Parabulbäre und intravitreale Medikamentapplikation bei AMD
-Triamcinolon -

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Geschichte der i.o. Triamcinoloneacetonide

70´er : akzidentelle intraokuläre Injektion (Dermojet)

80´er : Robert Machemer grundlegende Tierversuche

1998: Jonas und Machemer in Erlangen

Intravitreale Injektion von Triamcinoloneacetonide (IVTA)

Intraocular Injection of Crystalline Cortisone as Adjunctive Treatment of Diabetic Macular Edema

Jost B. Jonas, MD, and Antje Söfker, MD

Am. J. Ophthalmology 2001: 425-427

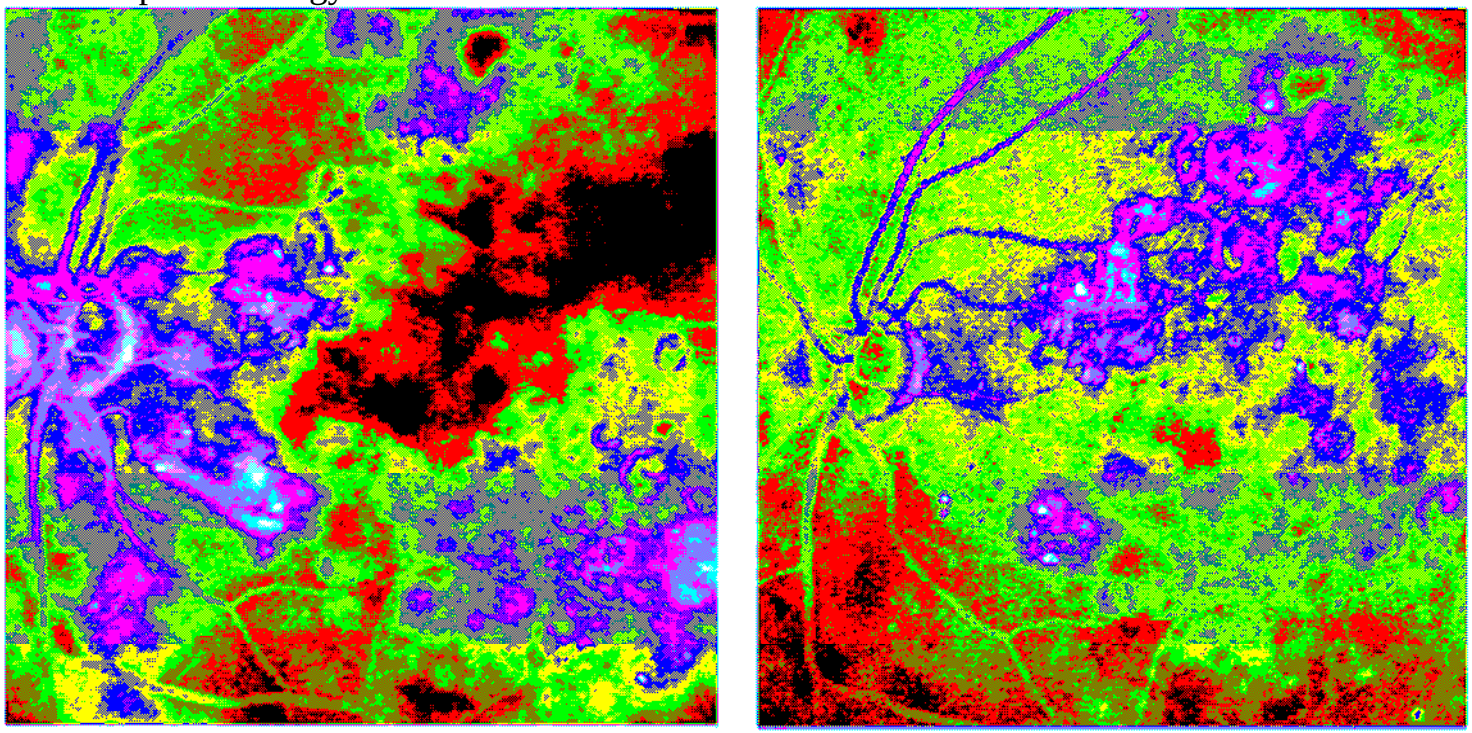
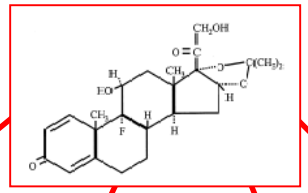


FIGURE 1. Fluorescein angiograms shows the macular region (left) before and (right) 3 months after the intravitreal injection of crystalline cortisone. Note: Regression of the diffuse fluorescein leakage in the macular region after the injection.

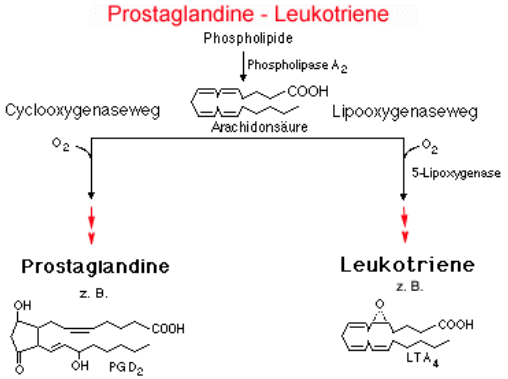
Einsatzgebiete

- proliferative diabetische Retinopathie
- diffuses diabetisches Makulaödem
- Makulaödem nach Venenverschluß
- Rubeosis iridis
- okuläre Hypotonie-Syndrome
- proliferative Vitreoretinopathie (Re-Operationen)
- Uveitis
- vor Kataraktoperation bei Rubeosis iridis
- zystoides Makulaödem nach Kataraktoperation
- exsudative altersabhängige Makuladegeneration

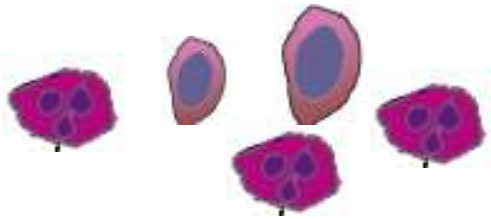
Triamcinoloneacetonide



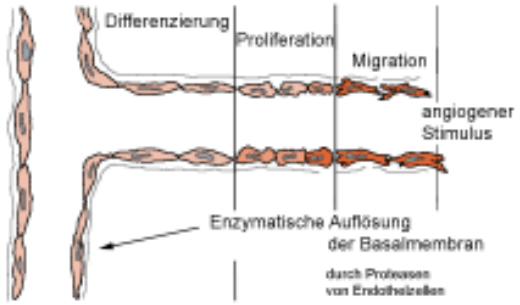
- antiphlogistisch



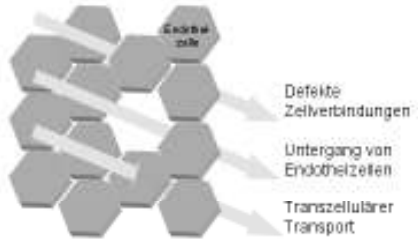
- immunsuppressiv



- antiproliferativ



- antiexsudativ



Triamcinoloneacetonide: antiproliferative Wirkung

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Graefe's Arch Clin Exp Ophthalmol
(2002) 240:42–48

