OEDEME MACULAIRE DIABETIQUE

Stratégie thérapeutique

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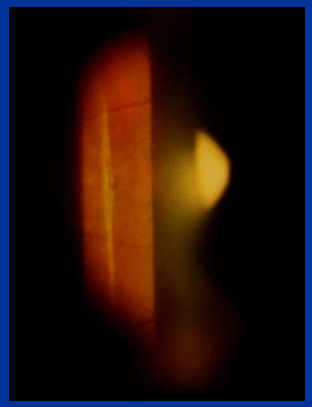
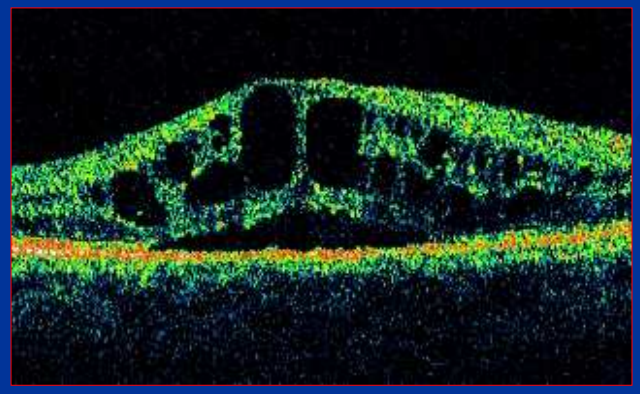
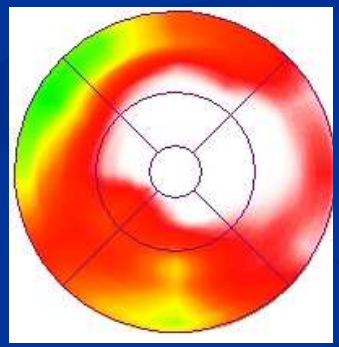
UNIVERSITE PARIS 7

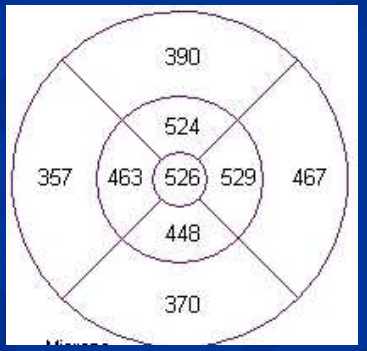
OEDEME MACULAIRE DIABETIQUE

- Principal problème thérapeutique au cours de la RD
- Diagnostic: EPAISSISSEMENT rétinien maculaire, secondaire à une rupture de la BHR interne
  - Examen biomicroscopique /OCT









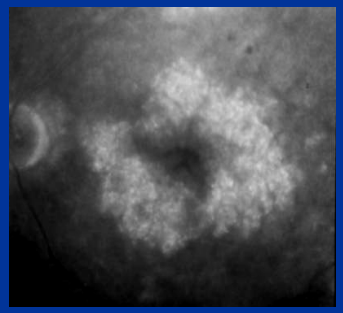
- BILAN: Angiographie, OCT
- Surveillance : Examen biomicroscopique, OCT

