of bevacizumab when injected intravitreally in rabbits. Bevacizumab has been approved by the US Food and Drug Administration for the treatment of metastatic colorectal cancer.

Materials and Methods: Twelve New Zealand albino rabbits were used for this study and divided into four groups. Four concentrations of bevacizumab were prepared: 500 μg/0.1 mL, 1.0 mg/0.1 mL, 2.5 mg/0.1 mL, and 5.0 mg/0.2 mL. Each concentration was injected intravitreally in one eye of each of three rabbits; 0.1 mL volume of sterile balanced saline solution was injected into the contralateral eyes. Slit-lamp and funduscopic examinations were performed and the animals were observed for 2 weeks for signs of infection, inflammation, or toxicity. A baseline electroretinogram (ERG) was performed before the drug treatment and at day 14 before the animals were killed. The enucleated eyes were prepared for histologic evaluation of retinal toxicity.

Results: Histologic and ERG results in all groups showed no retinal toxicity. However, some inflammatory cells were found in the vitreous at the 5–mg dose.

Conclusions: Intravitreal bevacizumab did not appear toxic to the retina in albino rabbits at a concentration of 2.5 mg. Intravitreally injected bevacizumab should be evaluated for efficacy in choroidal neovascularization and macular edema.

RETINA 26:257–261, 2006

Intravitreale Injektion von Bevacizumab (Avastin®)

ELECTROPHYSIOLOGIC AND RETINAL PENETRATION STUDIES FOLLOWING INTRAVITREAL INJECTION OF BEVACIZUMAB (AVASTIN)

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Purpose: Intravitreal bevacizumab (Avastin; Genentech Inc., San Francisco, CA) is a new treatment for age-related macular degeneration. The aim of this study was to evaluate retinal penetration and toxicity of bevacizumab.

Methods: Ten albino rabbits were injected intravitreally with 0.1 mL (2.5 mg) of Avastin into one eye and 0.1 mL saline into the fellow eye. The electroretinogram (ERG) was recorded after 3 hours, 3 days, and 1, 2, and 4 weeks. The visual evoked potential (VEP) was recorded after 4 weeks. Confocal immunohistochemistry was used to assess retinal penetration.

Results: The ERG responses of the control and experimental eyes were similar in amplitude and pattern throughout the follow-up period. The flash VEP responses of the experimental eyes were of normal pattern and amplitude and did not differ from those recorded by stimulation of the control eye alone. Full thickness retinal penetration was present at 24 hours and was essentially absent at 4 weeks.

Conclusions: Bevacizumab was found to be nontoxic to the retina of rabbits based on electrophysiologic studies. Full thickness retinal penetration may explain observed clinical effects of intravitreal bevacizumab. Although it is difficult to directly extrapolate to humans, our study supports the safe use of intravitreal bevacizumab injection.

RETINA 26:262–269, 2006

Intravitreale Injektion von Bevacizumab (Avastin®)

Intravitreal Avastin appears safe and effective in wet AMD patients

- retrospective study: 81 eyes (79 patients, mean age 77) with subfoveal neovascular AMD
- 1.25 mg of bevacizumab IVT on a monthly basis until macular edema, subretinal fluid (SRF), and/or pigment epithelial detachment (PED) resolved.
- majority (78 percent) had prior treatment with photodynamic therapy and/or injection of pegaptanib

- At four and eight weeks, mean V.A. improved from 20/200 to 20/125 ($P<0.0001$)

Ophthalmology, March 2006

Genentech: *no plans for large, long-term clinical study of Avastin for wet AMD. Despite growing evidence supporting the off-label use of its colorectal cancer drug to treat wet AMD, a company spokesperson this week said there are no plans for supporting a long-term clinical study.*

