Ente Ecclesiastico
Ospedale Generale Regionale
"F. Miulli"
Unità Operativa Complessa Oculistica
Direttore: *Dott. T. Micelli Ferrari*

TERAPIA MEDICA E PARACHIRURGICA NELL'EDEMA MACULARE DIABETICO

Dott. Tommaso Micelli Ferrari

Dott. Giancarlo Sborgia

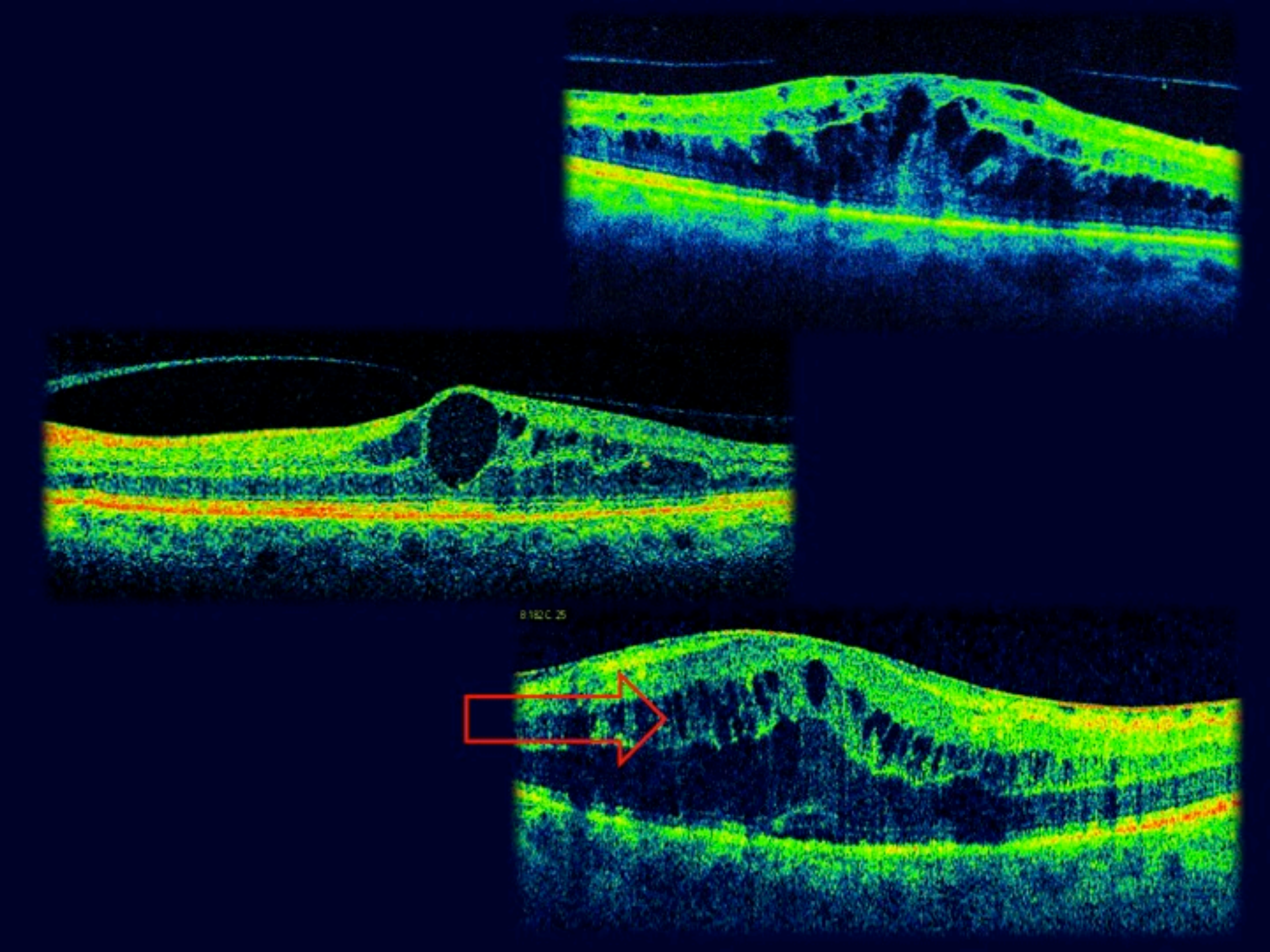
Bari, 8 Novembre 2013

Edema Maculare Diabetico

Accumulo abnormale di fluido extravascolare nella macula secondario a rottura della BER
Pelzek C, Lim JI. Diabetic macular edema: review and update. Ophthalmol Clin North Am. 2002;15(4):555-563

Classificato in:
ischemico e non ischemico
Focale e diffuso
Johnson M. Perspective - Etiology and treatment of macular edema. Am J Ophthalmol 2009;147(1):11

Edema definito cistoide: evidenza alla biomicroscopia, FA, OCT come un accumulo di fluido in spazi multipli simili a cisti +/- componente trazionale, con orientamento radiale in zona maculare
Rotsos TG, Moschos MM. Cystoid macular edema. Clin Ophthalmol 2008;2:919-30



Edema Maculare Diabetico
Trattamento

Fotocoagulazione laser

Rimane il gold standard dell'EMD

Bhagat N, Grigorian RA, Tutela A, Zarbin MA. Diabetic macular edema: pathogenesis and treatment. Surv Ophthalmol 2009; 54: 1-32.

Meccanismo di azione esatto non ben definito;
L'OSSIGENO che normalmente diffonde dalla coriocapillare verso la retina esterna, attraverso la cicatrice del laser, può diffondersi nella retina interna;

Yu DY, Cringle SJ, Su E, Yu PK, Humayun MS, Dorin G. Laser-induced changes in intraretinal oxygen distribution in pigmented rabbits. Invest Ophthalmol Vis Sci 2005; 46: 988-999.

Fotocoagulazione laser

Linee guida: ETDRS Trial 1985

1° studio randomizzato che ha stabilito l'efficacia del laser per l'EMD e la RDP

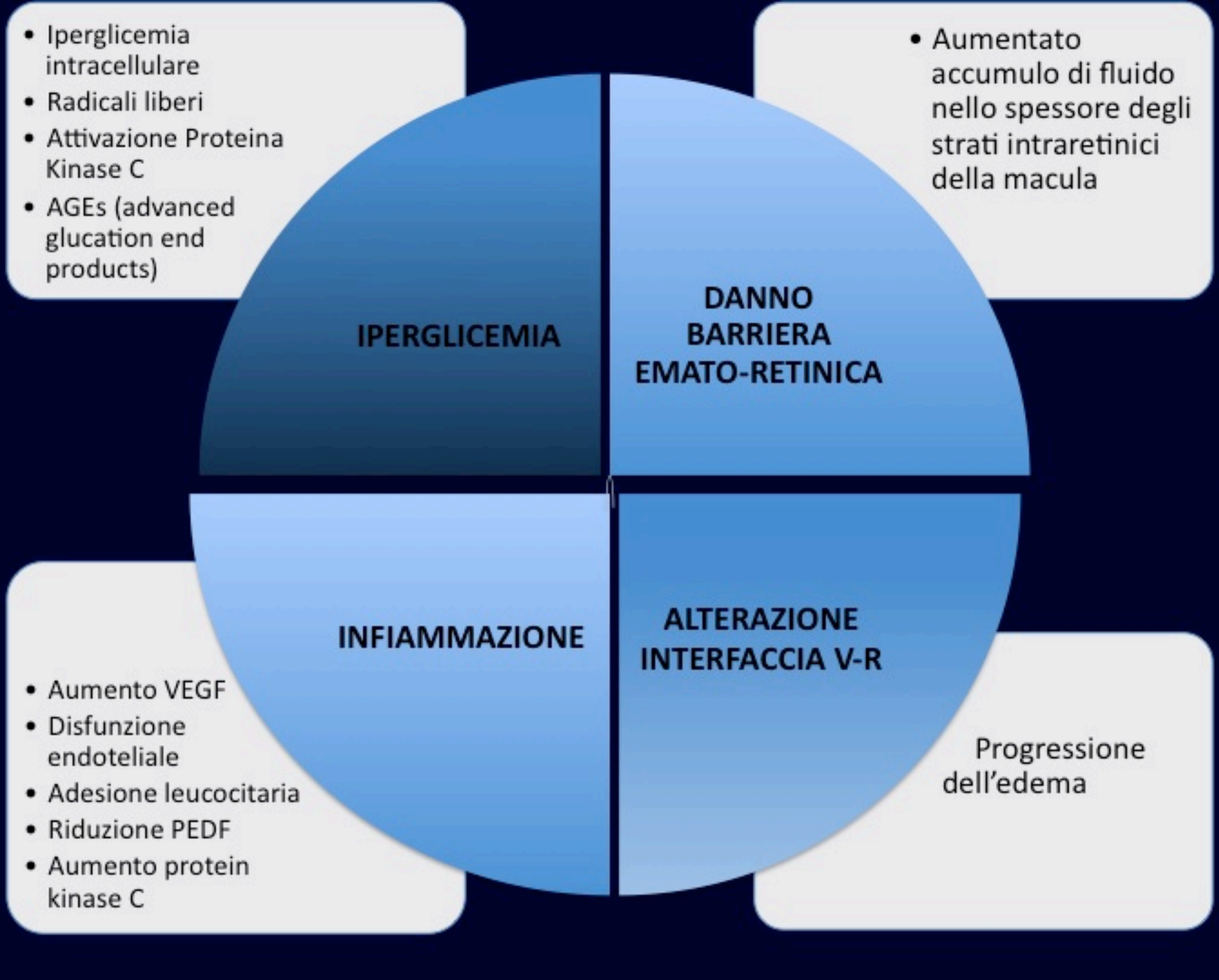
La fotocoagulazione FOCALE riduce del 50% il rischio di moderata perdita visiva definita come perdita ≥3 linee AV (da 24% a 12%) dopo 3 anni