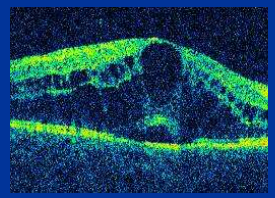
CLASSIFICATIONS

ALFEDIAM

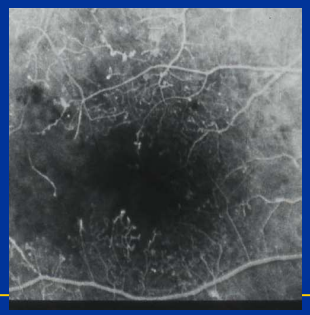
- OM **Focal**

- OM **Diffus**





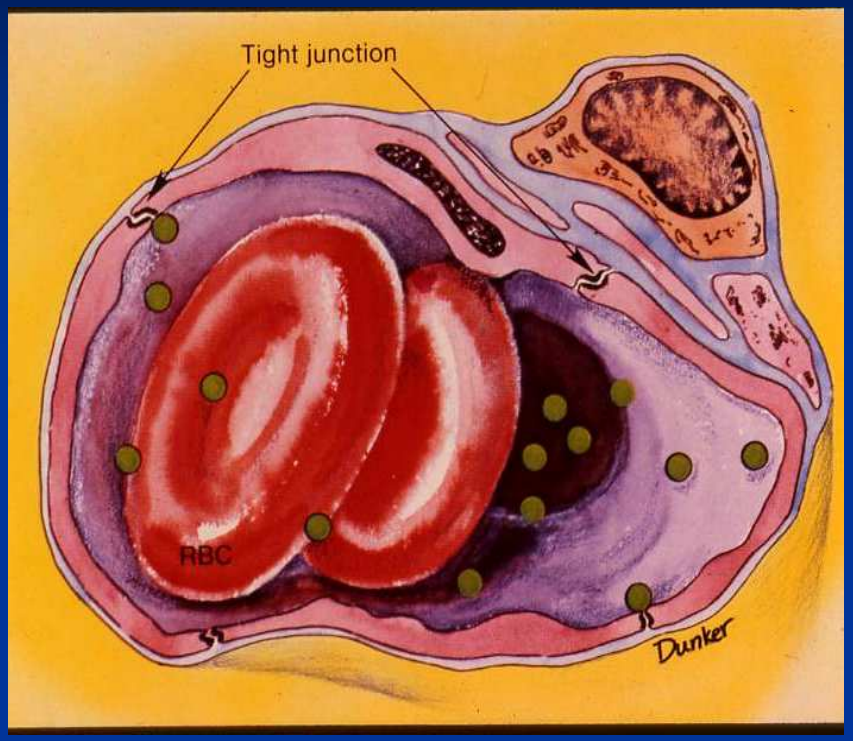
- Maculopathie **ischémique**

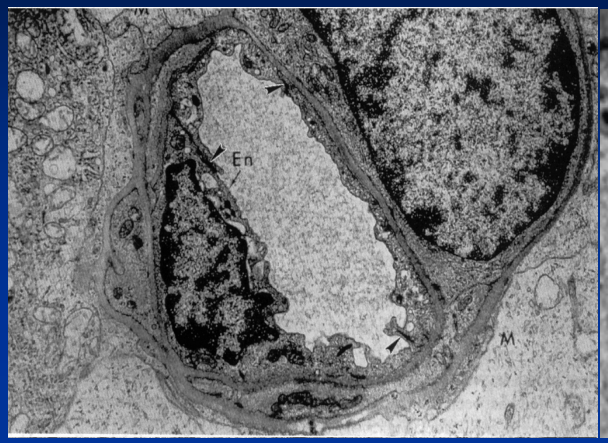


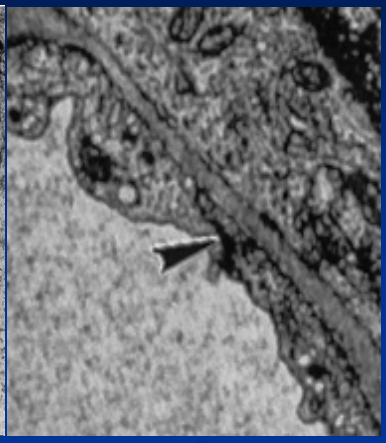
INTERNATIONALE

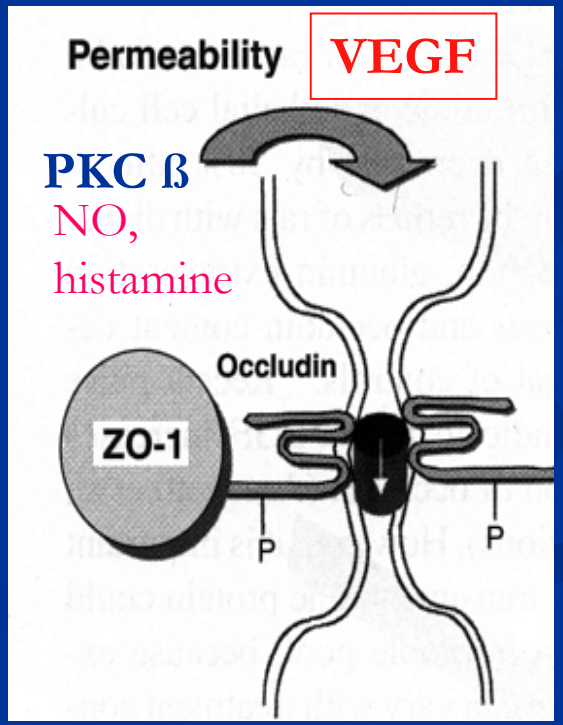
- *OM minime* : épaississement rétinien ou exsudats à distance du centre de la macula
- *OM modéré* : épaississement rétinien ou exsudats à proximité du centre de la macula, mais ne l ’atteignant pas
- OM *sévère* : épaississement rétinien ou exsudats atteignant le centre de la macula