LABORATORY INVESTIGATION

DOI 10.1007/s00417-001-0398-y

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Stephan Hoffmann
Peter Wiedemann

Inhibitory effects of triamcinolone acetonide on bFGF-induced migration and tube formation in choroidal microvascular endothelial cells

Received: 11 June 2001
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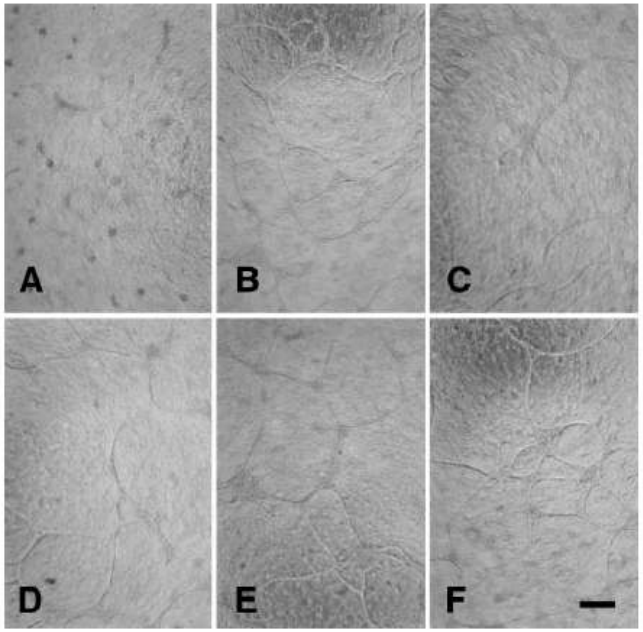
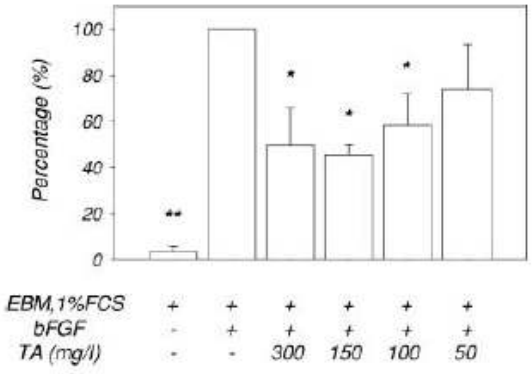
Published online: 17 November 2001

Abstract *Background:* Angiostatic drugs might provide desirable modulation of choroidal angiogenesis-related diseases, including histoplasmosis and the exudative form of age-related macular degeneration. However, the precise effects of this class of compounds in the choroidal neovascularization are still unclear. In the present Boyden chamber and the Vitrogen collagen assay, respectively. The activities of matrix metalloproteinases (MMP)-2 and -9 were examined using gelatin zymography. *Results:* The stimulation of CEC with 50 ng/ml bFGF resulted in an increase of about 100% in migration activity ($P<0.01$). Preincubation of CEC with TA at the

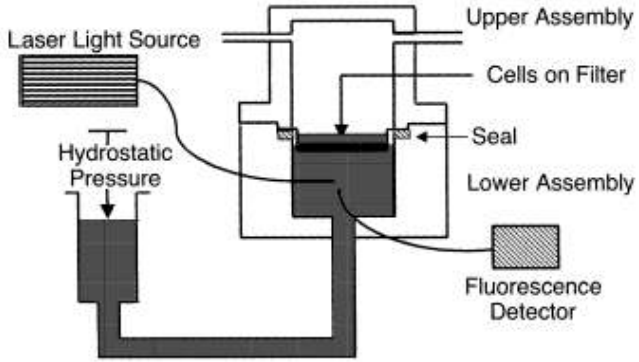




Triamcinoloneacetonide: antiexsudative Wirkung

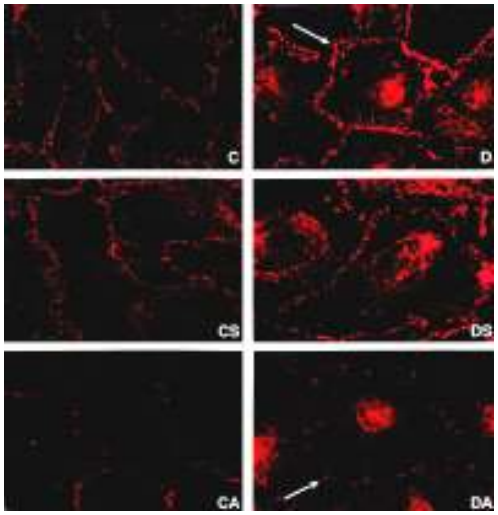
Antonetti et al. Journal of Neurochemistry, 2002: 667-677

- Hydrocortisone reduziert den Transport von Wasser durch Endothelmonolayer
- Hydrocortisone verstärkt die Occludin Expression und Phosphorylierung



Underwood et al. Am J Physiol, 1999: 46: C330-342

- Dexamethasone verstärkt die Expression von Tight Junction Molekülen in Endothelzellen des Schlemmschen Kanals
- Erhöhung des Flußwiderstandes um 3-5 fach



ZO-1 Expression in Endothelzellen des Schlemmschen Kanals

Intravitreale Injektion von Triamcinoloneacetonide (IVTA)

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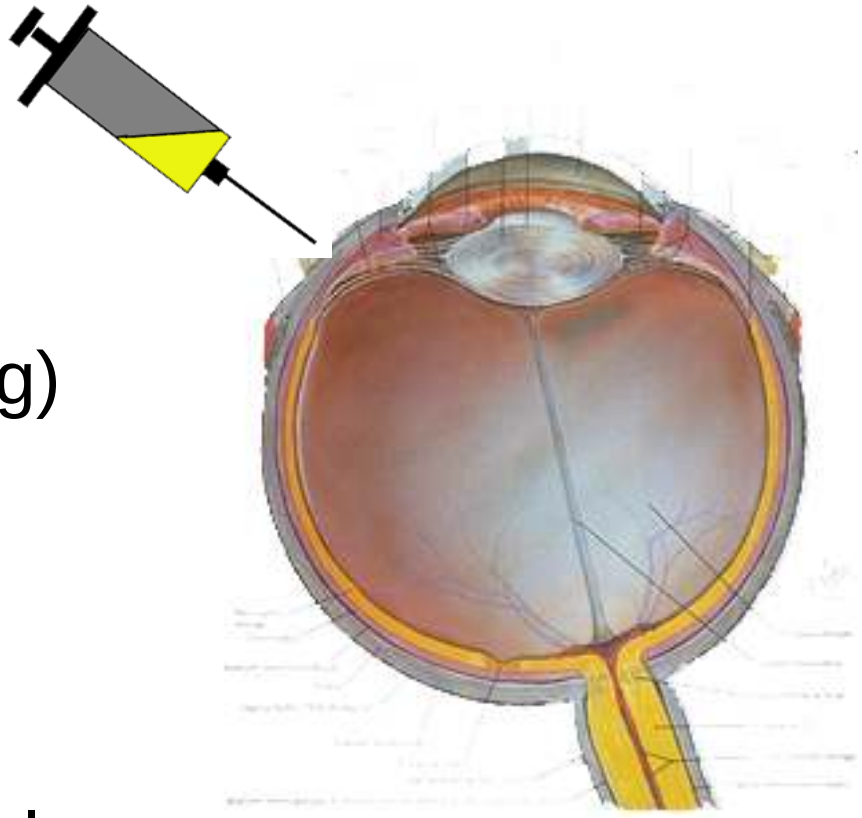
Löslichkeitsgleichgewicht