A 3 anni solo il 16% dei pazienti ha guadagnato ≥15 lettere di AV

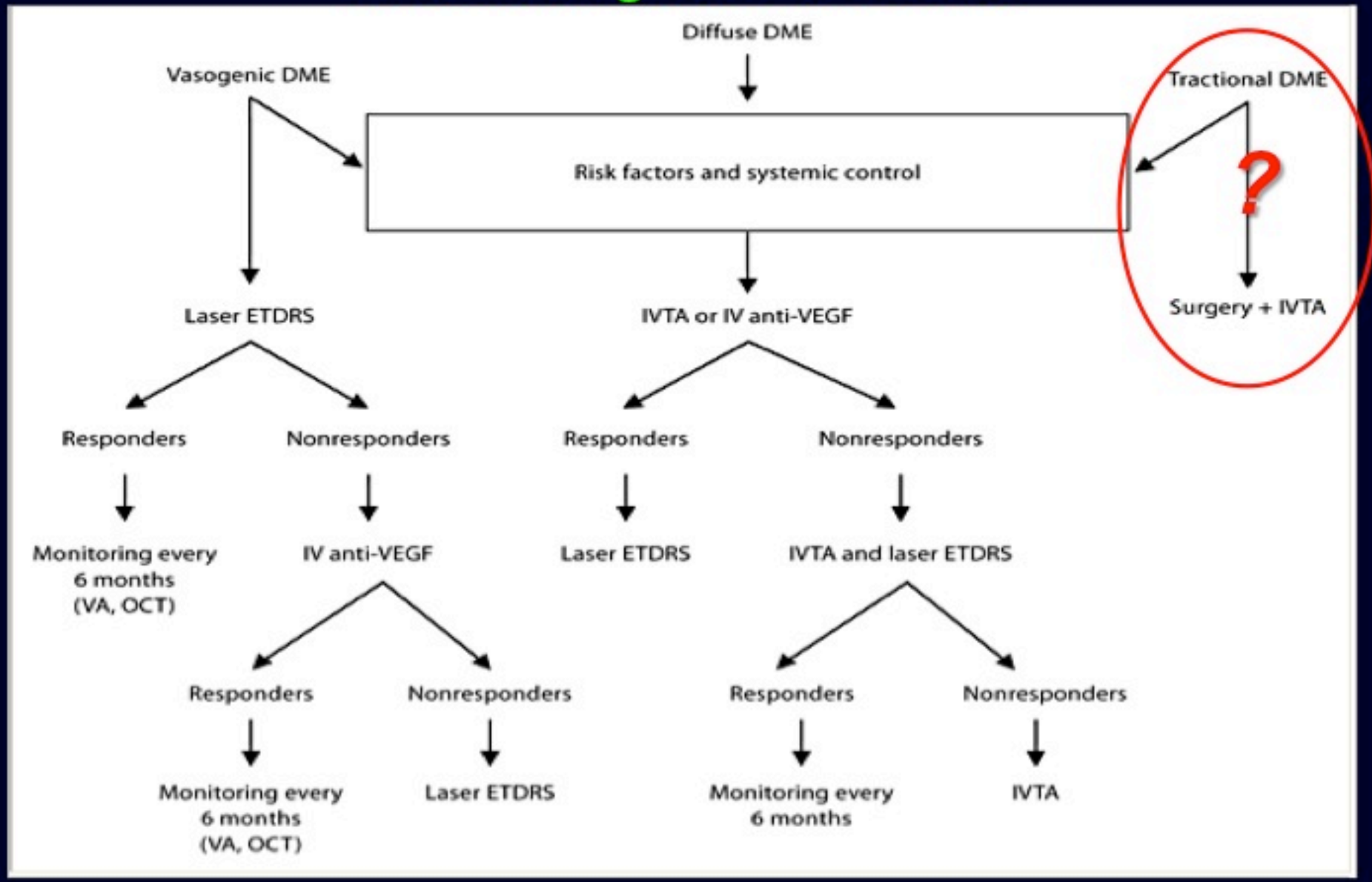
Early Treatment Diabetic Retinopathy Study research group.
Arch Ophthalmol 1985;103:1796-1806

Malgrado il trattamento con fotocoagulazione laser, esiste una popolazione di pazienti con EM refrattario che continuano ad avere perdita visiva

Attualmente sono state studiate nuove terapie con target la BER


• Iperglicemia intracellulare
• Radicali liberi
• Attivazione Proteina Kinase C
• AGEs (advanced glucation end products)
IPERGLICEMIA
DANNO BARRIERA EMATO-RETINICA
• Aumentato accumulo di fluido nello spessore degli strati intraretinici della macula
INFIAMMAZIONE
ALTERAZIONE INTERFACCIA V-R
• Aumento VEGF
• Disfunzione endoteliale
• Adesione leucocitaria
• Riduzione PEDF
• Aumento protein kinase C
Progressione dell'edema

Treatment algorithm for DME



Ophthalmologica. 2010

Steroids as part of combination treatment: the future for the management of macular edema?

Bandello F, Battaglia Parodi M, Tremolada G, Lattanzio R, De Benedetto U, Iacono P

Intravitreal Injection Technique

- Preinjection topical antibiotics can be applied at the discretion of the treating ophthalmologist.
- Confirm and mark the eye for injection.
- Apply topical anesthetic.
- Place the lid speculum.
- Apply povidone iodine directly over and surrounding the injection site (allowing sufficient time for the povidone iodine to dry).
- Locate the injection site 3.0–4.0 mm posterior to the limbus.
- Prepare the proper volume of drug to be injected.
- Inject the drug using a sterile 30-gauge needle into the vitreous cavity pointing toward the optic nerve via the pars plana.
- Remove the lid speculum, avoiding any excess pressure on the eye.
- Assess for any complications and confirm that the central artery is perfused using indirect ophthalmoscopy or confirmation of vision.
- Topical antibiotic can be provided at the discretion of the treating ophthalmologist.

TERAPIA INTRAVITREALE & CORTICOSTEROIDI

Triamcinolone acetonide (IV)

Fluocinolone acetonide (IMPIANTO)

Desametasone (IMPIANTO)

CORTICOSTEROIDI

Triamcinolone acetonide

Fluocinolone (drug delivery systems (DDSs) – non biodegradabile)

Dexamethasone ((drug delivery systems (DDSs) – non biodegradabile)

Dexametasone (drug delivery system (DDSs) – biodegradabile)

Riducono la iper-permeabilità vascolare

Inibiscono la produzione di VEGF

Potere anti-angiogenico; inibitore di ICAM e TNF; stabilizzatore della BER; antiedemigeno; anti-infiammatorio; anti-apoptotico

Risultati promettenti usando steroidi intravitreali per DME refrattario
Jonas 2001; Martidis 2002;

Triamcinolone acetonide Intravitreale (IVTA)

2002 DRCR Network (large series of clinical trials evaluating efficacy of different treatments for DME)

A Randomized Clinical Trial - Comparing Intravitreal Triamcinolone Acetonide and Focal/Grid Photocoagulation for Diabetic Macular Edema

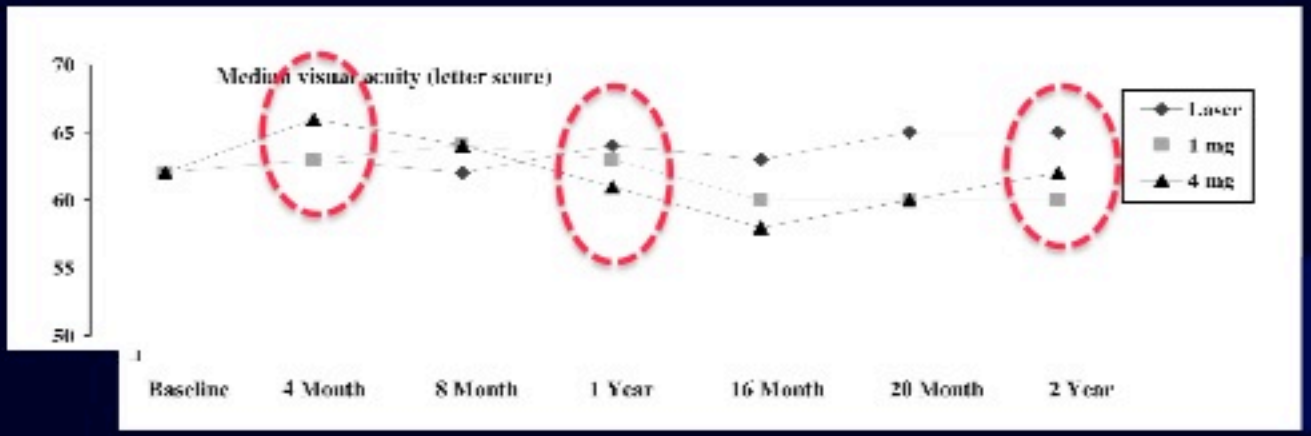
Ophthalmology. 2008. 115(9): 1447–1449,1449 e 1-10

840 occhi con EMD clinicamente significativo

Ritrattamento ogni 4 mesi per edema persistente o di nuova comparsa

2 years follow-up

Risultati AV



49% high IOP
84% cataract surgery

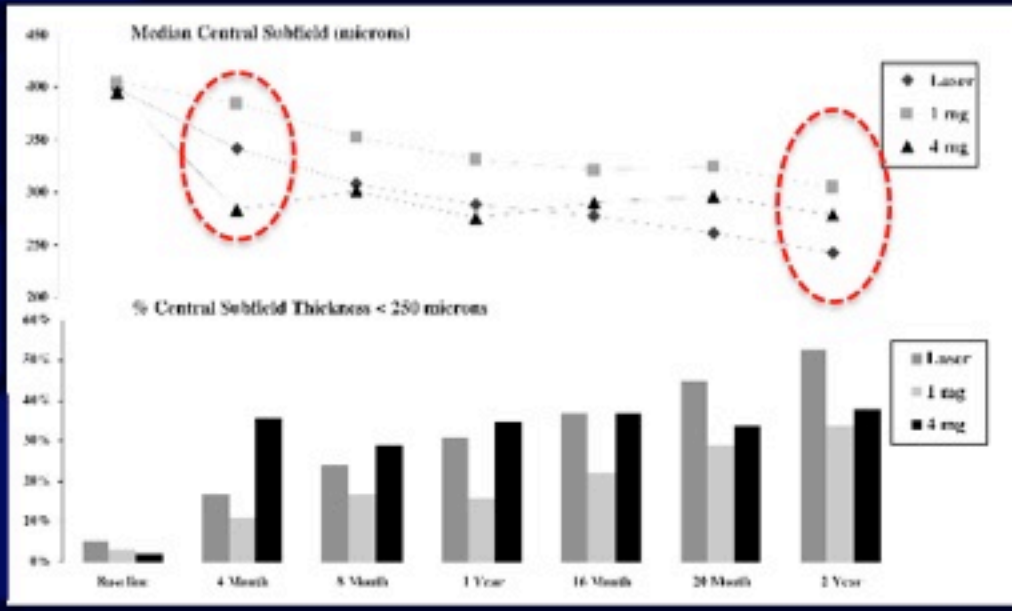
4 mesi
gruppo TA 4mg = AV media e CRT migliori

Risultati CRT

1 anno
no differenze significative fra i gruppi

2 anni
gruppo laser = AV media e CRT migliori

Risultati simili fra occhi fachici e pseudofachici



Triamcinolone acetonide Intravitreale (IVTA)

Diversi studi hanno cercato di valutare l'efficacia dell'IVTA in combinazione con laser focale/a griglia in confronto con solo laser o solo IVTA

Lam et al.
Avitabile et al.
Kang et al.
Terapia combinata più efficace rispetto alla monoterapia con IVTA o laser a breve termine ma nessuna differenza fra i vari gruppi a distanza di 2 anni

Recentemente
DRCR Network group
Phase III study
Nessuna differenza in termini di AV fra il gruppo di terapia combinata e il gruppo laser dopo 1 anno

Triamcinolone acetonide Intravitreale (IVTA) plus laser vs laser alone in DME

Mark C. Gillies et al. Ophthalmology 2011

Prospective, randomized, double-masked, placebo-controlled study

24 months

84 eyes

Combined group
BCVA >10 letters
36%
CRT no difference

Laser group
BCVA >10 letters
7%

Cataract 61%
Raised intraocular pressure 64%

COMPLICANZE IVTA

Ipertono oculare

- Alcuni report hanno evidenziato una serie di potenziali complicanze associate all'iniezione intravitreale di TA quali lo sviluppo di cataratta e la comparsa di ipertensione oculare, in genere legate all'uso di dosi di farmaco pari o superiori a 4 mg
- Roth et al. hanno evidenziato che un aumento della pressione intraoculare in pazienti trattati con TA è un reperto comune, particolarmente in soggetti giovani, con presistente glaucoma o responsivi agli steroidi. L' incidenza di occhi con una pressione intraoculare >25 mmHg era del 14.6%, 19.1%, 24.1%, e 28.2% rispettivamente a 6, 12, 18, e 24 mesi dall' iniezione. **Only 3 eyes (0.3%) required IOP-lowering surgery**

Roth DB, Verma V, Realini T, Prenner JL, Feuer WJ, Fechtner RD. Long-term incidence and timing of intraocular hypertension after intravitreal triamcinolone acetonide injection. Ophthalmology. 2009 Mar;116(3):455-60.

Yilmaz T, Weaver CD, Gallagher MJ, Cordero-Coma M, Cervantes-Castaneda RA, Klisovic D, Lavaque AJ, Larson RJ. Intravitreal triamcinolone acetonide injection for treatment of refractory diabetic macular edema: a systematic review. Ophthalmology. 2009 May;116(5):902-11; quiz 912-3. Review.

Conservanti & TA

Invest Ophthalmol Vis Sci. 2007 Jun;48(6):2792-8.