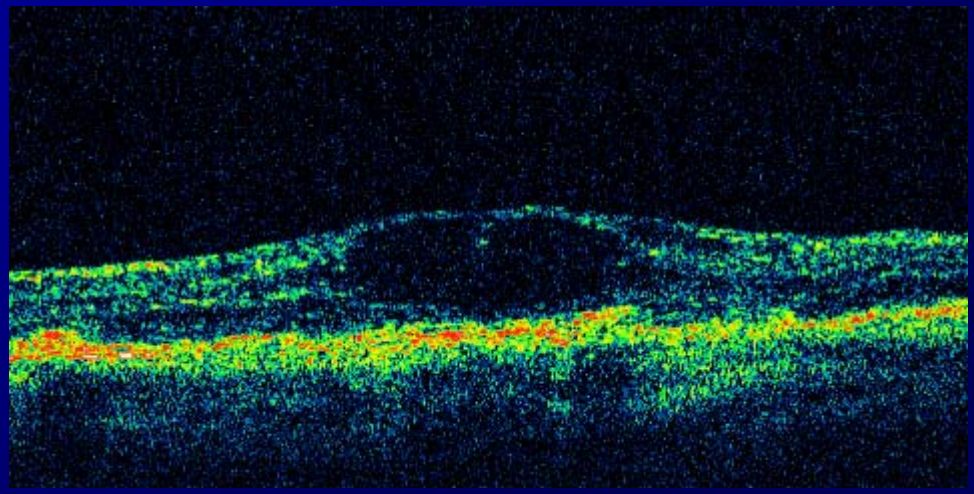
Eigene Beobachtungen mit IVT - Bevacizumab

Augenklinik der LMU München, Mathildenstrasse

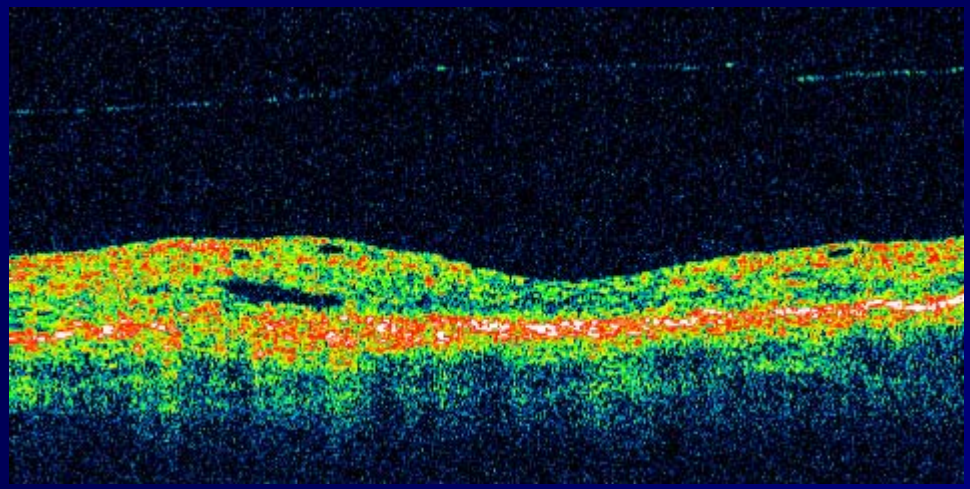
- **„feuchte“ AMD**
  - okkulte subfoveale CNV
  - minimal klassische CNV
  - RAP, Stadium 1 bis 3
  - exsudative fibrovaskuläre Narben
- **Intravitreale Injektion: 1,25 mg Bevacizumab (0,05 ml)**
  ETDRS Visus, FLA / ICGA, OCT

  Kontrolle nach 2, 6, 12, 18, 24 Wochen
- **Re - Injektion alle 6 Wochen bis zum Verschwinden von Makulaödem, SRF, PED**

Intravitreale Injektion von Bevacizumab (Avastin®)



Vor Injektion



14 Tage nach Injektion

Anstieg von 9 auf 28 Zeichen (ETDRS)