- 25 - 30 µg/ml

Kammerwasserkonzentration

- 2,1 - 7,2 µg/ml



Eliminationshalbwertszeit (4mg)

- 18.6 d bei Augen mit Glaskörper
- 3.2 d in vitrektomierten Augen

Messbare Konzentrationen

- ca. 93 d (13 Wochen)

Wirkkonzentration noch nicht klar

(Beer et al. Ophhtalmology 2003,110: 681-688)

SW

Intravitreale Injektion von Triamcinoloneacetonide (IVTA)

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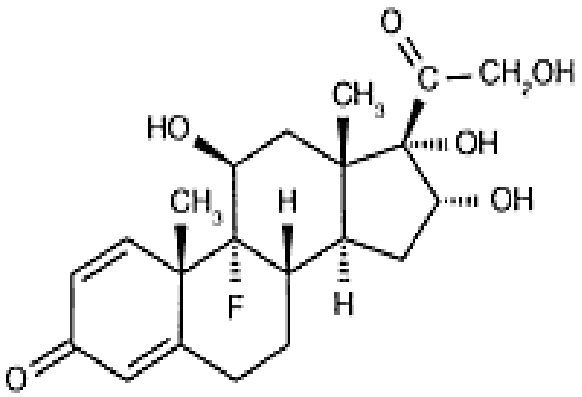
Dosisfindung am Menschen

- pragmatisch – empirisch
- 4 mg - 10 mg - 25 mg - 40 mg

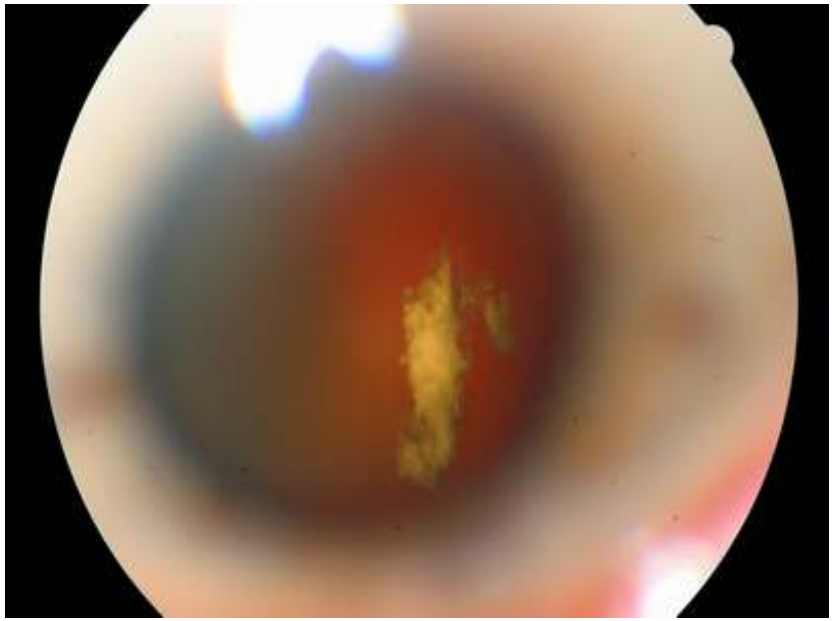


Triamcinolon

Intravitreale Injektion von Triamcinoloneacetonide (IVTA)

Applikationsarten

- intravitreal, mit und ohne Vitrektomie
- als „Farbstoff“ bei Vitrektomie
- subretinal
- parabulbär



SW

Intravitreale Injektion von Triamcinoloneacetonide (IVTA)

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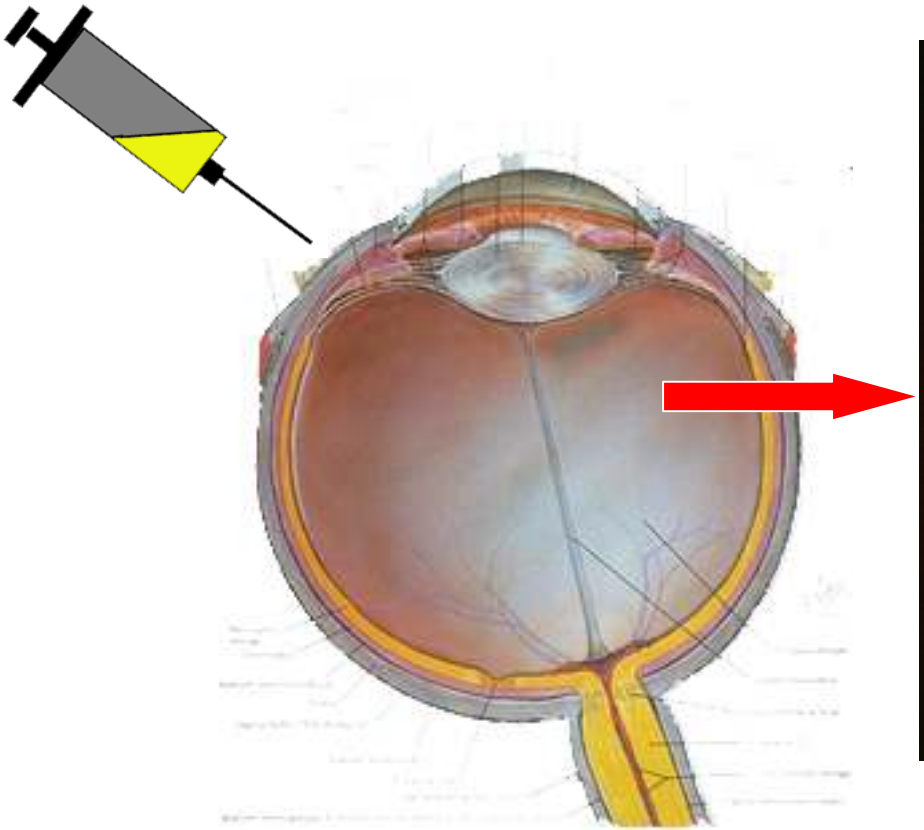