Cytotoxicity of triamcinolone acetonide on human retinal pigment epithelial cells.

Chang YS, Wu CL, Tseng SH, Kuo PY, Tseng SY.

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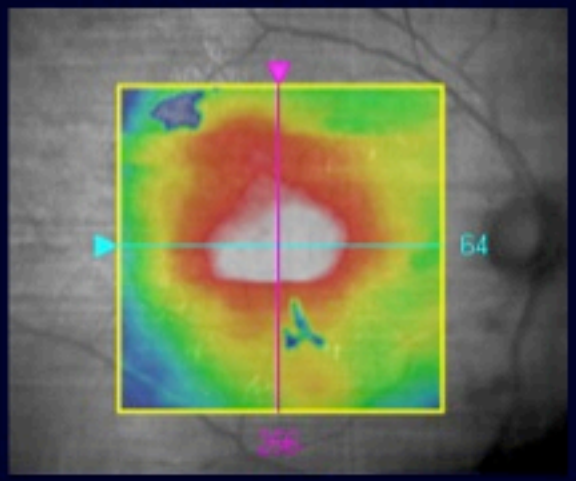
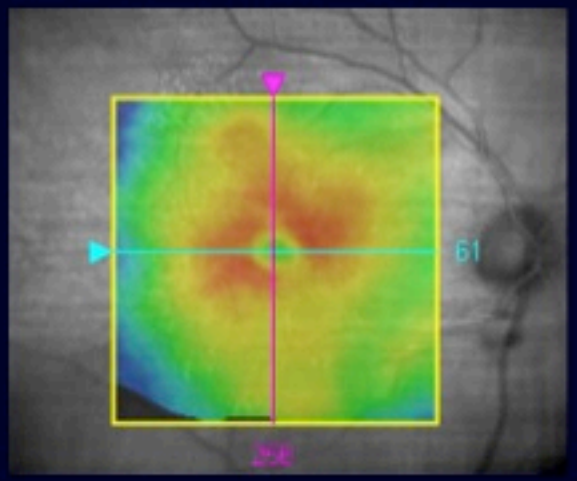
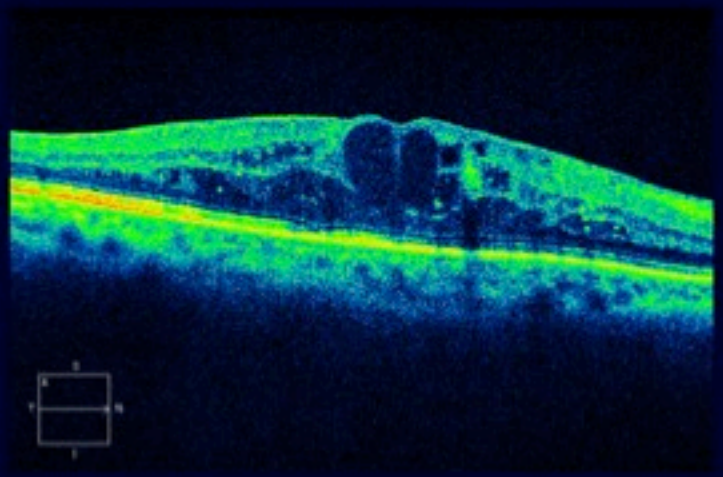
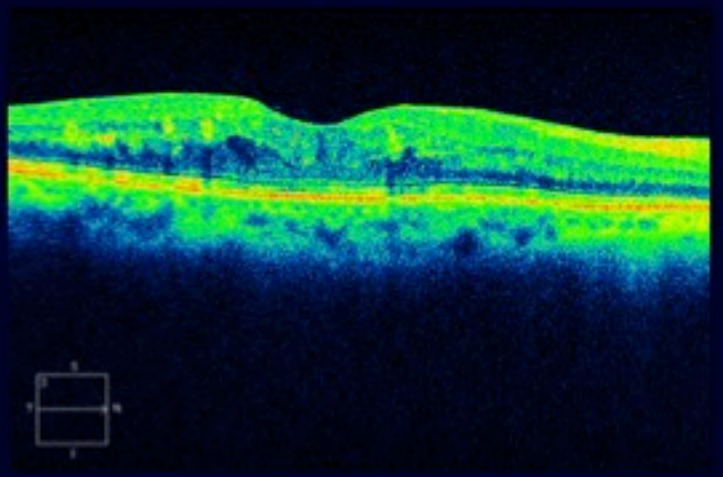
PURPOSE: To investigate the toxic effects of triamcinolone acetonide (TA) suspensions on human retinal pigment epithelial (RPE) cells. METHODS: Cultured human RPE cells were exposed for up to 2 hours to one of seven solutions: control (balanced salt solution, BSS; Alcon Laboratories, Ft. Worth TX), commercial TA suspension (cTA), cTA from which the vehicle (which contains the preservative benzyl alcohol) had been removed (vehicle-removed TA, -vTA), vehicle of the cTA (V), or a 1:10 dilution (in BSS; Alcon) of cTA, -vTA or V. Solution effects were evaluated by phase-contrast microscopy of cells stained in situ with trypan blue and in vitro by trypan blue exclusion assay. RPE cell function was assessed by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) assay. The mechanism of TA toxicity was studied by acridine orange-ethidium bromide staining and epifluorescence microscopy, and ultrastructural changes were examined by transmission electron microscopy (TEM). RESULTS: The effects of vehicle-removed solutions were similar to those of the control solution. Exposure for 1 hour or longer to a vehicle-containing solution (cTA and V) resulted in similar and significant degrees of cell damage that were dose and time dependent. The major mechanism of cell death was necrosis, and the early ultrastructural change was swelling of organelles in the cytoplasm. CONCLUSIONS: Preserved commercial TA suspensions damaged human RPE cells, but vehicle-free solutions did not. The authors suggest removing the vehicle as completely as possible from TA solutions before they are administered intravitreally. Furthermore, they recommend that a commercial formulation of preservative-free TA suspension be made available for intraocular use.

Risultati preliminari sull'efficacia dell'iniezione intravitreale di una nuova formulazione di triamcinolone acetonide senza conservanti (VITREAL® S) nella terapia dell' edema maculare diabetico refrattario.

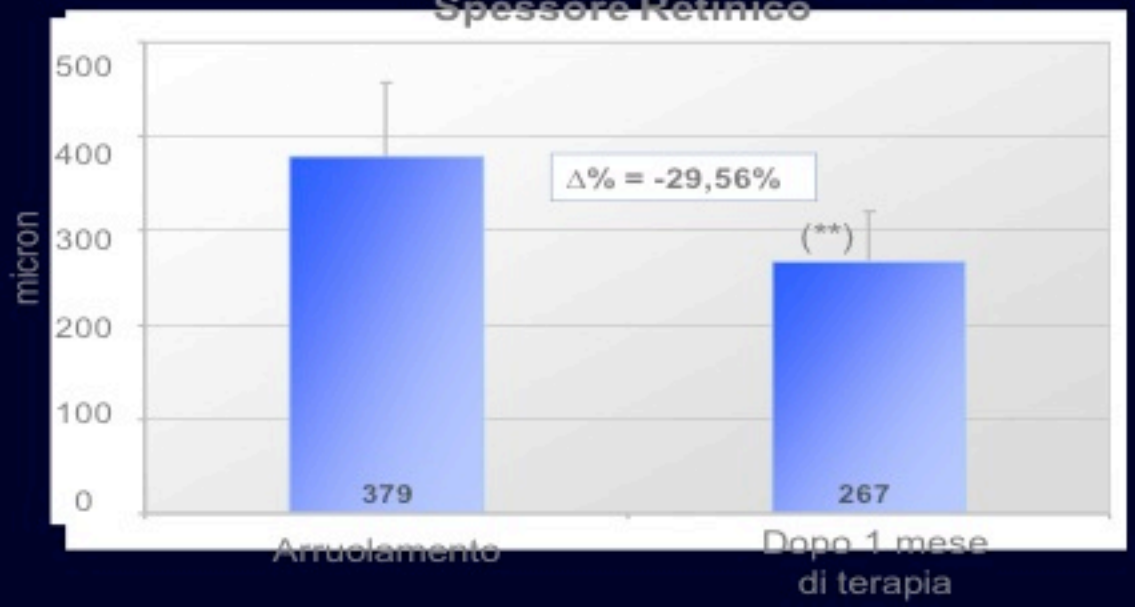






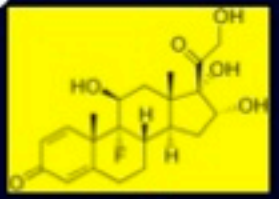


Risultati preliminari sull'efficacia dell'iniezione intravitreale di una nuova formulazione di triamcinolone acetonide senza conservanti (VITREAL® S) nella terapia dell' edema maculare diabetico refrattario.



Risultati preliminari sull'efficacia dell'iniezione intravitreale di una nuova formulazione di triamcinolone acetonide senza conservanti (VITREAL® S) nella terapia dell' edema maculare diabetico refrattario.

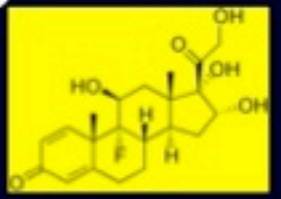
TA vs Bevacizumab in EMD



In conclusion, a single intravitreal injection of 4 mg TA appears to offer certain short-term advantages over IBe for the management of patients with **refractory DMO**, particularly with regard to CMT as measured by OCT. However, the visual results are grossly comparable, and the well-known toxicities of TA must be considered. Moreover, limitations inherent in the study's design, such as small sample size and limited length of follow-up, preclude extrapolation of our results. Finally, the potential benefits of TA or IBe, if any, over additional laser therapy for the management of refractory diffuse DMO remains to be determined, particularly in the long-term.

Intravitreal triamcinolone versus bevacizumab for treatment of refractory diabetic macular oedema (IBEME study);BJO 2008

TA vs Bevacizumab in EMD



Acta Ophthalmol. 2012 Feb;90(1):56-60. doi: 10.1111/j.1755-3768.2009.01817.x. Epub 2009 Dec 16.

Comparing intravitreal triamcinolone acetonide and bevacizumab injections for the treatment of diabetic macular oedema: a randomized double-blind study.

Isaac DL, Abud MB, Frantz KA, Rassi AR, Avila M.

Department of Ophthalmology, Federal University of Goias, Goiania, Brazil.

Abstract

PURPOSE: To compare the effect of a single intravitreal injection of triamcinolone acetonide and bevacizumab in reducing macular thickness, which was measured by optical coherence tomography (OCT) in patients with diabetic macular oedema (DMO). Methods: The patients received a single intravitreal injection of 1.25 mg bevacizumab in one randomly selected eye and 4.0 mg triamcinolone acetonide in the contralateral eye. Central foveal thickness measurement (CFT) with OCT was taken at the initial visit and at the 4-week, 12-week and 24-week visits.

RESULTS: Eleven patients (22 eyes) were enrolled and statistically analysed. CFT reduced in the eyes treated with triamcinolone and those treated with bevacizumab in weeks 4 and 12 ($p < 0.05$). At the 24-week follow-up, no significant difference was noted, relative to the initial visit. Comparing the two groups treated with different drugs, a statistically significant difference in CFT in weeks 4 and 12 was noted, with a more significant reduction in triamcinolone-treated eyes ($p < 0.05$). Regarding visual acuity (VA), patients treated with triamcinolone had improvement in VA at 4-week ($p = 0.02$) and 12-week follow-up ($p = 0.01$), while the group treated with bevacizumab had VA improvement at 4 -week follow-up ($p = 0.02$). Among the eyes treated with triamcinolone, intraocular pressure (IOP) measurement of more than 21 mmHg was found in three eyes (27.3%).

CONCLUSIONS: Intravitreal triamcinolone proved to be more efficient in reducing DMO, providing longer lasting visual improvement, relative to bevacizumab. Eyes treated with triamcinolone had the highest percentage increase in IOP. Further studies are needed to corroborate these findings.