Pathogénie de l'OM diabétique



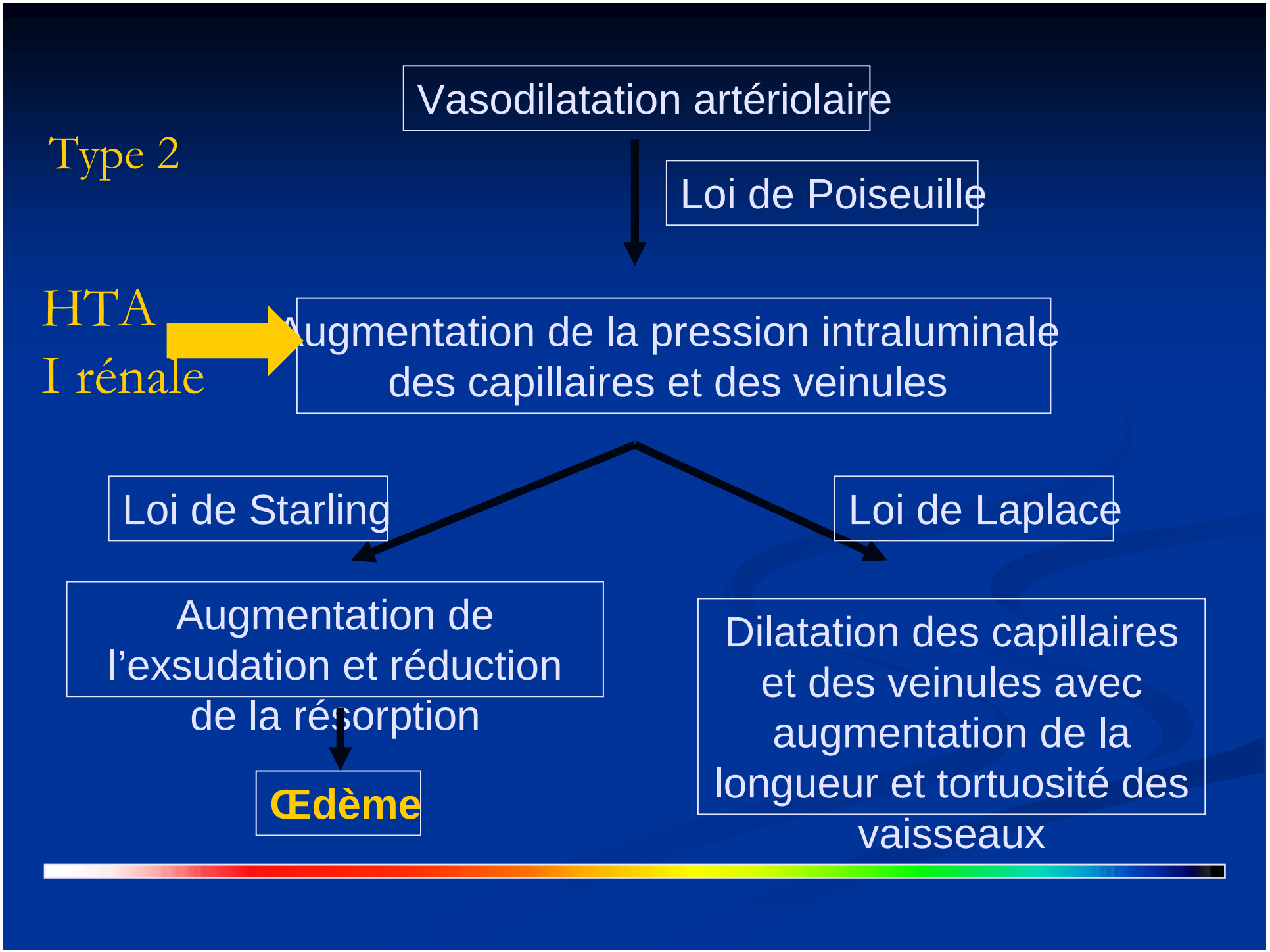




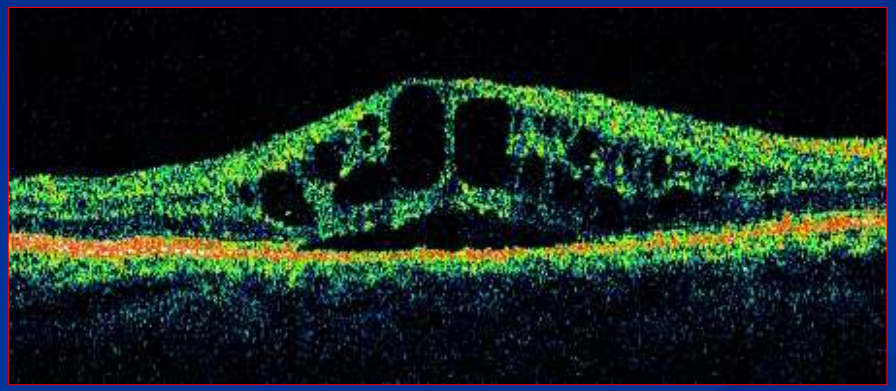


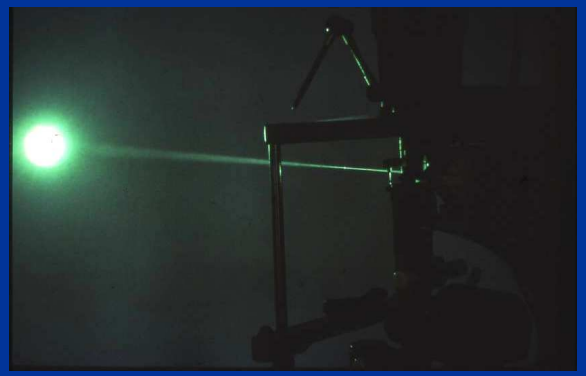
Rupture
de la barrière hémato-rétinienne interne

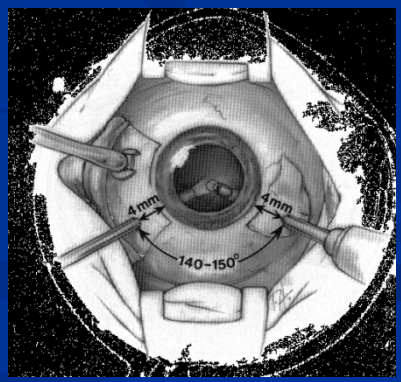
Type 1


Type 2
Vasodilatation artériolaire
Loi de Poiseuille
HTA
I rénale
Augmentation de la pression intraluminale
des capillaires et des veinules
Loi de Starling
Loi de Laplace
Augmentation de
l'exsudation et réduction
de la résorption
Œdème
Dilatation des capillaires
et des veinules avec
augmentation de la
longueur et tortuosité des
vaisseaux

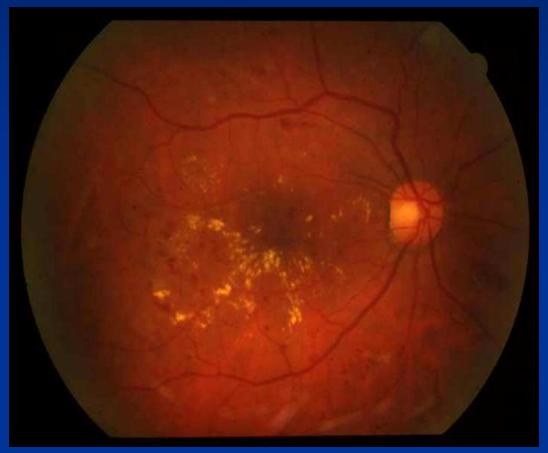
Quel traitement pour quel œdème diabétique ?