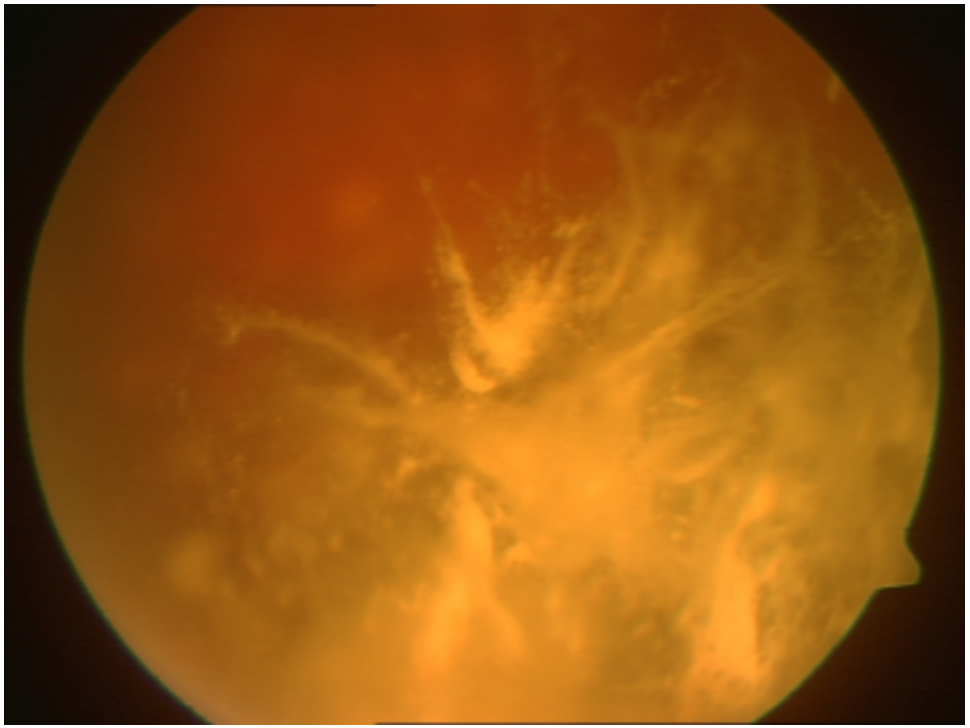

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Intravitreale Injektion von Triamcinoloneacetonide (IVTA)

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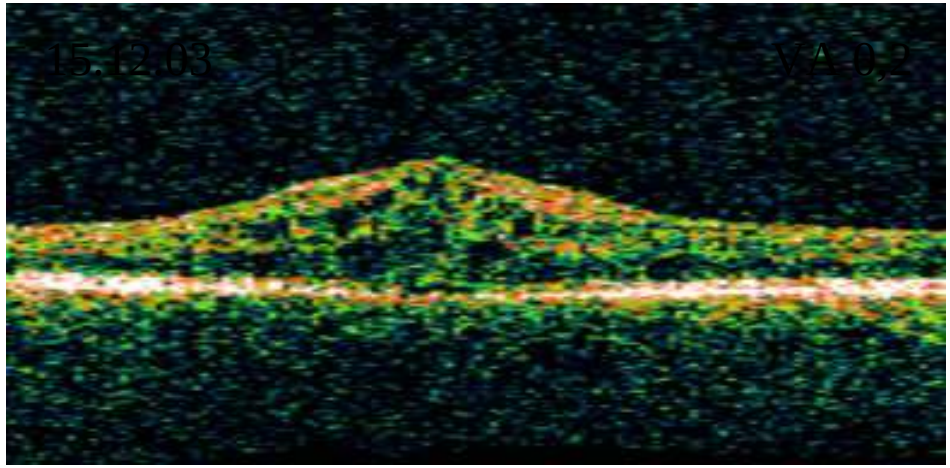
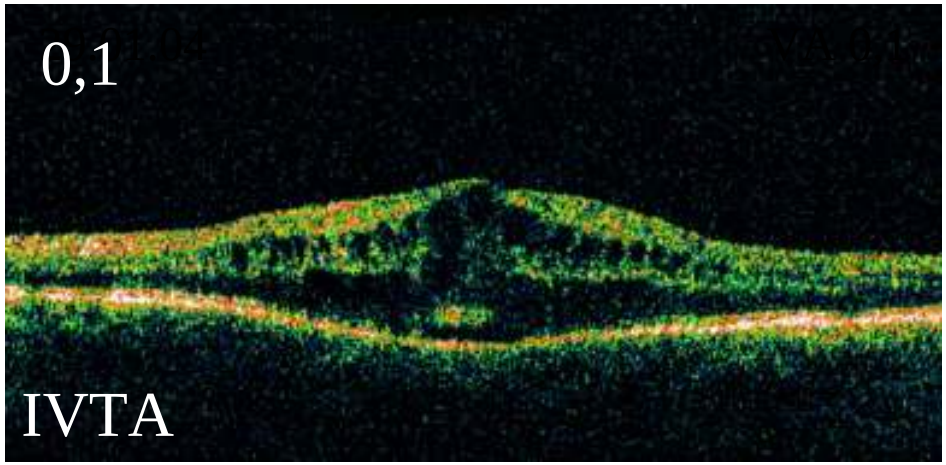
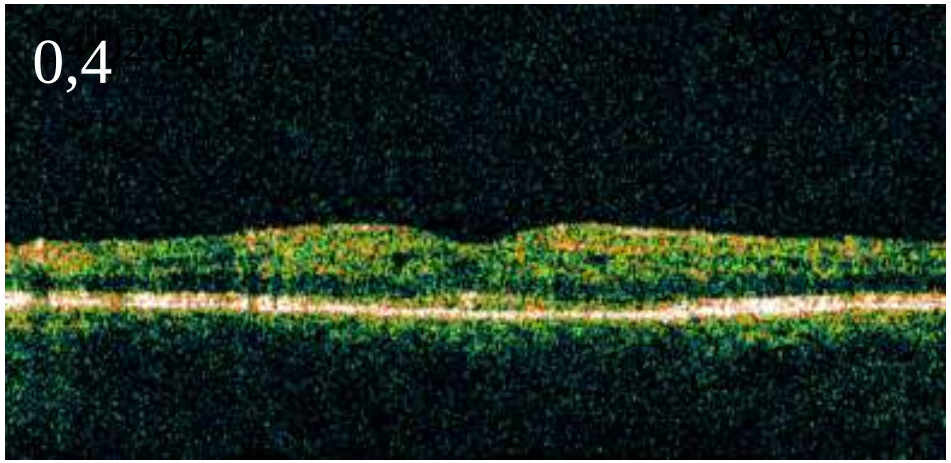






SW

IVTA bei diabetischem Makulaödem

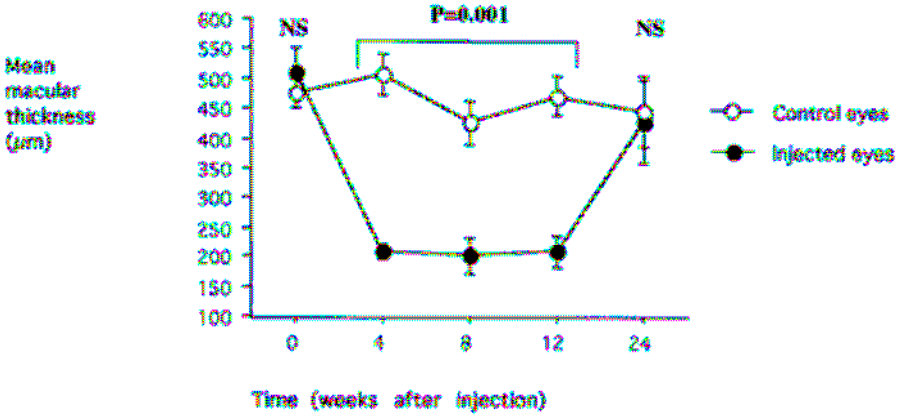
Intravitreal Triamcinolone Acetonide for Diabetic Diffuse Macular Edema