VANTAGGI IMPIANTO A LENTO RILASCIO

- rilascio controllato del principio attivo
- minori complicanze legate alle ripetute iniezioni intravitreali
- maggiore compliance paziente

IMPIANTO IDEALE

- Rilascio omogeneo, senza picchi indesiderati
- Facilità di impianto e stabilità dello stesso
- Assenza di effetti tossici nei confronti del principio attivo e dei composti del sistema
- Biodegradabilità (finalizzata ad evitare l'espianto del sistema)

DDSs non biodegradabili

RETISERT ® (Bausch & Lomb) → FLUOCINOLONE acetonide

ILUVIEN ® (Alimera Sciences) → FLUOCINOLONE acetonide

I-VATION ™ (SurModics) → TRIAMCINOLONE acetonide

Rimozione chirurgica quando il farmaco finisce

Aumentato rischio di complicazioni (DR, emovitreo, endoftalmite)

L'impianto necessita incisione e sutura

DDSs non biodegradabili

RETISERT ® (Bausch & Lomb) → FLUOCINOLONE acetonide

Clinical trials.gov. Efficacy of Fluocinolone Acetonide Intravitreal Implant in Diabetic Macular Edema. Phase III
Dopo 3 anni → 27,6% gain >3 linee retisert vs 14,5% standard care
MA !!! 80-90% cataratta e 20% chirurgia filtrante per ipertono
Approvato dal FDA per le UVEITI (0,59 µg/day)

ILUVIEN ® (Alimera Sciences) → FLUOCINOLONE acetonide

Iuvien, an innovative treatment for diabetic Macular Edema. Alimera Sciences.
FAME study (1000 pazienti)
Dopo 2 anni → 26% guadagno >15 letters; 7% ipertono → chirurgia filtrante
In attesa di approvazione

I-VATION ™ (Sur Modics) →TRIAMCINOLONE acetonide

Trial phase I appena terminato

Clinical Trials. gov. A Study of MK0140 in Diabetic Patients With Macular Edema.

DDSs biodegradabili

OZURDEX ® /Allergan Inc, Irvine, California

Novel, biodegradable, sustained-release drug delivery system for 6 months
Marketed as OZURDEX (DEXAMETHASONE DDS)

Approved by the US FDA for the treatment of ME following retinal vein occlusion (RVO) and uveitis

20-gauge pars plana injection
Dimension 6,5mm x 0,45m
Sutureless
No surgical removal

DDSs biodegradabile

Randomized Controlled Trial of an Intravitreous Dexamethasone Drug Delivery System in Patients With Diabetic Macular Edema

Julia A. Haller; Baruch D. Kuppermann et al. Arch Ophthalmol 2011;128(3):289-296

INCLUSION CRITERIA

ME only secondary to diabetic retinopathy

>12 years old

Persistent edema >90 days after laser or medical therapy

BCVA 20/40 – 20/200

EXCLUSION CRITERIA

BCVA<20/200

History of vitrectomy surgery

Use of systemic, periocular or intraocular corticosteroids within 30 days of enrollment

Poorly controlled hypertension and diabetes

DDSs biodegradabile

Primary outcome
- Proportion of eyes achieving 10 letters improvement at day 90

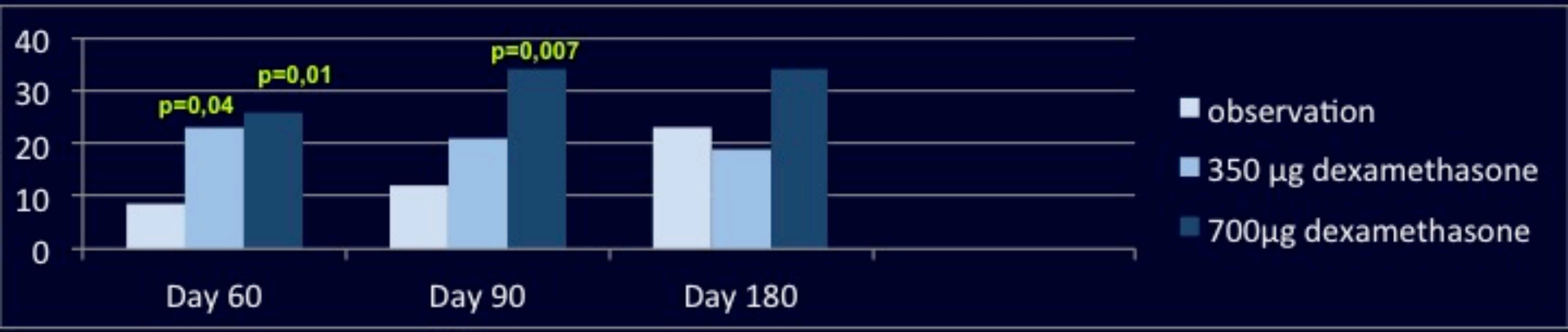
Secondary outcomes
- Proportion of eyes achieving 15 letters improvement at day 90
- Proportion of eyes achieving 2-3 grade improvement in fluorescein angiographic leakage
- Change in CRT using OCT
- Safety

Patients evaluated at baseline and days 1, 7, 30, 60, 90 and 180.
FA and OCT performed at baseline and days 30 and 90

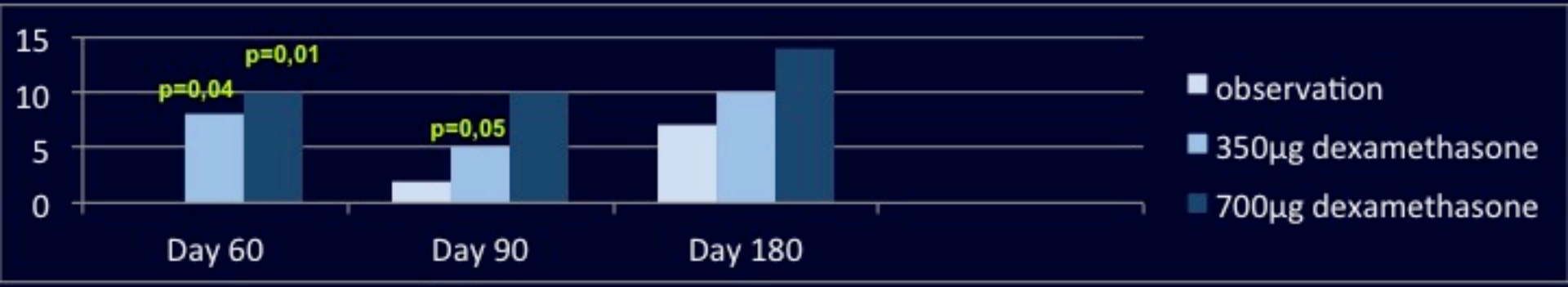
DDSs biodegradabile

92% of patients completed the day 90 study visit - 89% of patients completed the day 180 study visit

Differences between the 700 and 350 dexamethasone DDS groups were not statistically significant



≥10 letters



≥15 letters

DDSs biodegradabile

Statistically improvement in both CRT and fluorescein leakage in eyes received 700µg dexamethasone DDS compared to the observation group

Side effects

No significant difference in the number of cataract among the study groups

IOP>25 mmHg at day 90
7,5% in the 700µg dexamethasone
12,7% in the 350µg dexamethasone
0 in the observation group

Single occurences
Successfully managed with observation or topical IOP lowering medication
No surgical intervention

STEROIDI per via intravitreale

Authors concluded
In eyes with persistent ME due to DR, treatment with the 700µg of dexamethasone DDS is well tolleerated and significantly ($p<0,05$ at day 90) improves BCVA, CRT and fluorescein leakage compared to observation

Haller JA, Kuppermann BD, Blumenkranz MS, et al. Randomized controlled trial of an intravitreous dexamethasone drug delivery system in patients with diabetic macular edema. Arch Ophthalmol 2010

Same efficacy across patients with DME regardless of the pattern of ME (focal, cystoid, diffuse, cystoid/diffuse)

Kuppermann BD, Chou C, Weinberg DV, et al. Intravitreous dexamethasone effects on different patterns of diabetic macular edema. Arch Ophthalmol 2010

Dexamethasone DDS is well tollerated and safe; sutureless intravitreal placement

Haller JA, Dugel P, Weinberg DV, et al. Evaluation of the safety and performance of an applicator for a novel intravitreal dexamethasone drugs delivery system for the treatment of macular edema. Retina 2009

IV Ozurdex

Ophthalmologica. 2012;228(2):117-22. Epub 2012 Feb 3.

Intravitreal dexamethasone implant in patients with persistent diabetic macular edema.

Zucchiatti I, Lattanzio R, Querques G, Querques L, Del Turco C, Cascavilla ML, Bandello F.
Department of Ophthalmology, University Scientific Institute San Raffaele, Milan, Italy.

Abstract

Purpose: To evaluate the effects of a single injection of Ozurdex over 6 months in eyes with persistent diabetic macular edema (DME). Methods: In this retrospective interventional study, 9 patients with decreased visual acuity, as a result of persistent DME, received Ozurdex (intravitreal dexamethasone implant 0.7 mg). Main outcome measures included changes in best-corrected visual acuity (BCVA) and central retinal thickness (CRT). Results: Nine eyes of 9 patients (5 males, 4 females; mean age 58 years) were included in the analysis. The mean duration of DME was 49.9 months (range 24-85). All patients had undergone previous treatments for DME (intravitreal injection of anti-vascular endothelial growth factor, steroids or laser photocoagulation) before entering the study. At baseline, the mean BCVA was 0.74 ± 0.33 logMAR, and the mean CRT was 502 ± 222.16 μm. The mean BCVA was unchanged on the third day (0.74 ± 0.38 logMAR, p = 0.5), improved to 0.62 ± 0.32 logMAR (p = 0.02), 0.59 ± 0.26 logMAR (p = 0.02) and 0.63 ± 0.38 logMAR (p = 0.6) after the first, third and fourth months, respectively, and decreased again to 0.73 ± 0.35 logMAR (p = 0.4) at 6 months. The mean CRT improved to 397 ± 115.31 μm (p = 0.17), 271 ± 99.97 μm (p = 0.007), 325 ± 133.05 μm (p = 0.03) and 462 ± 176.48 μm (p = 0.36) on the third day and after 1, 3 and 4 months of follow-up and then increased again to 537 ± 265.42 μm (p = 0.33) at 6 months. Eight patients needed retreatments in the sixth month. One eye developed a transient intraocular pressure (IOP) increase 1 month after injection, which was successfully managed with topical IOP-lowering medication. Conclusion: In eyes with persistent DME, Ozurdex produces improvement in BCVA and CRT as soon as the first days after the injection. Such improvement is maintained until the fourth month.

STEROIDI per via intravitreale

Necessario dimostrare efficacia a lungo termine e in combinazione ad altri trattamenti

Trials ongoing

Results in 2014

2 Controlled, double-masked study

- To determine efficacy and safety of 350 and 700 dexamethasone DDS against sham control over 3 years

- To determine efficacy of the intravitreal implant in combination with laser treatment versus laser alone

Terapia anti-VEGF nell'edema maculare diabetico

VEGF-A

- principale fattore di permeabilità vascolare
- maggior stimolo angiogenico
- interazione con tutti i sottotipi di cellule infiammatorie, monociti, piastrine, contribuendo all'infiammazione locale

TERAPIA INTRAVITREALE & ANTI VEGF

Ranibizumab (Lucentis)

Bevacizumab (Avastin)

Pegaptanib (Macugen)

Vegf trap-Eye Aflibercept (Eylea)

Anti-VEGF per via intravitreale

Ranibizumab (Lucentis®, Novartis)

Pegaptanib sodium (Macugen, OSI Eyetech)

VEGF trap-Eye Aflibercept (Eylea, Regeneron/Bayer)

Bevacizumab (Avastin, Genentech/Roche)

- Framento di Ab umanizzato; tutte le isoforme del VEGF-A; fabbricato solo per uso IV
- Approvato FDA per AMD neovascolare e EM 2° a OVR
- Approvato per EMD refrattario

Studi iniziali...