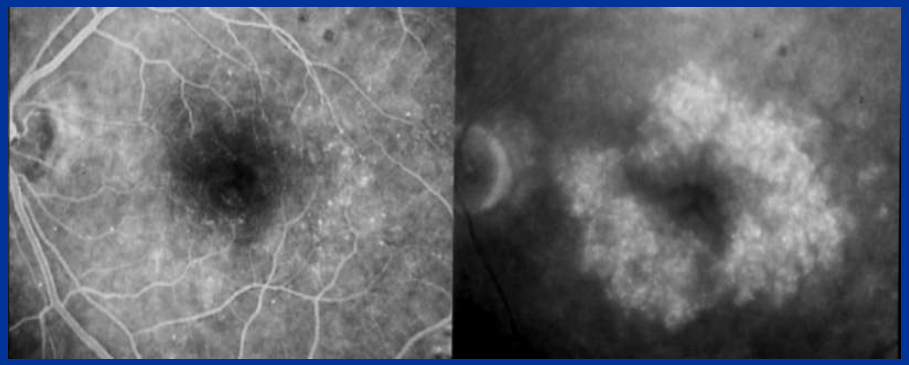


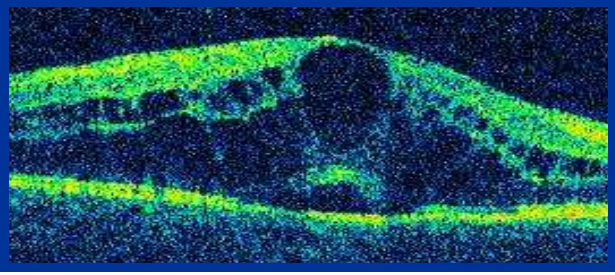




OM diabétique







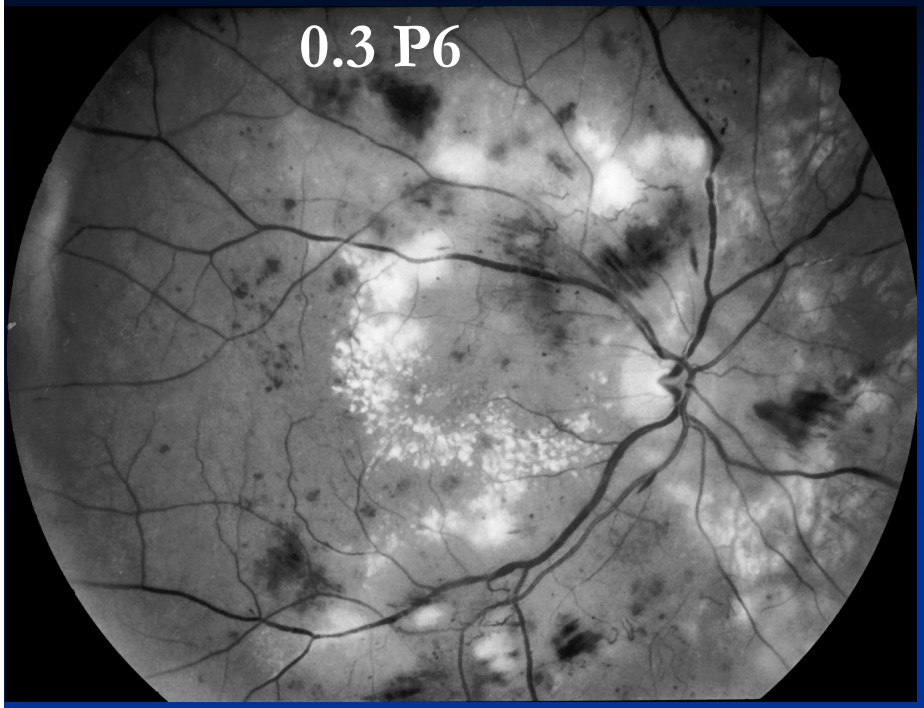
Choix thérapeutique

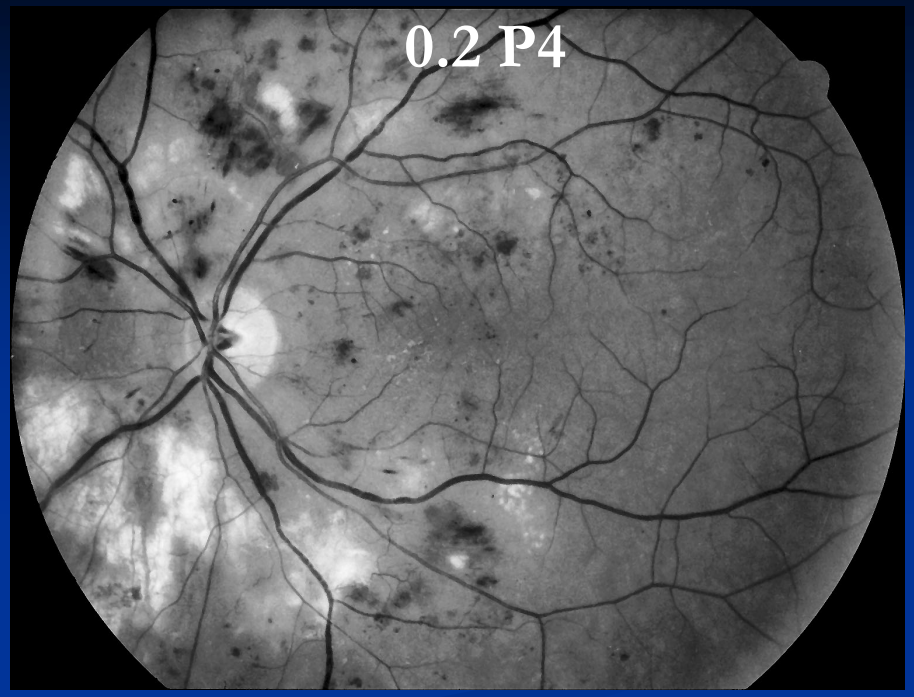
- TTT médical
- Laser
- IVT acétonide triamcinolone
- Chirurgie (vitrectomie)
- Anti VEGFs

Traitement de l'OM diabétique

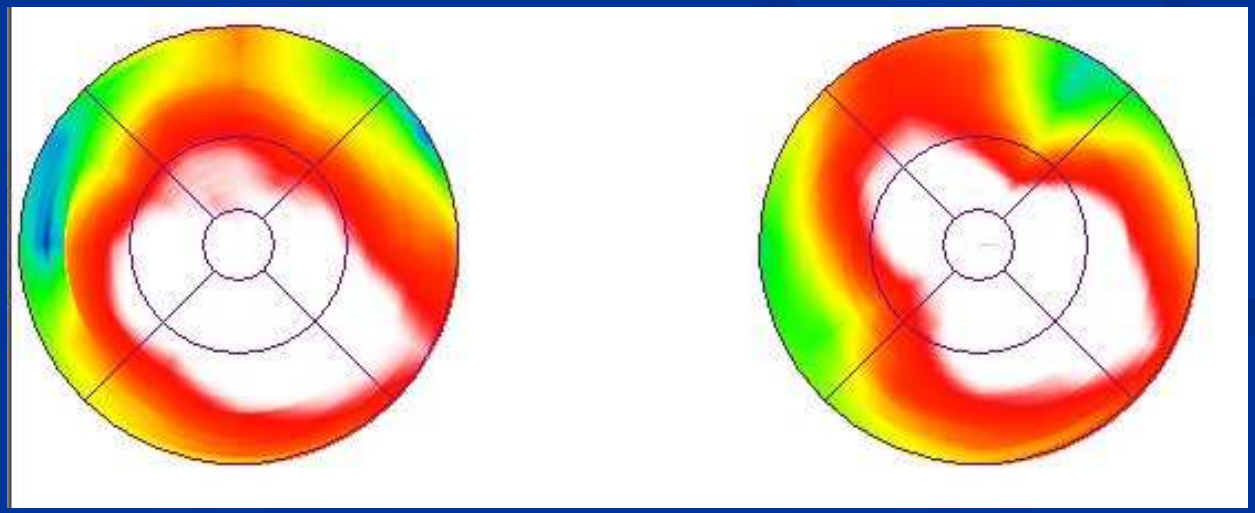
- Traitement médical toujours indiqué ++++ en prévention primaire et secondaire
  - UKPDS 1998 : la baisse de la PA de 10mmHg réduit de 49% l'incidence de l'OM à 9 ans