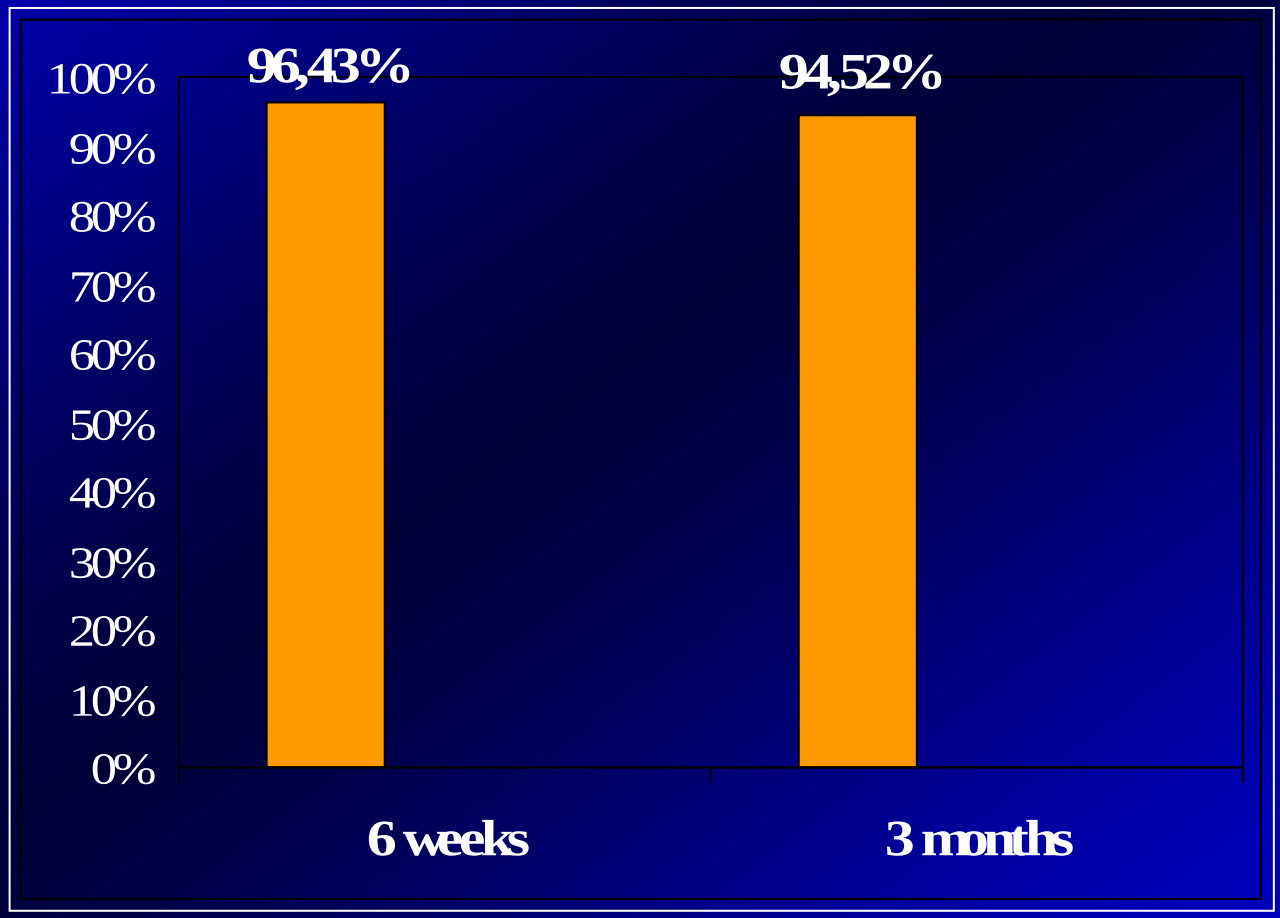
Charakterisierung der Patienten (n=203)

Baseline Characteristics”

	Bevacizumab 1,25 mg
Geschlecht (% Frauen)	64.4%
Alter (Mittelwert)	76.8
Mediane Sehschärfe	0.25
Mean VA (ETDRS letter score)	53.7
CNV Classification	
Occult with no classic	**69.3 %**
Minimally Classic	**5.9 %**
Predominantly Classic	**5.4 %**
RAP (1-3)	**17.8%**

“Percent responders”

= patients losing less than 15 letters



Zusammenfassung

- Avastin agiert nach klinischer Beobachtung ähnlich wie Lucentis in Bezug auf Wirksamkeit und Wirkdauer
- Klinischer Gebrauch ist „off label“
- Beispiel für eine Abkehr von den Prinzipien der „Evidence based Medicine“ aufgrund einheitlicher positiv klinischer Erfahrung
- Bisherige Publikationen lassen keine negativen Nebenwirkungen erkennen
- Avastin ist eine mögliche Alternative in der Behandlung der AMD bei fehlenden präklinischen Studien

Aktuelle Therapie bei der exsudativen AMD

Erstmals liegen Ergebnisse vor, die eine Verbesserung der Sehschärfe bei exsudativer AMD versprechen !!!

- Offene Fragen

- Optimale Zeitpunkte / Intervalle der IVT-Injektion
- Welche Subgruppen profitieren von kombinierter Behandlung
- Welche Substanz am besten für welche Untergruppe der AMD
- Bewertung von Nutzen / Risiko / Behandlungsintervall