Chun et al Ophthalmology 2006

First pilot study

10 pazienti con CSME

2 dosing regimens of ranibizumab:

5 patients 0,3mg + 5 patients 0,5mg at baseline, 1 and 2 months

Follow-up 24 months

At month 3 → ACUITA' VISIVA

40% gain > 15 letters

50% gain > 10 letters

80% gain of at least 1 letter in BCVA

Mean decrease in CRT →

low-dose group: 45,3micron

high-dose group: 197,8micron

Nguyen QD. Am J Ophthalmol. 2006

Trial clinico prospettivo, non randomizzato

10 pazienti

0,5 mg ranibizumab

al baseline, a 1, 2, 4 e 6 mesi

Miglioramento significativo dell' AV media pari a 12,3 lettere

Significativa riduzione del CRT da 503 a 257 micron al 7° mese (riduzione del 85% dal baseline)

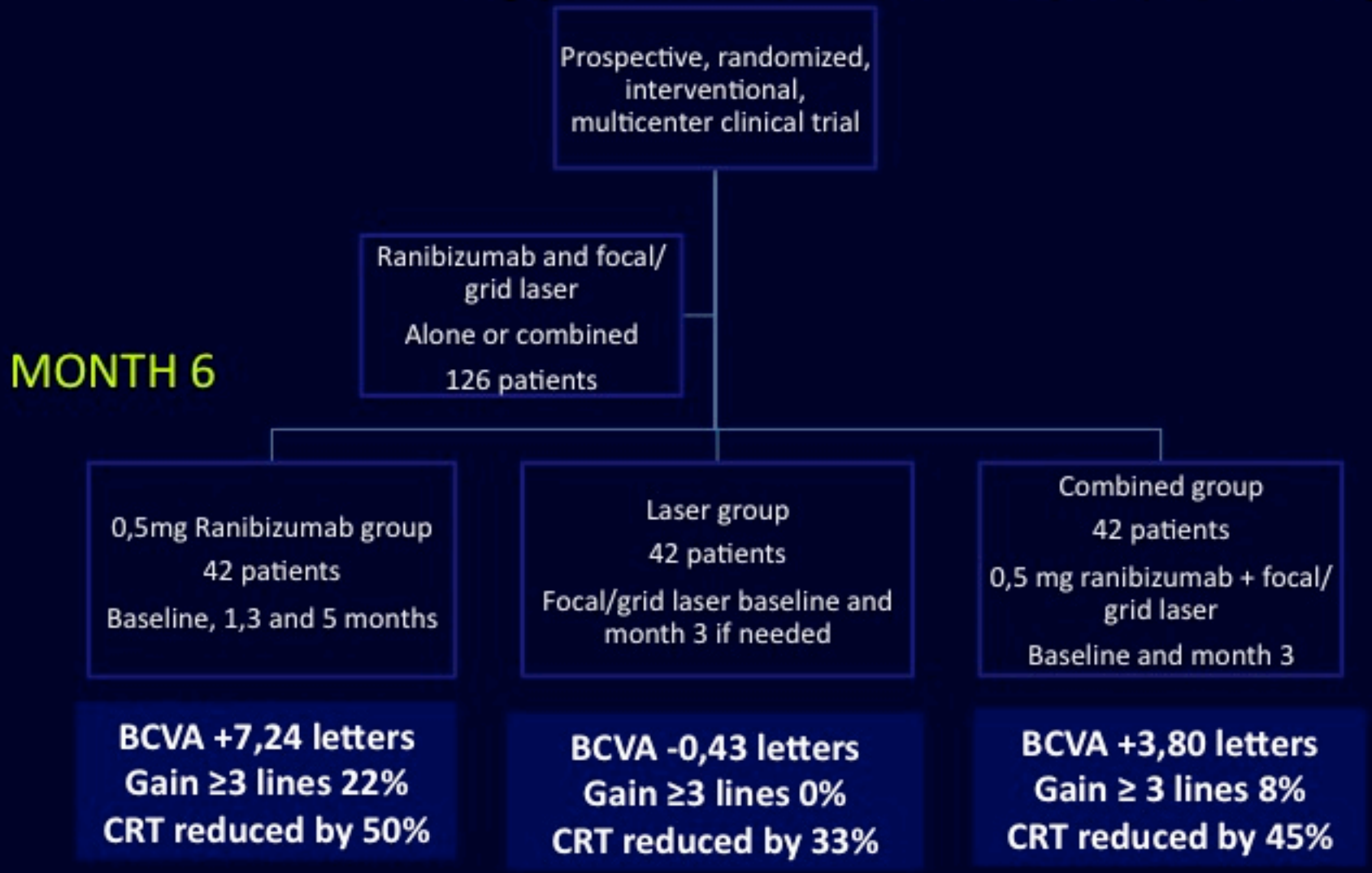
9° mese: peggioramento dell'edema maculare;

READ-2 Phase I-II	Ranibizumab 0,5mg vs laser vs combination	At month 24 Letters gained 7,70 vs 5,10 vs 6,80 % gaining 3 lines 24 vs 18 vs 26
RISE Phase III	Lucentis 0,3mg vs Lucentis 0,5mg vs Sham	% gaining 3 lines 39 vs 44,8 vs 18
RIDE Phase III	Lucentis 0,3mg vs Lucentis 0,5mg vs Sham	% gaining 3 lines 33 vs 45,7 vs 12
RESOLVE Phase II 1 year	Ranibizumab 0,3-0,6 mg Ranibizumab 0,5-1 mg Sham	Letters gained 10,3 vs 6,4 vs -1,4 Mean CRT reduction -194 vs 187 vs 48
RESTORE Phase III	Ranibizumab 0,5mg Ranibizumab e Laser Laser alone	% gaining 3 lines 22,6 vs 22,9 vs 8,2 Mean CRT reduction 118 vs 128 vs 61
DRCR.net Phase III	Sham + prompt laser Ranibizumab + prompt laser Ranibizumab + deferred laser Triamcinolone + prompt laser	Letters gained 3 vs 9 vs 9 vs 4 Mean CRT reduction 102 vs 131 vs 137 vs 127

READ-2 study

Primary End Point (Six Months) Results of the Ranibizumab for Edema of the Macula in diabetes.

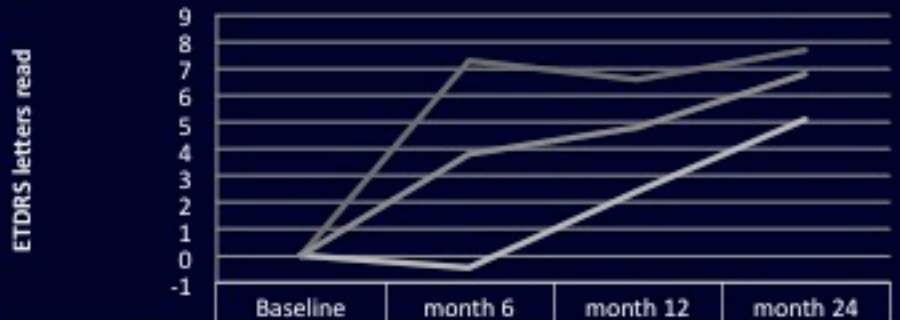
Nguyen QD, Shah SM, et al. READ-2 Study Group. Ophthalmology. 2009



Ranibizumab is effective in the treatment of recurrent and persistent DME

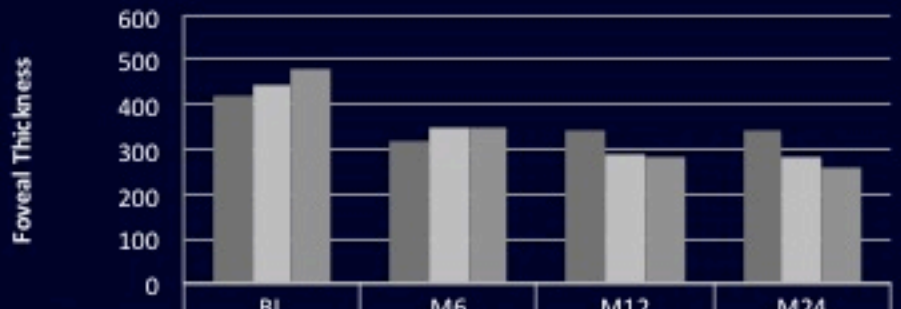
Improvement maintained during a follow-up of 2 years

mean BCVA



	Baseline	month 6	month 12	month 24
RBZ	0	7,24	6,61	7,7
LASER	0	-0,43	2,39	5,1
RBZ+LASER	0	3,8	4,81	6,8

mean foveal thickness

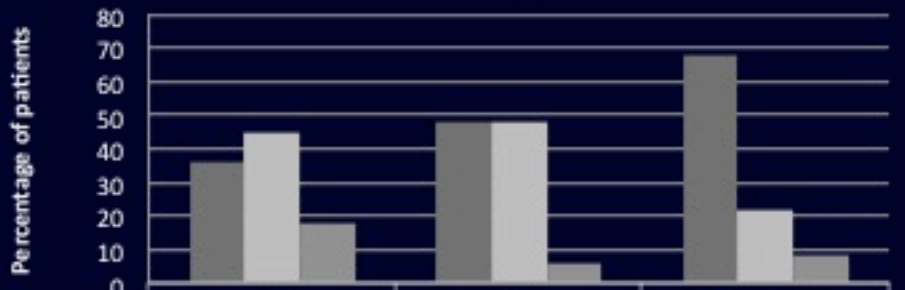


	BL	M6	M12	M24
RBZ	420	320	340	340
LASER	440	350	290	280
RBZ+LASER	480	350	280	260

REDUCED FREQUENCY OF INJECTIONS IN THE COMBINED GROUP

2,9 vs 9,3 RBZ group vs 4,4 Laser group)

Foveal Thickness at Month 24



	RBZ	LASER	RBZ+LASER
<250	36	48	68
250-500	45	48	22
>500	18	6	8

HbA(1c) & DME

J Diabetes Complications. 2011 Sep-Oct;25(5):298-302. Epub 2010 Nov 13.

Glucose regulation influences treatment outcome in ranibizumab treatment for diabetic macular edema.

Ozturk BT, Kerimoglu H, Adam M, Gunduz K, Okudan S.

Department of Ophthalmology, Meram Faculty of Medicine, Selcuk University, Konya, Turkey. ozturkbanuturgut@yahoo.com

Abstract

PURPOSE: To evaluate the effect of glucose regulation on intravitreal ranibizumab injection for clinically significant diabetic macular edema (DME).

METHODS: This retrospective study enrolled 65 eyes of 65 patients with persistent DME treated with intravitreal ranibizumab injection. The main outcome measures were the change in best corrected visual acuity (BCVA), the central subfield macular thickness (CSMT) recorded with optical coherence tomography (OCT), and its correlation with the serum hemoglobin A(1c) values (HbA(1c)).

RESULTS: The study included 24 (36.9%) female and 41 (63.1%) male patients with a mean age of 58.90±9.45 years. The mean HbA(1c) of the enrolled patients was 8.25±1.74% (range 5.7-12.7%). The median value of BCVA at baseline examination was 20/80 (52 letters), and the median CSMT was 468 μm (range 255-964 μm). In the final control after 4-6 weeks following injection, the median value of BCVA increased to 20/50 (59.50 letters) and the median CSMT decreased to 310 μm (range 129-652 μm). This change in BCVA and macular thickness was found to be significant ($P<.001$ for both). There was no correlation between BCVA and the change in macular thickness (coefficient=0.04, $P=.78$). The serum HbA(1c) values were found to be negatively correlated with the change in CSMT (coefficient=-0.50, $P<.001$).