- Equilibrer les facteurs de risque
  - HbA1C < 7%
  - **TA < 130/ 80 +++ (125/75 si microalbuminurie associée)**
  - LDL cholestérol < 1g/l
  - arrêt du tabac
  - Aspirine 100 mg/ jour

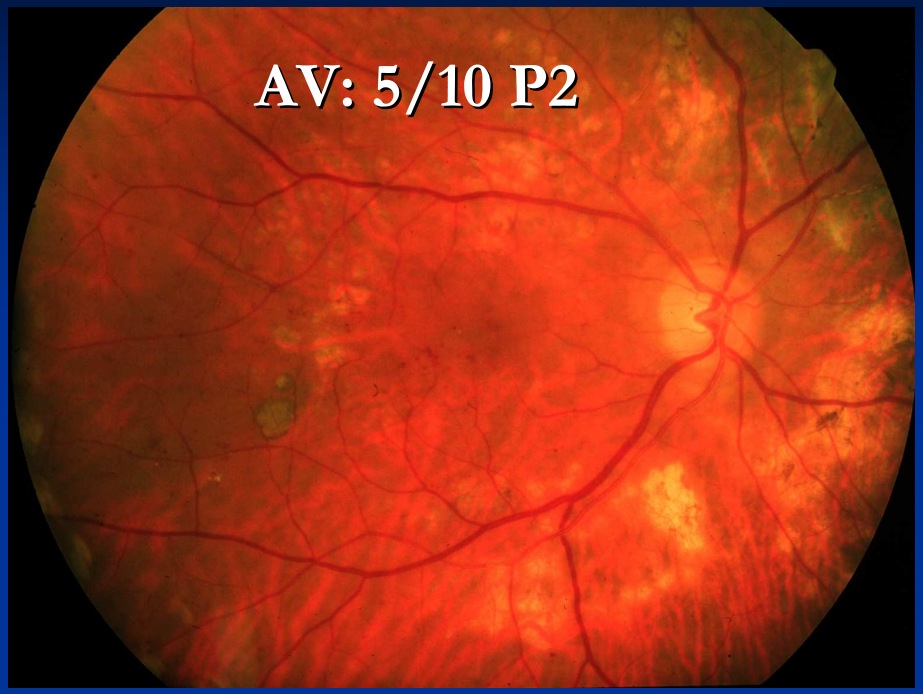


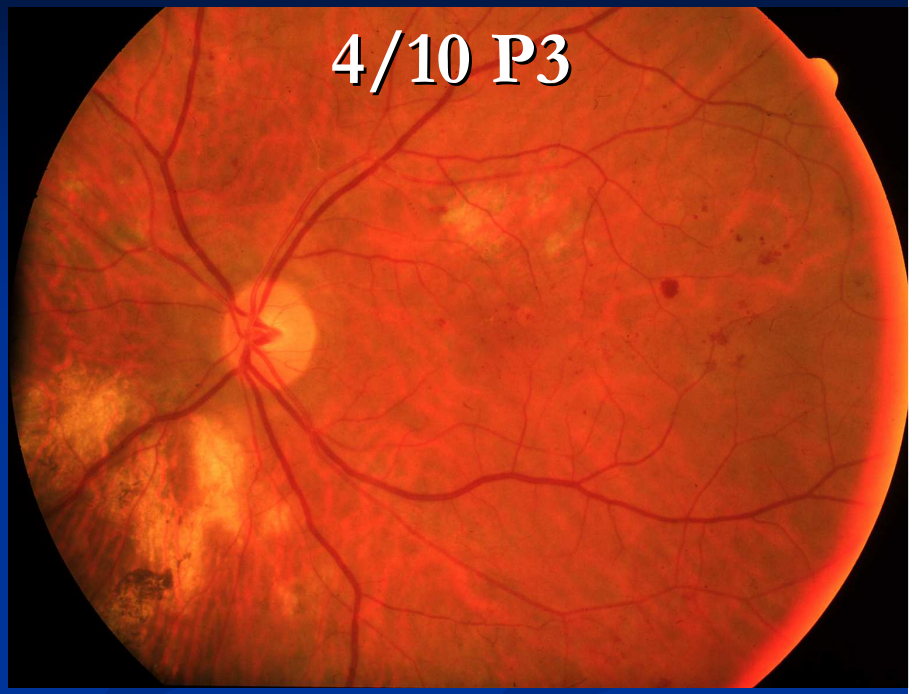


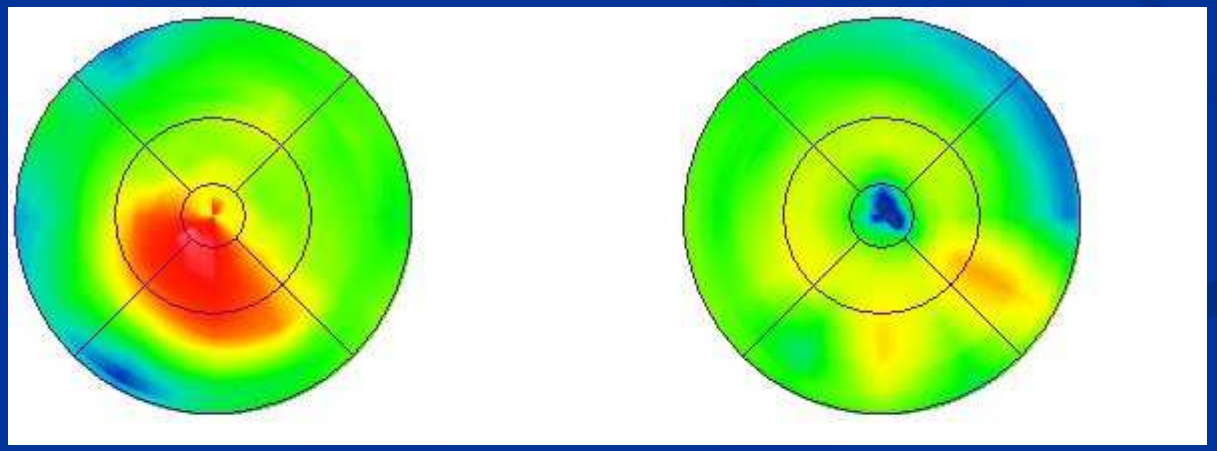
TA : 160/90, HbA1C: 8%



12 mois plus tard



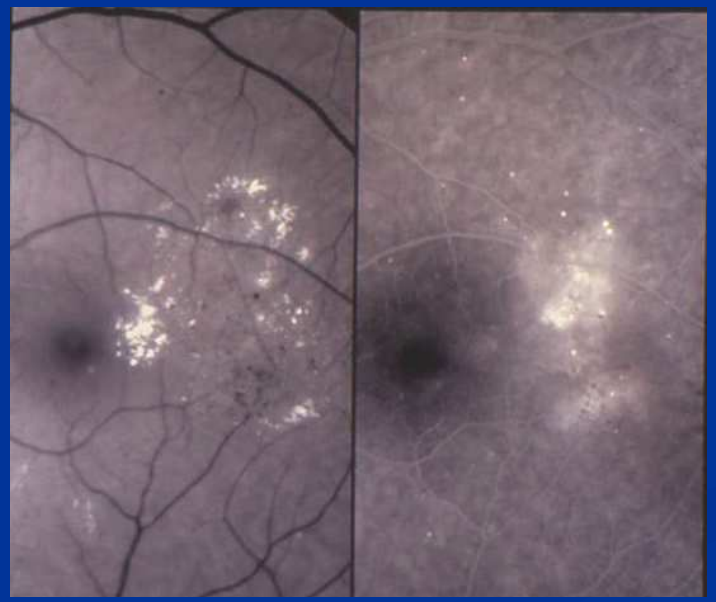




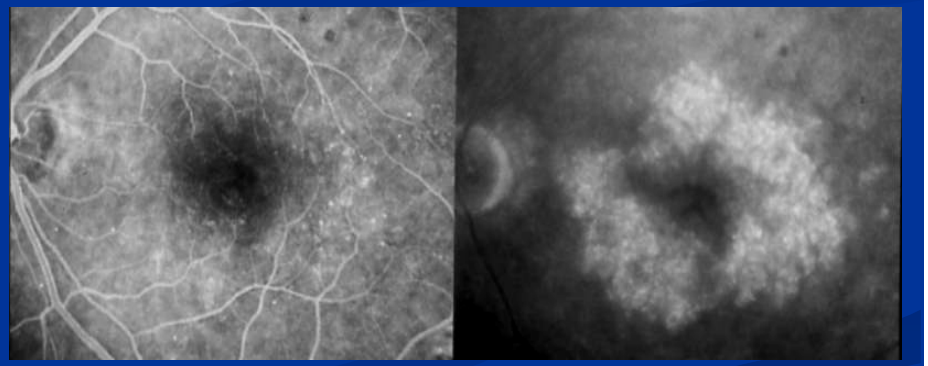
Traitement de l'OM diabétique

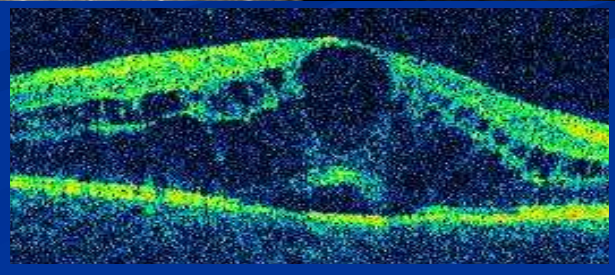
- Le traitement par LASER reste le traitement de référence