Preliminary Results of a Prospective Controlled Trial

Pascale Massin, MD, PhD,[1] François Audren, MD,[1] Belkacem Haouchine, MD,[1] Ali Erginay, MD,[1] Jean-François Bergmann, MD,[2] Rym Benosman, MD,[1] Charles Caulin, MD,[2] Alain Gaudric, MD[1]

Table 3. Comparison of Mean (± Standard Deviation) Early Treatment Diabetic Retinopathy Study (ETDRS) Scores for Eyes Injected with 4 mg of Triamcinolone Acetonide (TA) and Control Contralateral Eyes

ETDRS Score	Injected Eyes	Control Eyes	P of ETDRS Variation between Groups
Before TA injection	47.8 ± 13	51.9 ± 14.6	>0.1
4 wks after injection	53.4 ± 11.3	52.5 ± 15.1	>0.1
12 wks after injection	52.7 ± 10.8	50.8 ± 14.3	>0.1
24 wks after injection	54.7 ± 7.6	50.6 ± 18.4	
	n = 7	n = 7	>0.1



Massin et al. Ophthalmology 2004:218-224

IVTA bei AMD

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IVTA bei AMD

CLINICAL SCIENCES

A Randomized Clinical Trial of a Single Dose of Intravitreal Triamcinolone Acetonide for Neovascular Age-Related Macular Degeneration

One-Year Results

Mark C. Gillies, FRANZCO, PhD; Judy M. Simpson, PhD; Wei Luo, MPH; Philip Penfold, PhD; Alex B. L. Hunyor, FRANZCO; William Chua, FRANZCO; Paul Mitchell, FRANZO, PhD; Frank Billson, FRANZCO

Objective: To determine if a single intravitreal injection of 4 mg of triamcinolone acetonide in patients with classic choroidal neovascularization associated with age-related macular degeneration can safely reduce the risk of severe visual loss.

Methods: A double-masked, placebo-controlled, randomized clinical trial was performed in patients 60 years or older who had choroidal neovascularization with any classic component, a duration of symptoms of less than 1 year, and a visual acuity of 20/200 or better. Best-corrected visual acuity, intraocular pressure, and cataract grading were performed before the injection and then at 3, 6, and 12 months.

Main Outcome Measure: The development of severe loss of vision (30 letters) by survival analysis on an intention-to-treat basis.

Results: One hundred fifty-one eyes were randomized into the study, and follow-up data were obtained for 73 (97%) of the 75 eyes in the treated group and for 70 (92%) of the 76 eyes in the control group. There was no difference between the 2 groups for the development of severe visual loss during the first year of the study (log-rank χ^2_1=0.03, P=.90). In both groups, the 12-month risk of severe visual loss was 35%, with a hazard ratio of 1.05 (95% confidence interval, 0.59-1.86). The change in size of the neovascular membranes, however, was significantly less in eyes receiving triamcinolone than in those receiving placebo 3 months after treatment (P=.01), although no difference was noted after 12 months. After 12 months, treated eyes had a significantly higher risk of an elevated intraocular pressure (31/75 [41%] vs 3/76 [4%]; P<.001), but not of cataract progression (P=.29).

Conclusions: A single dose of intravitreal triamcinolone had no effect on the risk of loss of visual acuity during the first year of the study in eyes with age-related macular degeneration and classic choroidal neovascularization, despite a significant antiangiogenic effect found 3 months after treatment. This biological effect warrants further study.

Arch Ophthalmol. 2003;121:667-673

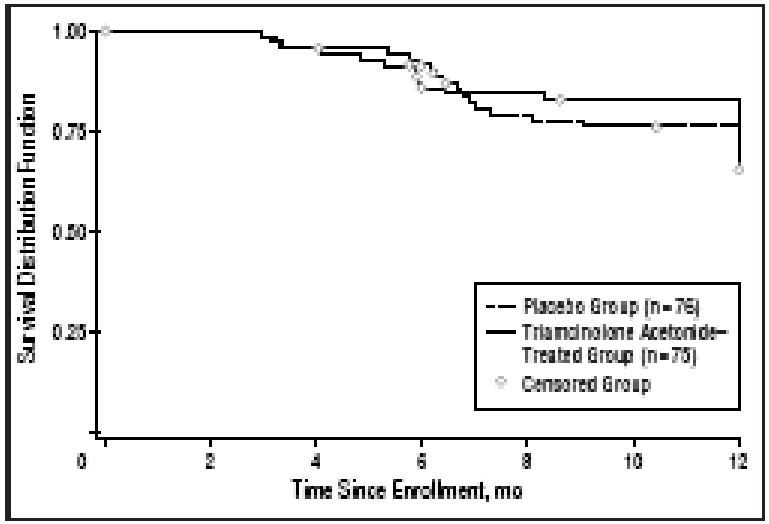
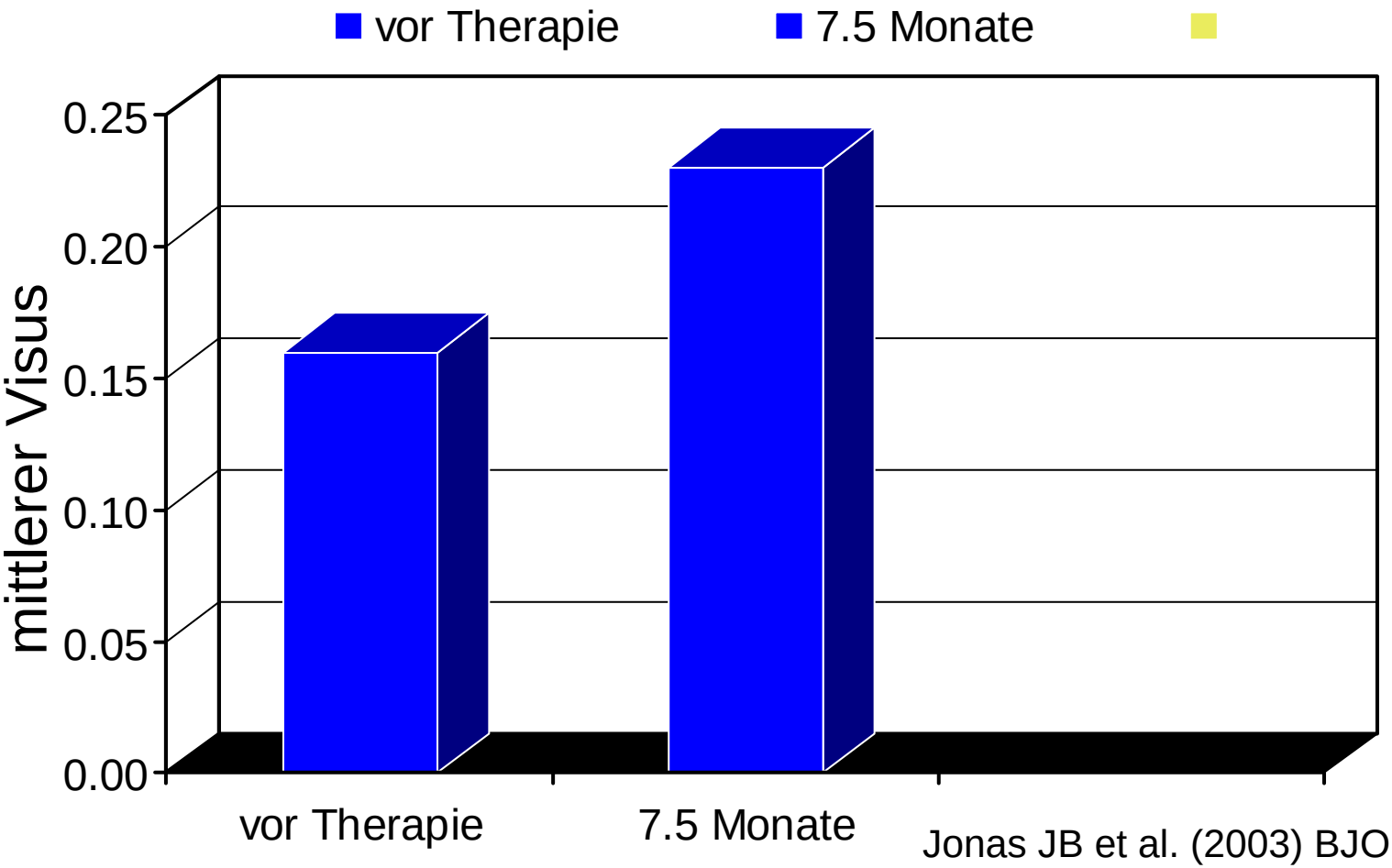