CONCLUSIONS: The results of intravitreal ranibizumab injection for DME demonstrated a beneficial effect on visual acuity and a decrease in CSMT which is inversely correlated with the serum HbA(1c) level.

JAMA Ophthalmol. 2013 Feb;131(2):139-45.

Ranibizumab for edema of the macula in diabetes study: 3-year outcomes and the need for prolonged frequent treatment.

Do DV, Nguyen QD, Khwaja AA, Channa R, Sepah YJ, Sophie R, Hafiz G, Campochiaro PA; READ-2 Study Group. Collaborators (101)

- **OBJECTIVE:**
- To assess the benefit of increased follow-up and treatment with ranibizumab between months 24 and 36 in the Ranibizumab for Edema of the Macula in Diabetes (READ-2) Study.
- **DESIGN:**
- Prospective, interventional, multicenter follow-up of a randomized clinical trial.
- **METHODS:**
- Patients who agreed to participate between months 24 and 36 (ranibizumab, 28 patients; laser, 22; and ranibizumab + laser, 24) returned monthly and received ranibizumab, 0.5 mg, if foveal thickness (FTH, center subfield thickness) was 250 µm or greater. Main outcome measures were improvement in best-corrected visual acuity (BCVA) and reduction in FTH between months 24 and 36.
- **RESULTS:**
- Mean improvement from the baseline BCVA in the ranibizumab group was 10.3 letters at month 36 vs 7.2 letters at month 24 (ΔBCVA letters = 3.1, P = .009), and FTH at month 36 was 282 µm vs 352 µm at month 24 (ΔFTH = 70 µm, P = .006). Changes in BCVA and FTH in the laser group (-1.6 letters and -36 µm, respectively) and the ranibizumab + laser group (+2.0 letters and -24 µm) were not statistically significant. The mean number of ranibizumab injections was significantly greater in the ranibizumab group compared with the laser group (5.4 vs 2.3 injections, P = .008) but not compared with the ranibizumab + laser group (3.3, P = .11).
- **CONCLUSIONS:**
- More aggressive treatment with ranibizumab during year 3 resulted in a reduction in mean FTH and improvement in BCVA in the ranibizumab group. More extensive focal/grid laser therapy in the other 2 groups may have reduced the need for more frequent ranibizumab injections to control edema.
- **APPLICATION TO CLINICAL PRACTICE:**
- Long-term visual outcomes for treatment of diabetic macular edema with ranibizumab are excellent, but many patients require frequent injections to optimally control edema and maximize vision.

Ophthalmology. 2013 Oct;120(10):2004-12. doi: 10.1016/j.ophtha.2013.02.019. Epub 2013 May 29.

Two-Year Safety and Efficacy of Ranibizumab 0.5 mg in Diabetic Macular Edema: Interim Analysis of the RESTORE Extension Study.

Lang GE, Berta A, Eldem BM, Simader C, Sharp D, Holz FG, Sutter F, Gerstner O, Mitchell P; RESTORE Extension Study Group.

- **OBJECTIVE:**
- To evaluate the 2-year safety and efficacy of ranibizumab 0.5 mg in diabetic macular edema (DME).
- **DESIGN:**
- Twenty-four-month, open-label, multicenter, Phase IIIb extension study.
- **PARTICIPANTS:**
- Two hundred forty of 303 patients with visual impairment due to DME who completed the RESTORE core study and entered the extension.
- **METHODS:**
- All patients were eligible to receive ranibizumab 0.5 mg pro re nata (PRN) from month 12 (end of core study) to month 36 based on best-corrected visual acuity (BCVA) stability and disease progression retreatment criteria. Patients were also eligible to receive laser PRN according to Early Treatment Diabetic Retinopathy Study guidelines. A preplanned interim analysis was performed at month 24, stratifying by treatment groups as in the RESTORE core study and referred to as prior ranibizumab, ranibizumab plus laser, or laser groups in the extension.
- **MAIN OUTCOME MEASURES:**
- Incidence of ocular and nonocular adverse events (AEs) and mean change in BCVA.
- **RESULTS:**
- Two hundred twenty patients (92%) completed the month 24 visit. Over 2 years, the most frequent ocular serious AE (SAE) and AE were cataract (2.1%) and eye pain (14.6%), respectively. The main nonocular AEs were nasopharyngitis (18.8%) and hypertension (10.4%). There were no cases of endophthalmitis, and the incidences of nonocular SAEs were low. Of the patients entering the extension, 4 deaths were reported in the second year, none of which were related to study drug or procedure. Mean BCVA gain, central retinal thickness (CRT) decrease, and National Eye Institute Visual Functioning Questionnaire-25 (NEI VFQ-25) composite score observed at month 12 were maintained at month 24 (prior ranibizumab: +7.9 letters, -140.6 μm, and 5.6, respectively; prior ranibizumab plus laser: +6.7 letters, -133.0 μm, and 5.8, respectively), with an average of 3.9 (prior ranibizumab) and 3.5 ranibizumab injections (prior ranibizumab plus laser). In patients treated with laser alone in the core study, the mean BCVA, CRT, and NEI VFQ-25 composite score improved from month 12 to month 24 (+5.4 letters, -126.6 μm, and 4.3, respectively), with an average of 4.1 ranibizumab injections.
- **CONCLUSIONS:**
- Ranibizumab 0.5 mg administered according to prespecified visual stability and disease progression criteria was well tolerated, with no new safety concerns identified over 2 years. Overall, an average of 3.8 ranibizumab injections was sufficient to maintain (prior ranibizumab) or improve (prior laser) BCVA, CRT, and NEI VFQ-25 outcomes through the second year.

Anti–Vascular Endothelial Growth Factor Pharmacotherapy for Diabetic Macular Edema

A Report by the American Academy of Ophthalmology

Allen C. Ho, MD, Ingrid U. Scott, MD, MPH, Stephen J. Kim, MD, Gary C. Brown, MD, MBA, Melissa M. Brown, MD, MBA, Michael S. Ip, MD, Franco M. Recchia, MD

Objective: To review the evidence regarding the safety and efficacy of current anti–vascular endothelial growth factor (VEGF) pharmacotherapies for the treatment of diabetic macular edema (DME).

Methods: Literature searches last were conducted in September 2011, in PubMed with no date restrictions, limited to articles published in English, and in the Cochrane Library without a language limitation. The combined searches yielded 532 citations, of which 45 were deemed clinically relevant for the authors to review in full text and to assign ratings of level of evidence to each of the selected studies with the guidance of the panel methodologists.

Results: At this time, there are 5 studies that provide level I evidence for intravitreal ranibizumab, alone or in combination with other treatments for DME. There is also 1 study that provides level I evidence for intravitreal pegaptanib sodium for DME. Nine studies reviewed were rated as level II, and 2 additional studies reviewed were graded as level III. Most studies do not provide information about long-term results (i.e., more than 2 years of follow-up) or the comparative efficacy of anti-VEGF pharmacotherapies.

Conclusions: Review of the available literature indicates that anti-VEGF pharmacotherapy, delivered by intravitreal injection, is a safe and effective treatment over 2 years for DME. Further evidence is required to support the long-term safety of these pharmacotherapies and their comparative efficacy.

Financial Disclosure(s): Proprietary or commercial disclosure may be found after the references.
Ophthalmology 2012;xx:xxx

Table 1. Randomized Study Results (Level I Evidence) of Intravitreal Anti–Vascular Endothelial Growth Factor Therapy (Ranibizumab and Pegaptanib) for Diabetic Macular Edema

Author(s), Year	Purpose	Study Design	No. of Eyes or Patients	Outcomes Measures	Treatment Regimen	Duration of Study	Results
DRCR,[15] 2010 and Ehman et al,[16] 2011 (DRCR)	IVR plus prompt or deferred laser or IVT plus prompt laser	Randomized, prospective, multicenter	854 eyes of 691 patients	BCVA; CST	(A) 0.5 mg IVR plus prompt laser; (B) 0.5 mg IVR plus deferred laser (>24 wks); (C) 4 mg IVT plus prompt laser; (D) sham injection plus prompt laser	2 yrs	Mean VA letter improvement at 1 yr: (A) +9±1, P<0.001; (B) +9±12, P<0.001; (C) +4±13, P = 0.31; (D) +3±13. Mean VA letter improvement at 2 yrs compared with (D): (A) +3.7 (95% aCI, −0.4 to +7.7; P = 0.03); (B) +5.8 (95% aCI, +1.9 to +9.8; P<0.001); (C) −1.5 (95% aCI, −5.5 to +2.4; P = 0.35).
Mitchell et al,[17] 2011 (RESTORE)	IVR vs. focal/grid laser vs. combination for DME	Randomized, prospective, multicenter	345 patients	BCVA, foveal thickness	(A) 0.5 mg IVR monthly ×3 then PRN + sham laser; (B) 0.5 mg IVR monthly ×3 then PRN + laser; (C) sham injections + laser	12 mos	VA better for (A) and (B) from mos 1 to 12 compared with (C); 12-mo VA: (A) +6.1 letters, (B) +5.9 letters, (C) +0.8 letters (both P<0.0001); BCVA 20/40 or better: (A) 53%, (B) 44.9%, (C) 23.6%. No significant differences between (A) and (B) at 12 mos.
Googe et al,[18] 2011 (DRCR)	IVR or IVT in eyes receiving focal/grid laser for DME and PRP at 14 wks	Randomized, prospective, multicenter	345 eyes	BCVA, CRT	(A) Sham injection; (B) 0.5 mg IVR at baseline and 4 wks; (C) 4 mg IVT at baseline and sham at 4 wks. All eyes received focal/grid laser for DME and PRP for PDR.	14 wks	Mean changes in BCVA better in (B) (+1±11; P<0.001) and (C) (+2±11; P<0.001) as compared with (A) (−4±14). The differences were not maintained at 56 wks.
RISE Trial,[19] 2012	IVR for DME	Phase III, randomized, sham-controlled, multicenter	377 patients	BCVA	(A) 0.3mg IVR; (B) 0.5 mg IVR; (C) sham injection. All given monthly injections ×24 mos and with rescue laser available at 3 mos.	2 yrs	Improvement of ≥15 letters at 2 yrs: (A) 44.8% (56/125), (B) 39.2% (49/125), and (C) 18.1% (23/127). Statistically significant for both (A) and (B) compared with (C) at P<0.0001 and P<0.0002, respectively.
RIDE Trial,[19] 2012	IVR for DME	Phase III, randomized, sham-controlled, multicenter	382 patients	BCVA	(A) 0.3 mg IVR; (B) 0.5 mg IVR; (C) sham injection. All given monthly	2 yrs	Improvement of ≥15 letters at 2 yrs: (A) 33.6% (42/125), (B) 45.7% (58/127), and (C) 12.3% (16/130).

Author(s), Year	Purpose	Study Design	No. of Eyes or Patients	Outcomes Measures	Treatment Regimen	Duration of Study	Results
Sultan,[20] 2011	IVP for DME	Phase II/III randomized, sham-controlled, multicenter	260 patients	BCVA, CRT	(A) 0.3 mg IVP or (B) sham injections at baseline and every 6 wks in yr 1 and focal/grid laser beginning at wk 18. In yr 2, (A) 0.3 mg IVP or (B) sham up to every 6 wks PRN.	2 yrs	Improvement of ≥10 letters at 54 wks: (A) 36.8% and (B) 19.7% ($P = 0.0047$). BCVA letters gained at wk 102: (A) 6.1 letters and (B) 1.3 letters ($P<0.01$). No significant difference in CRT decrease at 54 and 102 wks between (A) and (B).

aCI = confidence interval adjusted for multiple comparison; BCVA = best-corrected visual acuity; CRT = central retinal thickness; CST = central subfield thickness; DME = diabetic macular edema; DRCR = Diabetic Retinopathy Clinical Research Network; IVB = intravitreal bevacizumab; IVP = intravitreal pegaptanib; IVR = intravitreal ranibizumab; IVT = intravitreal triamcinolone; logMAR = logarithm of minimum angle of resolution; LPC = laser photocoagulation; PDR = proliferative diabetic retinopathy; PRP = panretinal photocoagulation; VA = visual acuity.