- ETDRS 1986: réduction de 50% de la baisse visuelle à 3 ans
- Pas d'urgence à traiter: la baisse visuelle liée à l'OM est lente
- Distinguer :

OM focal



OM diffus





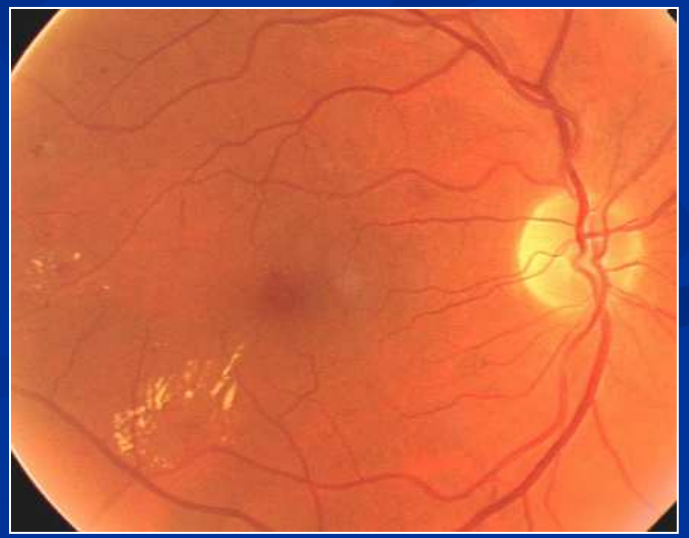
OM focal

- Outre le traitement médical général, le SEUL traitement à envisager est le LASER
- Laser très efficace ; il est indiqué pour tout OM modéré ou sévère, (selon la classification internationale de l'OM – AAO 2002), quelle que soit l'AV
- Aucune indication des corticoïdes ou des anti-VEGFs

OM minime :

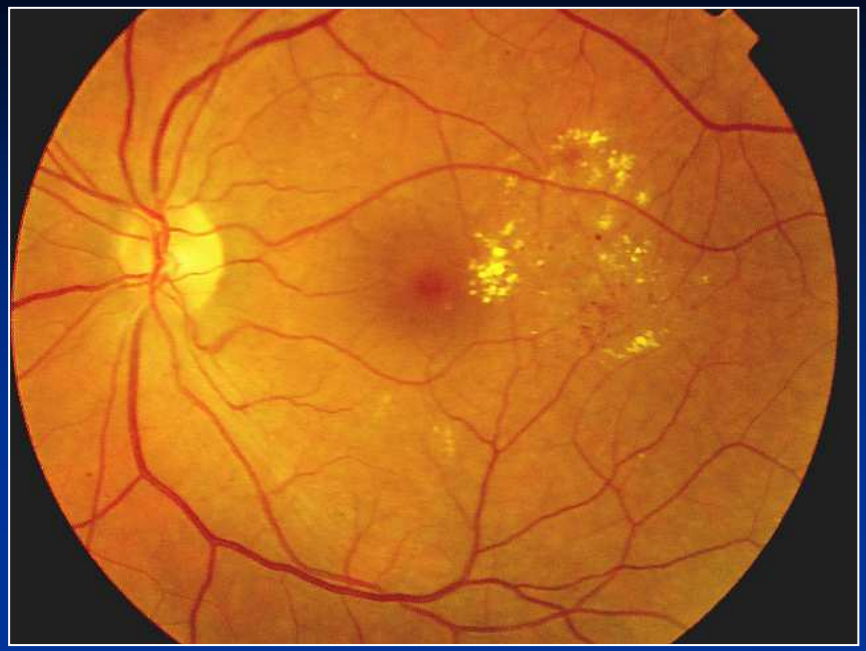
épaississement rétinien ou
exsudats à distance du centre
de la macula