Figure 2. Survival curve of severe vision loss in patients in the triamcinolone acetonide–treated group and the placebo group.

IVTA bei AMD



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IVTA und PDT bei AMD

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IVTA und PDT bei AMD

26 Augen mit CNV bei AMD

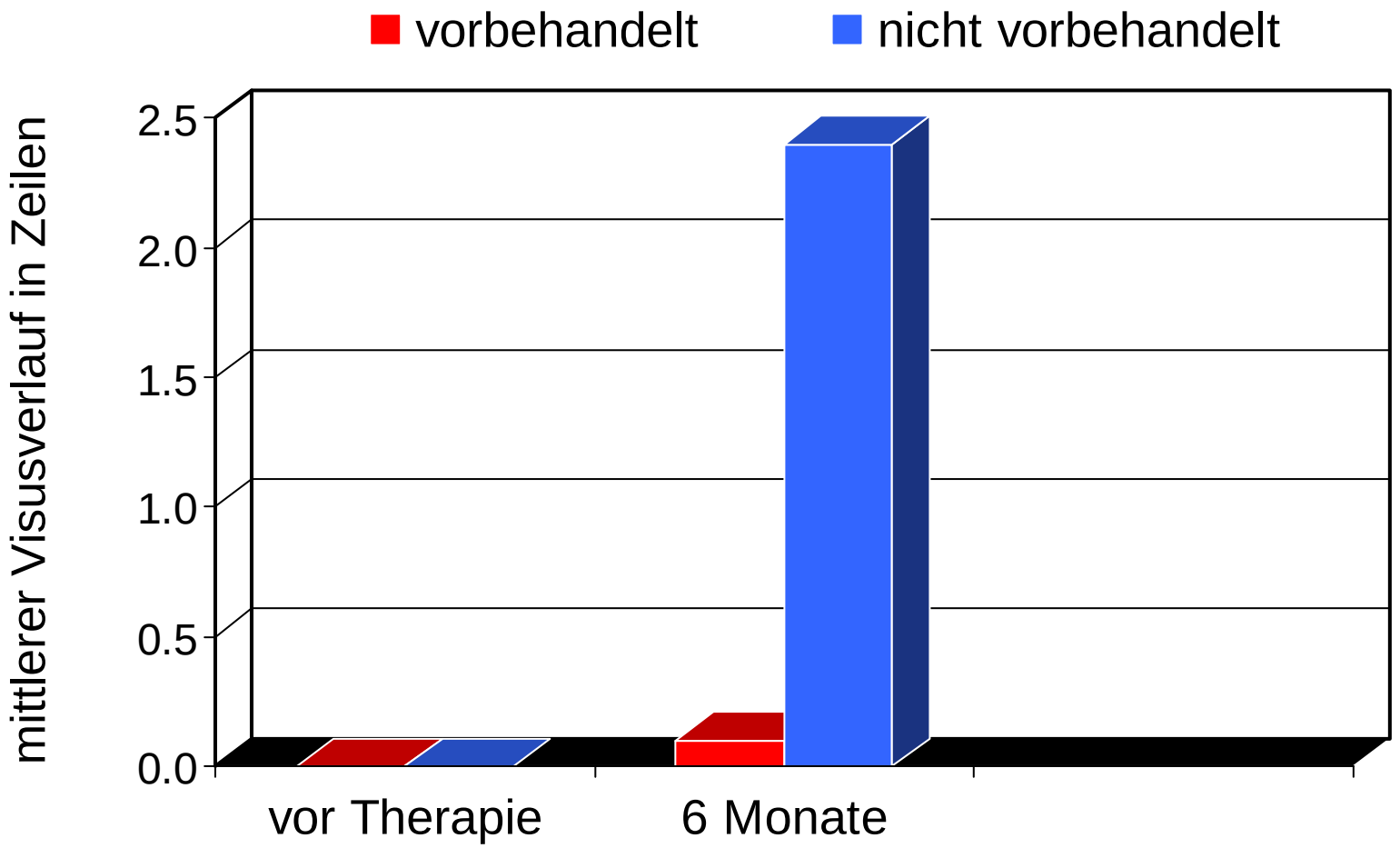
- alle Subtypen
- 13 ohne Vorbehandlung
- 13 nach PDT