Anti-VEGF per via intravitreale

Ranibizumab (Lucentis®, Novartis)

Pegaptanib sodium (Macugen, OSI Eyetech)

VEGF trap-Eye Aflibercept (Elya Regeneron/Bayer)

Bevacizumab (Avastin, Genentech/Roche)

- Ab umanizzato; la isoforma 168 del VEGF-A; fabbricato solo per uso IV;
- Approvato FDA per AMD neovascolare
- Per EMD in corso di studio
- Phase III 260 patients
- Dopo 54 settimane: 37% gain >2 linee BCVA vs 20% sham

Ophthalmology. 2011 Jun;118(6):1107-18. Epub 2011 May 6.

A phase 2/3, multicenter, randomized, double-masked, 2-year trial of pegaptanib sodium for the treatment of diabetic macular edema.

Sultan MB, Zhou D, Loftus J, Dombi T, Ice KS; Macugen 1013 Study Group.

⊕ Collaborators (140)

Pfizer Inc, New York, New York 10017, USA. marla.b.sultan@pfizer.com

Abstract

PURPOSE: To confirm the safety and compare the efficacy of intravitreal pegaptanib sodium 0.3 mg versus sham injections in subjects with diabetic macular edema (DME) involving the center of the macula associated with vision loss not due to ischemia.

DESIGN: Randomized (1:1), sham-controlled, multicenter, parallel-group trial.

PARTICIPANTS: Subjects with DME.

INTERVENTION: Subjects received pegaptanib 0.3 mg or sham injections every 6 weeks in year 1 (total = 9 injections) and could receive focal/grid photocoagulation beginning at week 18. During year 2, subjects received injections as often as every 6 weeks per prespecified criteria.

MAIN OUTCOME MEASURES: The primary efficacy endpoint was the proportion gaining ≥ 10 letters of visual acuity (VA) from baseline to year 1. Safety was monitored throughout.

RESULTS: In all, 260 (pegaptanib, n = 133; sham, n = 127) and 207 (pegaptanib, n = 107; sham, n = 100) subjects were included in years 1 and 2 intent-to-treat analyses, respectively. A total of 49 of the 133 (36.8%) subjects from the pegaptanib group and 25 of the 127 (19.7%) from the sham group experienced a VA improvement of ≥ 10 letters at week 54 compared with baseline (odds ratio [OR], 2.38; 95% confidence interval, 1.32-4.30; P = 0.0047). For pegaptanib-treated subjects, change in mean VA from baseline by visit was superior (P<0.05) to sham at weeks 6, 24, 30, 36, 42, 54, 78, 84, 90, 96, and 102. At week 102, pegaptanib-treated subjects gained, on average, 6.1 letters versus 1.3 letters for sham (P<0.01). Fewer pegaptanib- than sham-treated subjects received focal/grid laser treatment (week 54, 31/133 [23.3%] vs 53/127 [41.7%], respectively, P = 0.002; week 102, 27/107 [25.2%] vs 45/100 [45.0%], respectively, P = 0.003). The pegaptanib treatment group showed significantly better results on the National Eye Institute-Visual Functioning Questionnaire than sham for subscales important in this population. Pegaptanib was well tolerated; the frequencies of discontinuations, adverse events, treatment-related adverse events, and serious adverse events were comparable in the pegaptanib and sham groups.

CONCLUSIONS: Patients with DME derive clinical benefit from treatment with the selective vascular endothelial growth factor antagonist pegaptanib 0.3 mg. These findings indicate that intravitreal pegaptanib is effective in the treatment of DME and, taken together with prior study data, support a positive safety profile in this population.

Anti-VEGF per via intravitreale

Ranibizumab (Lucentis®, Novartis)

Pegaptanib sodium (Macugen, OSI Eyetech)

VEGF trap-Eye Aflibercept (Eylea, Regeneron/Bayer)

Bevacizumab (Avastin, Genentech/Roche)

Aflibercept → Next anti-VEGF drug
Fusion protein with high VEGF affinity attributed to binding
Approved for AMD

Target il leakage e la neovascolarizzazione associati al EMD

Ingerman A, Dewey-Mattia D. Emerging treatments for diabetic macular edema. August 2010;8:52-4

Anti-VEGF per via intravitreale

Ranibizumab (Lucentis®, Novartis)

Pegaptanib sodium (Macugen, OSI Eyetech)

VEGF trap-Eye Aflibercept (Elya Regeneron/Bayer)

Bevacizumab (Avastin, Genenthech/Roche)

Ab umanizzato ricombinante; tutte le isoforme di VEGF-A

Efficacia sovrapponibile al Ranibizumab
IV Bimestrali
Costi minori

Anti-VEGF per via intravitreale

Ranibizumab (Lucentis®, Novartis)

Pegaptanib sodium (Macugen, OSI Eyetech)

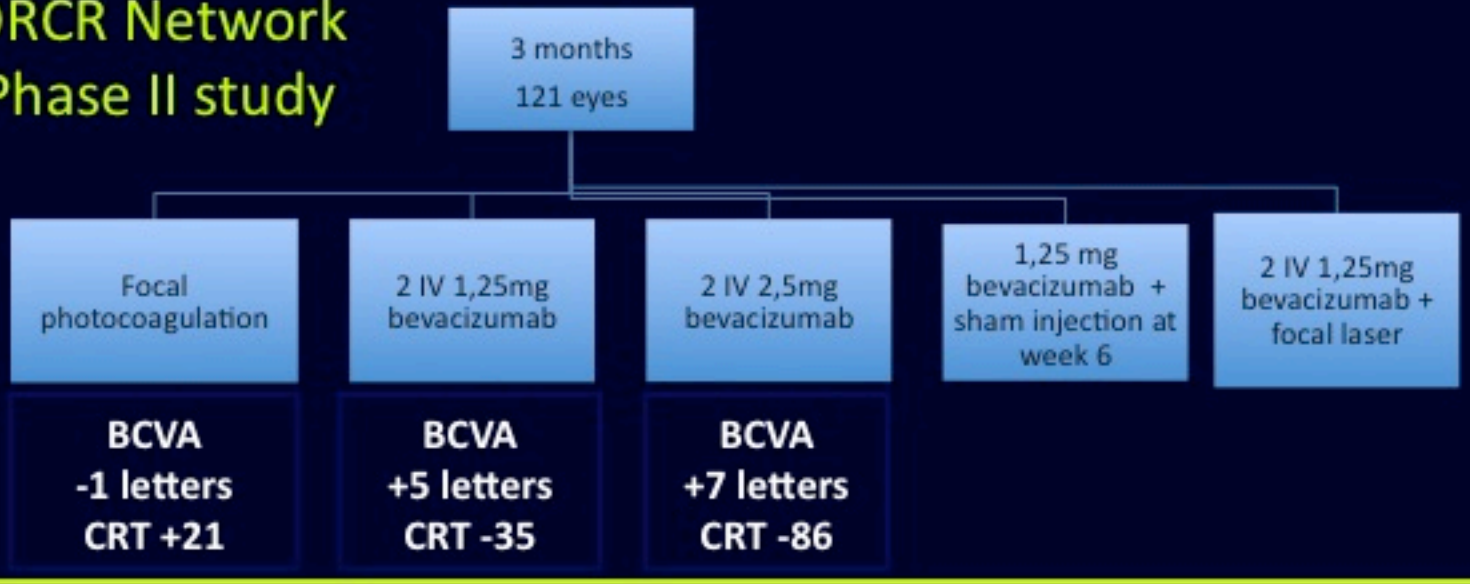
VEGF trap-Eye Aflibercept (Elya Regeneron/Bayer)

Bevacizumab (Avastin, Genenthech/Roche)

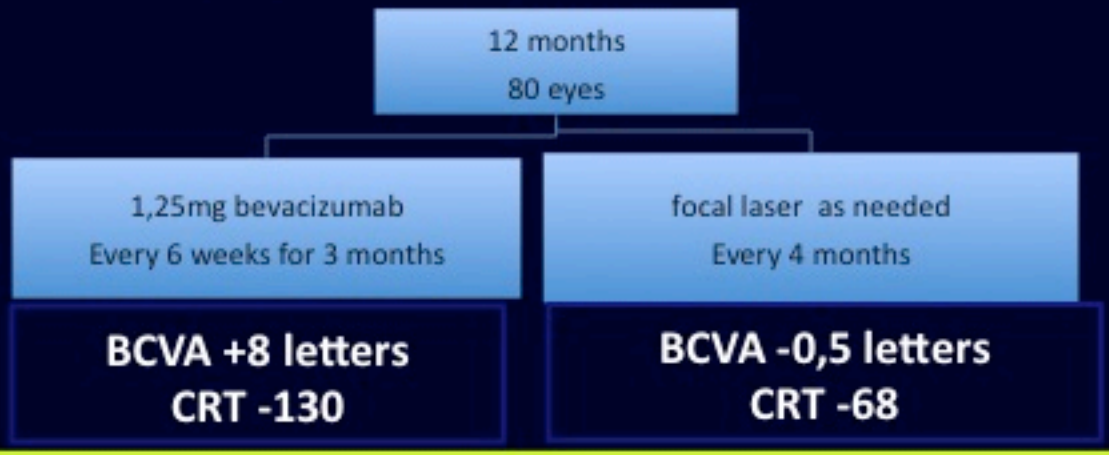
Ab monoclonale umanizzato – Off/Label

Bevacizumab

DRCR Network Phase II study



BOLT study Phase II study



Bevacizumab vs TMC

Clinical trials.gov. Efficacy Study of Triamcinolone and Bevacizumab Intravitreal for Treatment of Diabetic Macular Edema (ATEMD). Available from: http://clinicaltrials.gov/ ct2/show/NCT00737971

Conclusione

Risoluzione spontanea dell'edema rara

Spesso secondaria a miglioramento dei fattori di rischio sistemici (glicemia, ipertensione arteriosa o ipercolesterolemia)

Se non trattato, 29% occhi presentano moderata perdita visiva dopo 3 anni

Conclusione

Trattamento dell'EMD complesso
Necessario combinare multipli approcci terapeutici

Laser
Trattamento focale/griglia rimane il riferimento per la terapia dell'EMD, sopportato dall'evidenza di studi clinici multicentrici

Anti-VEGF
Maggior parte degli studi sono ben disegnati e hanno dimostrato l'effetto terapeutico e la sicurezza del ranibizumab per via intravitreale con risultati molto incoraggianti

Comunque sono necessari trials più estesi che possono consolidare l'uso dei farmaci anti-VEGF come terapia di routine e possono creare linee guida per il trattamento dell'EMD

Risultati a lungo termine?