Pas d'indication au traitement par laser



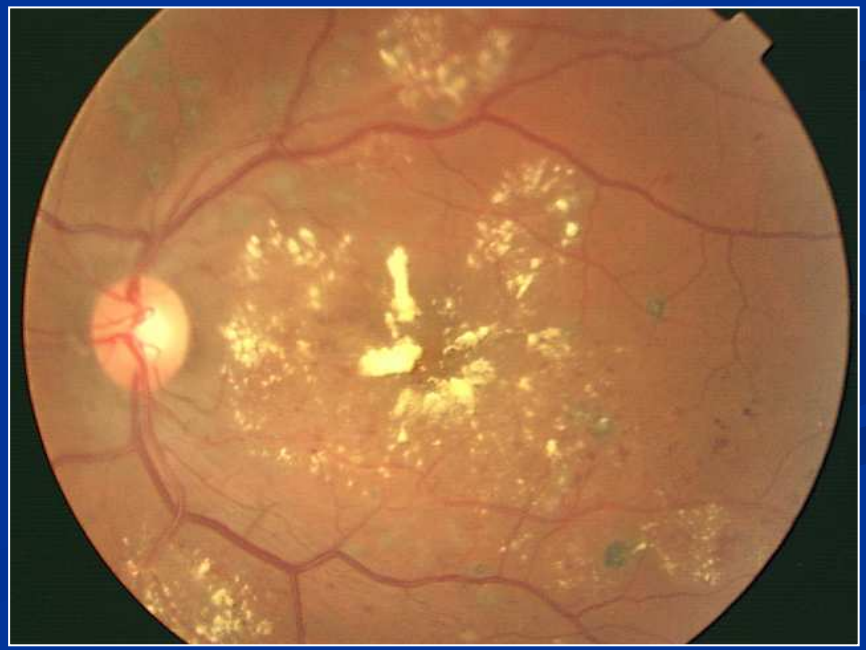
OM modéré :

épaississement rétinien
ou exsudats à proximité
du centre de la macula,
mais ne l ’atteignant pas



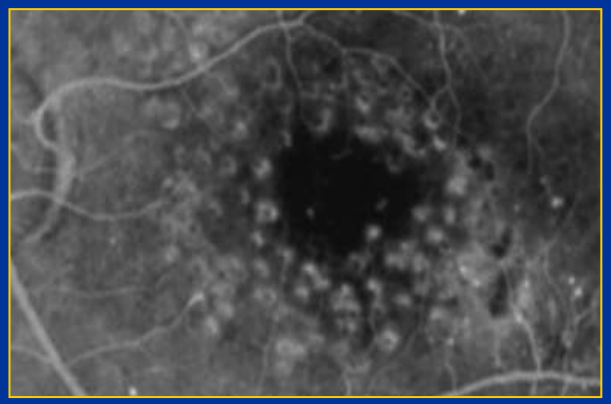
OM *sévère* :

épaississement rétinien
ou exsudats atteignant
le centre de la macula



OM diffus (mixte)

- **Le traitement par laser « grid » reste le traitement de référence, même s'il est inconstamment efficace**



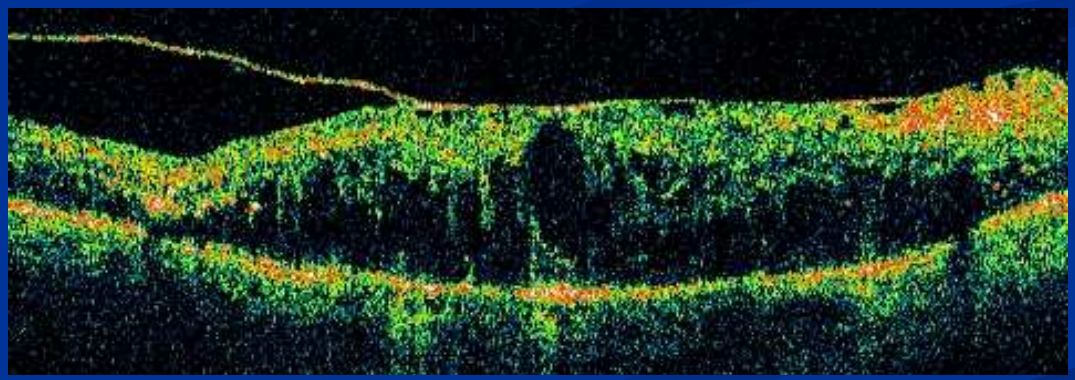
Il est impératif de traiter au moins la composante focale au laser avant d'envisager une autre alternative

Traitement de l 'OM diffus
Alternatives thérapeutiques

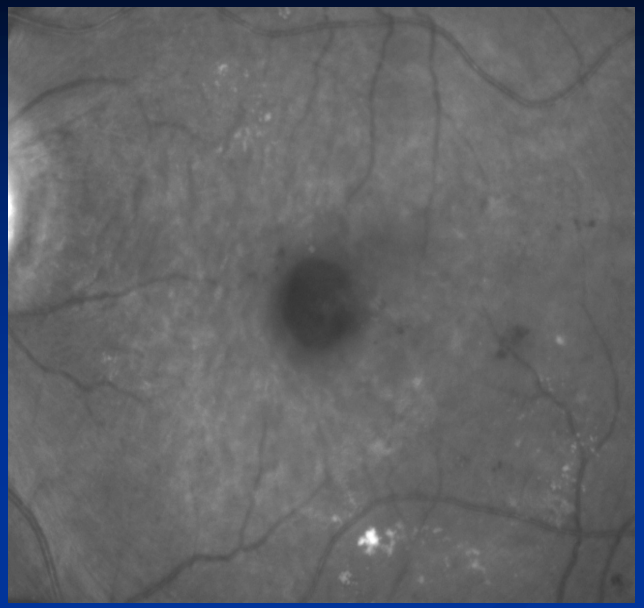
- Efficacité du traitement par laser limitée
- Baisse visuelle persistante dans 15 % des yeux malgré le laser (ETDRS 1985)