PDT + 4 mg Triamcinolon

Beobachtungszeitraum 6 Monate

Spaide RF, Sorenson J, Maranan L (2003) Ophthalmology ;110:1517-25

IVTA und PDT bei AMD



IVTA und PDT bei AMD

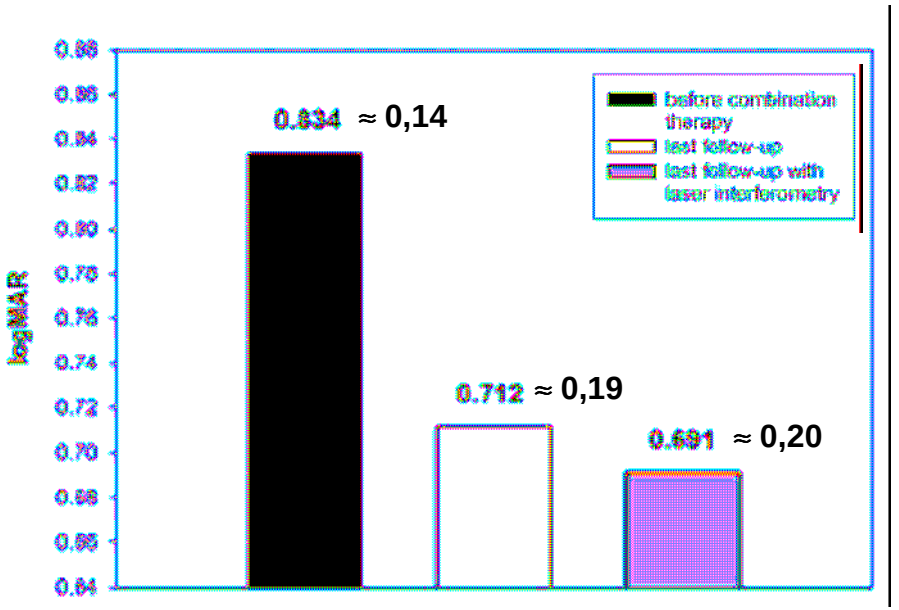
Verteporfin Therapy Combined with Intravitreal Triamcinolone in All Types of Choroidal Neovascularization due to Age-Related Macular Degeneration

Albert J. Augustin, MD,[1] Ursula Schmidt-Erfurth, MD[2]

Objective: To evaluate the efficacy and safety of photodynamic therapy with verteporfin combined with intravitreal triamcinolone in choroidal neovascularization secondary to age-related macular degeneration (AMD).
Design: Prospective, noncomparative, interventional case series.
Participants: One hundred eighty-four patients undergoing treatment for neovascular AMD at one retinal referral center.
Methods: One hundred eighty-four eyes of 184 consecutive patients (63.6% female, 36.4% male) with a mean age of 76.5 years and a follow-up of a median of 38.8 weeks (range, 12–103) were included in a case series. One hundred forty-eight (80.4%) patients had subfoveal choroidal neovascularization, 19 patients (10.3%) had juxtafoveal choroidal neovascularization, and 17 patients (9.2%) had extrafoveal choroidal neovascularization. Verteporfin photodynamic therapy was performed using the recommended standard procedure. A solution containing 25 mg of triamcinolone was injected intravitreally 16 hours after photodynamic therapy in 184 patients. The combined therapy procedure was repeated at the 3-month follow-up visits whenever persistent choroidal neovascularization leakage was documented angiographically.
Main Outcome Measures: Mean change in best-refracted visual acuity (VA) between baseline and the last visit, and number of treatments necessary to achieve absence of leakage.
Results: Visual acuity improved in the majority of patients (baseline VA, mean 20/125) by a mean increase of 1.22 Snellen lines and 1.43 lines using laser interferometry ($P<0.01$). The mean number of required treatments was 1.21. Twenty-three eyes (12.5%) required 2 treatments, 6 eyes (3.26%) required 3 treatments, and 1 eye (0.5%) required 4 treatments. The combination treatment including laser and intravitreal steroid administration was well tolerated. Forty-six patients (25%) required glaucoma therapy due to a transient steroid-induced intraocular pressure (IOP) increase. Twelve patients (6.5%) were on topical medication for preexisting glaucoma. Two patients (1%) whose IOP increase could not be controlled with topical therapy required surgery.
Conclusions: Verteporfin photodynamic therapy combined with intravitreal triamcinolone may improve the outcome of standard verteporfin photodynamic therapy in the treatment of choroidal neovascularization secondary to AMD. A significant improvement in VA was observed in a majority of treated patients and was maintained during the maximum follow-up. In addition, retreatment rates were lower than anticipated.
Ophthalmology 2006;113:14–22 © 2006 by the American Academy of Ophthalmology.

184 Augen mit exsudativer AMD

- 36 juxta- oder extrafoveal
- PDT → 16 h später IVTA (25 mg)



IVTA und PDT bei AMD

NIH clinical research studies

Protocol Number: 05-EI-0064

Active Accrual, Protocols Recruiting New Patients

Title:
Multi-Center, Randomized, Phase II/III Clinical Trial to Study the Effects of Preservative-Free Triamcinolone Acetonide as an Adjunct to Photodynamic Therapy in Participants with Neovascular Age-Related Macular Degeneration

Number:
05-EI-0064

IVTA: Probleme

Kataraktentwicklung

- Verletzung der Linse bei intravitrealer Injektion
- Kortisonwirkung

Augendruckerhöhung

- Inzidenz relativ hoch (30 – 40 %)

Endophthalmitis

- Entwicklung nach 2-5 Tagen
- Bei Injektion unter aseptischen Bedingungen geringes Risiko (< 0.05%)

IVTA: Augendruckerhöhung

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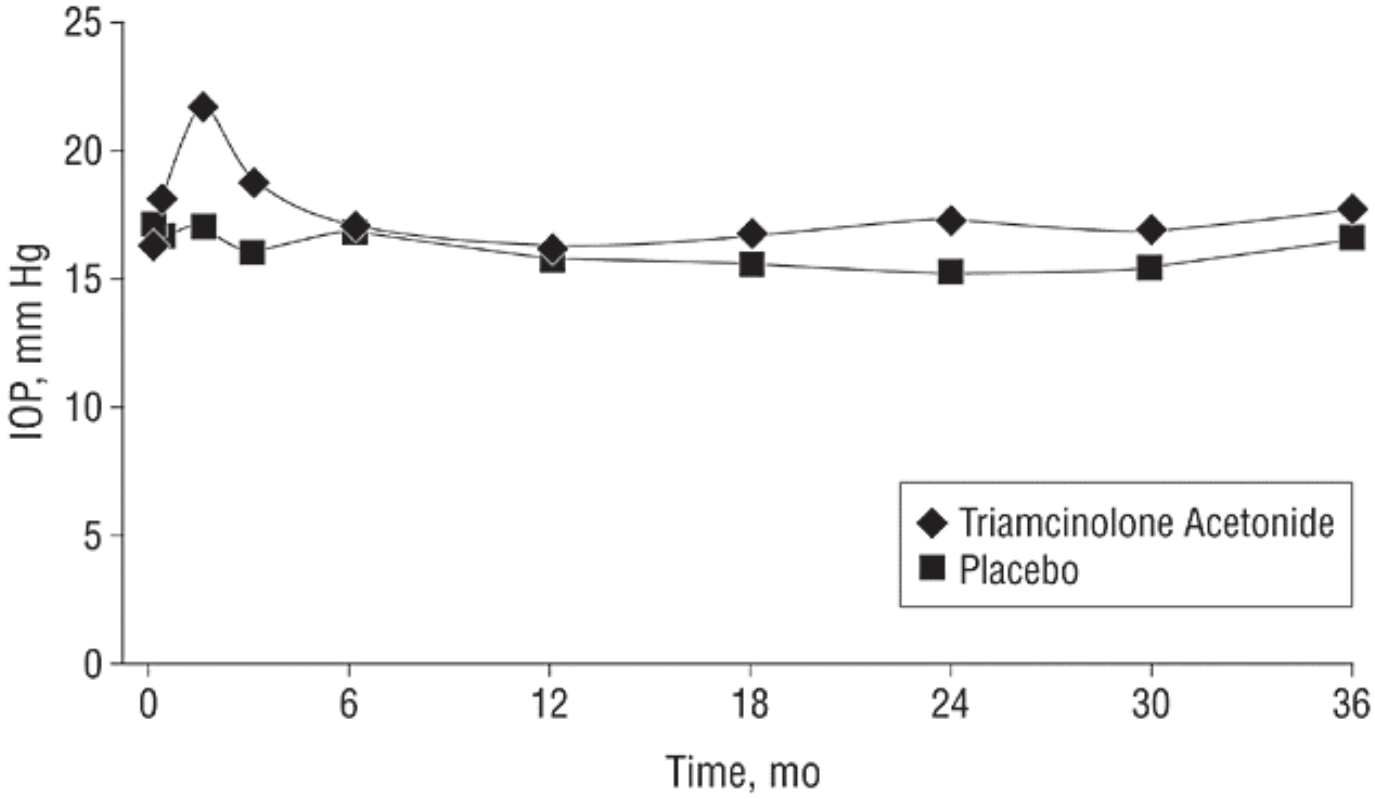
IVTA: Augendruckerhöhung