Conclusione

DDSs

Impianti biodegradabili dimostrano buoni risultati di efficacia e sicurezza
Preferibile iniettare un impianto biodegradabile, non necessita rimozione

Dati a lungo termine sulla risposta tissutale in seguito a esposizione farmacologica continua non sono noti

Beneficio economico rispetto alle iniezioni intravitreali singole ripetute

Impianti futuri di nuova generazione devono assicurare rilascio del farmaco ancora più prolungato con minor numero di effetti collaterali;
Biodegradabili; Formulazioni a base di liposomi o micro-nano-particelle

Kuno N, Fujii S. Biodegradable Intraocular therapies for retinal disorders. Drugs Aging 2010

Edema maculare diabetico
causa maggiore di perdita visiva

Fotocoagulazione laser focale
terapia standard per l'EMD clinicamente significativo ma non è la cura

Terapia combinata **steroidi IV** in occhi con EMD refrattario

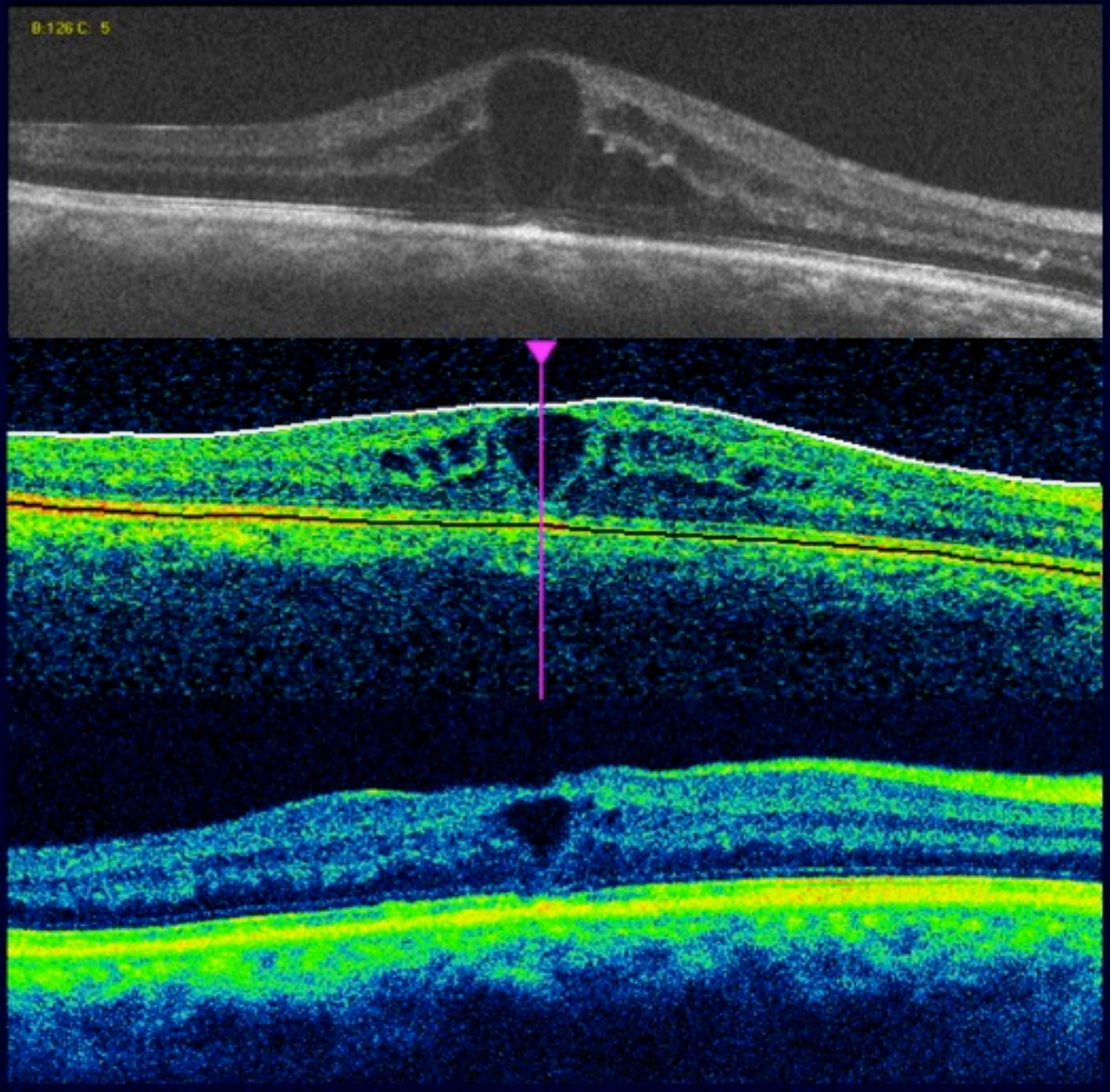
Terapia combinata **anti-VEGF**

VITRECTOMIA
In casi di evidenza clinica e tomografica di trazione vitreo-retinica

IN FUTURO !!!

TERAPIA FARMACO-MODULATORIA: inibitori delle protein kinasi C, anticorpi monoclonali anti-ICAM1 / CD18

MOLECOLE CON TARGET I FATTORI CHE CAUSANO ALTERAZIONE DELLA BARRIERA EMATO-RETINICA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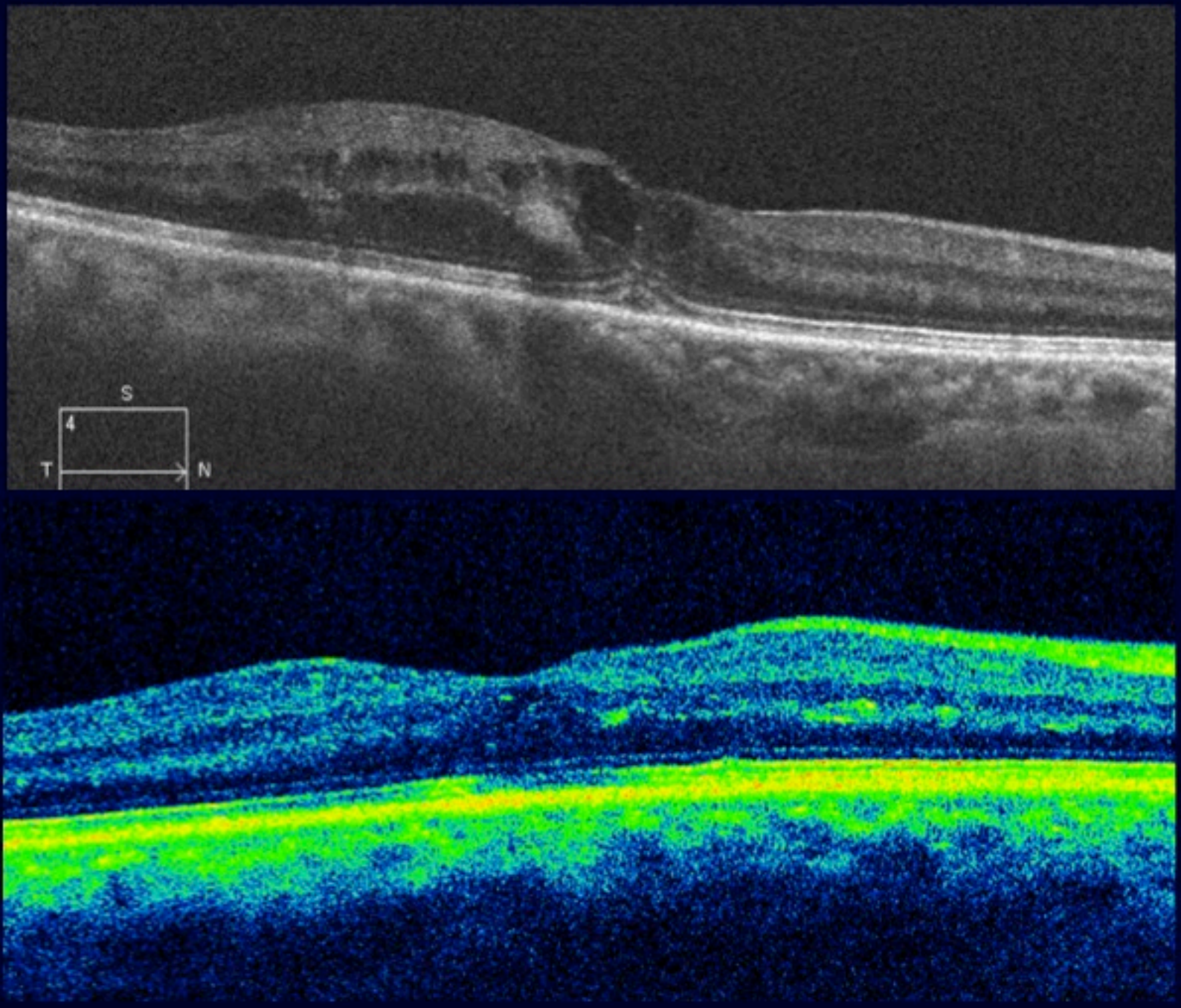
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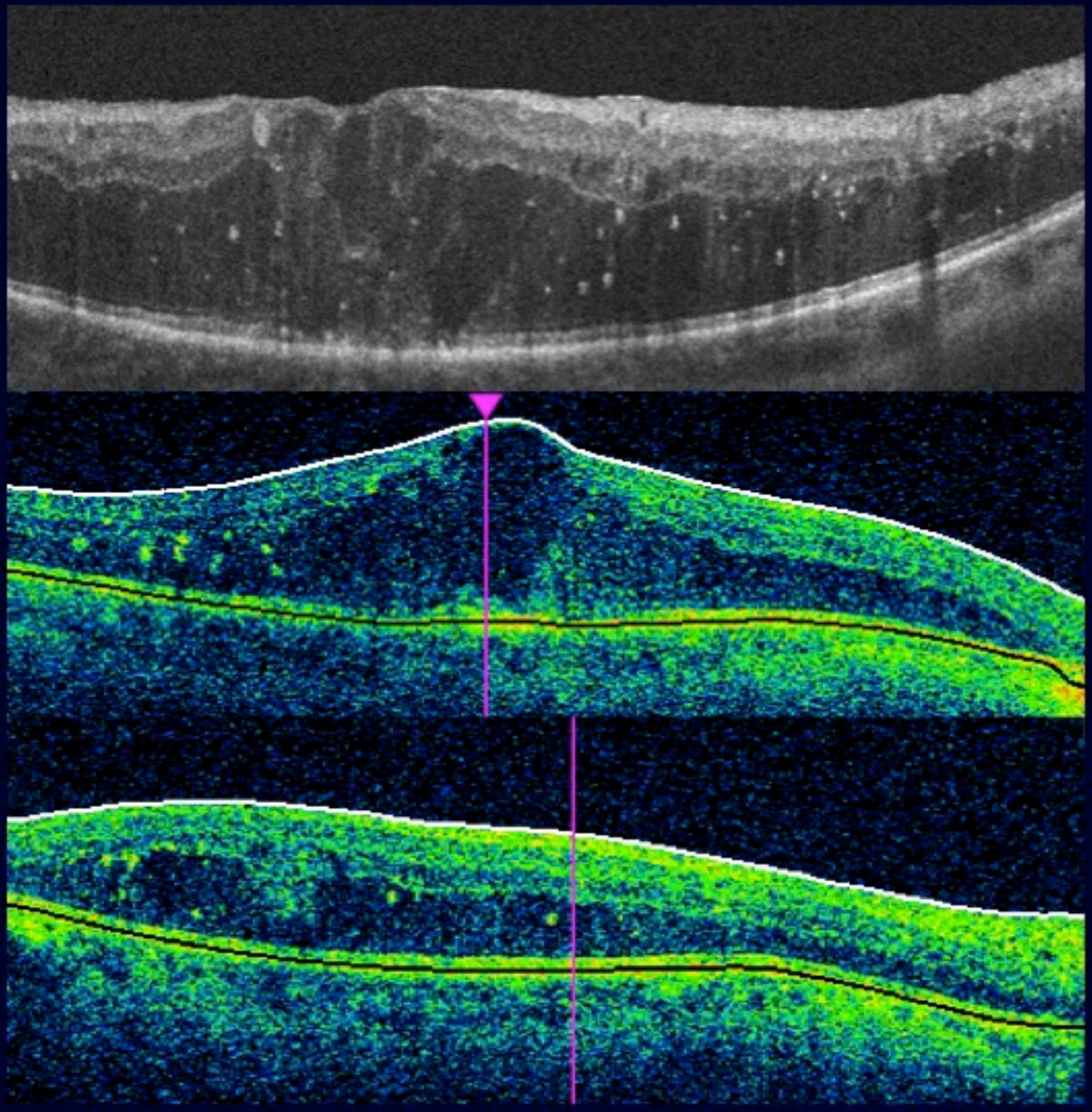


GRAZIE