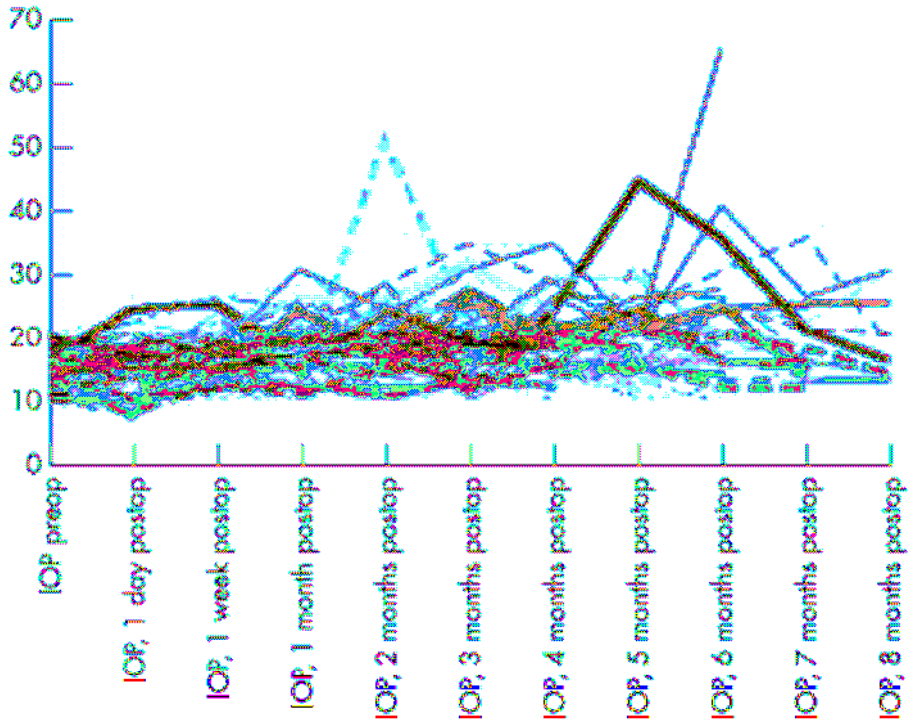
- Bei bis zu 40 % der Patienten wird ein IOD > 21 mmHg mindestens einmal gemessen.
- Ein Druckerhöhung um mindestens
  - 10 mmHg wird bei 22 % Patienten beobachtet.
  - 15 mmHg wird bei 11% Patienten beobachtet.
  - 20 mmHg wird bei 5% Patienten beobachtet.
- Eine filtrierende Operation ist bei etwa < 1 % der Patienten erforderlich.
- Höchste Wahrscheinlichkeit der Druckerhöhung 4 – 8 Wochen nach Injektion

IVTA: Augendruckerhöhung



Gilles et al. Arch Ophthalmol. 2004:336-40

IVTA: Augendruckerhöhung



Jonas et al. BJO 2003:24-27

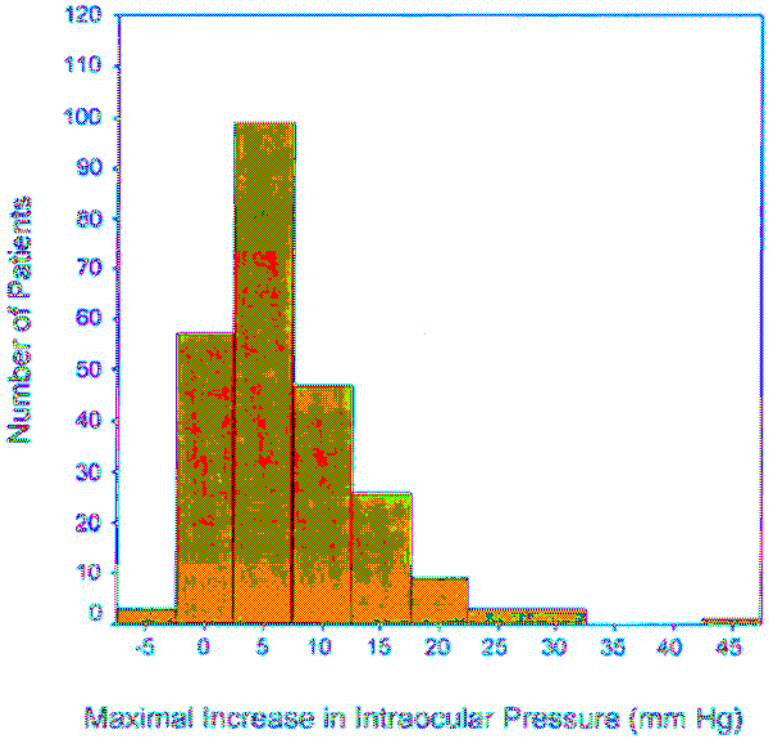


Figure 1. Histogram showing the maximal gain in intraocular pressure during follow-up in 272 patients after intravitreal injection of approximately 20 mg triamcinolone acetonide.

Jonas et al. Ophthalmology 2005:593-598

IVTA: Probleme

Kataraktentwicklung

- Verletzung der Linse bei intravitrealer Injektion
- Kortisonwirkung

Augendruckerhöhung

- Inzidenz relativ hoch (30 – 40 %)

Endophthalmitis

- Entwicklung nach 2-5 Tagen
- Bei Injektion unter aseptischen Bedingungen geringes Risiko (< 0.05%)

IVTA: Probleme

„Pseudo“- Endophthalmitis / Endophthalmitis

- 5 von 140 Augen bei 4 mg (Müller et al. DOG 2003)
- 0 von 327 Augen bei 25 mg (Kamppeter et al. DOG 2003)
- Alkoholtoxizität?

Zusammenfassung

Intravitrealer Injektion von Triamcinolon

- Schnelle Reduktion des Makulaödems
- Deutlichen Visusverbesserung möglich
- Wirkdauer unklar, evtl. mehrmalige Injektionen erforderlich
- Nebenwirkungen
  - Augendruckerhöhung
  - Kataraktentwicklung
- Off-Label Anwendung