- Vitrectomie : Indication formelle en cas d'œdème tractionnel

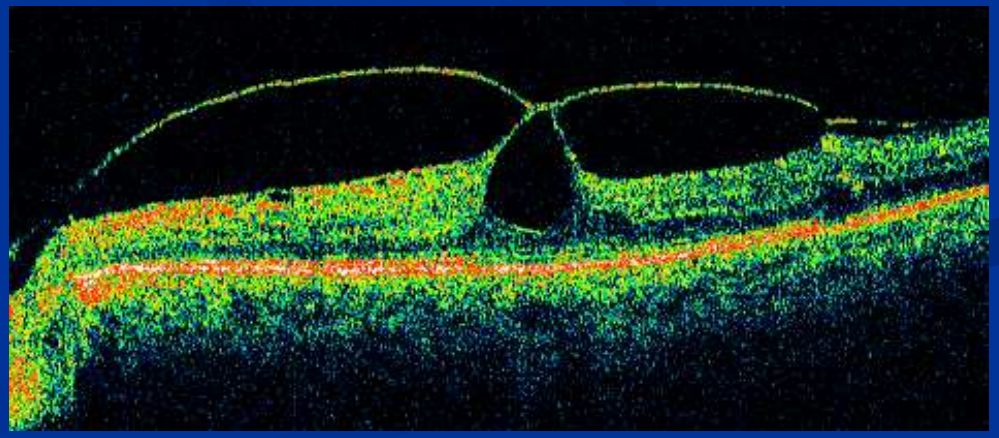
Si AV < 0,5



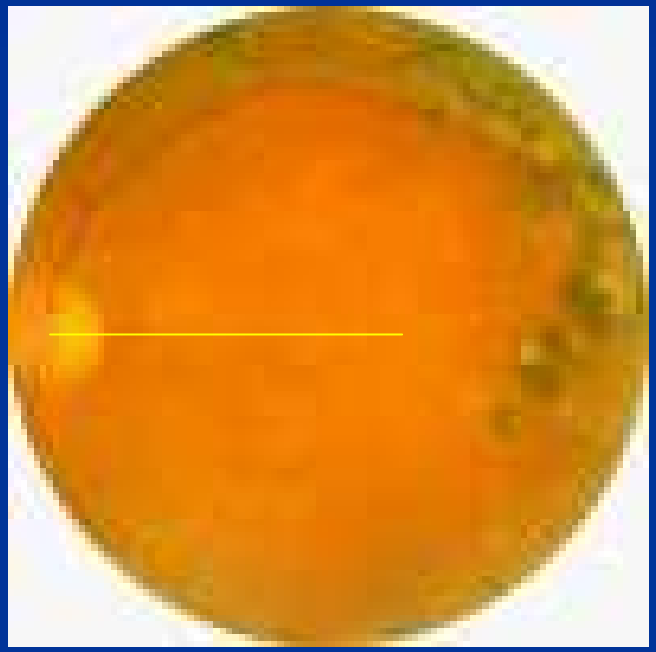
- Injections intravitréennes de triamcinolone
- Anti-VEGFs

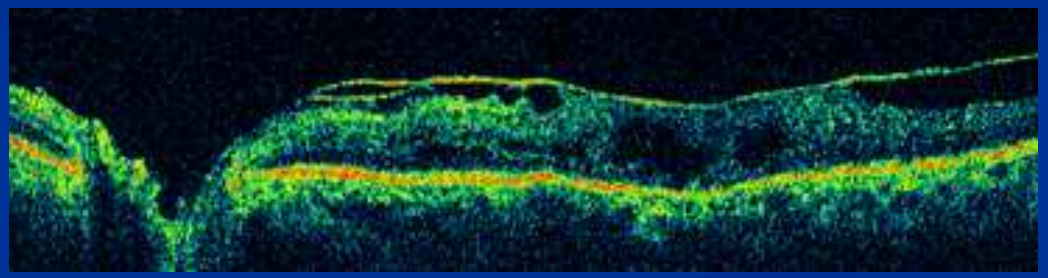


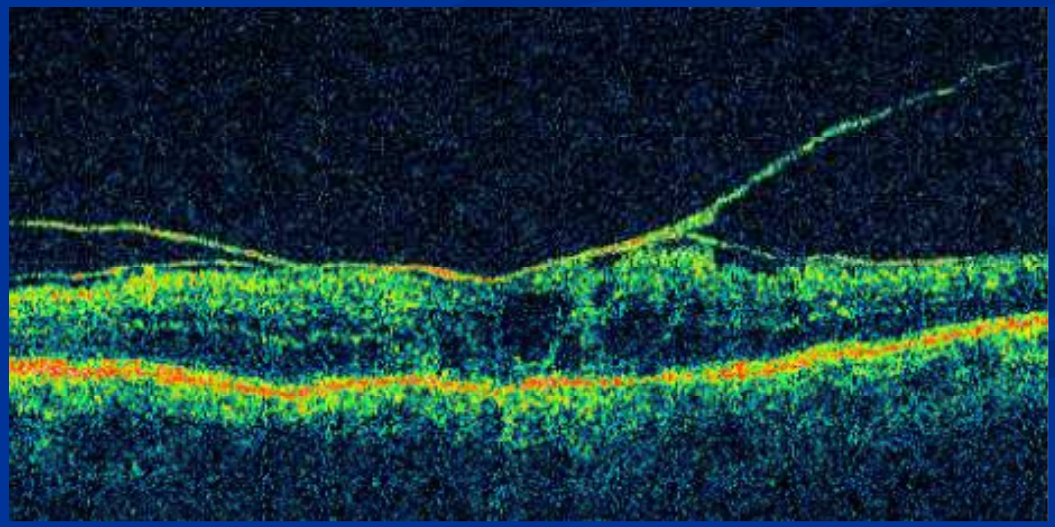
♦hyaloïde postérieure tendue, épaissie, brillante
♦pas de plissement rétinien, ni ectopie maculaire
♦ parfois aspect de kyste au biomicroscope

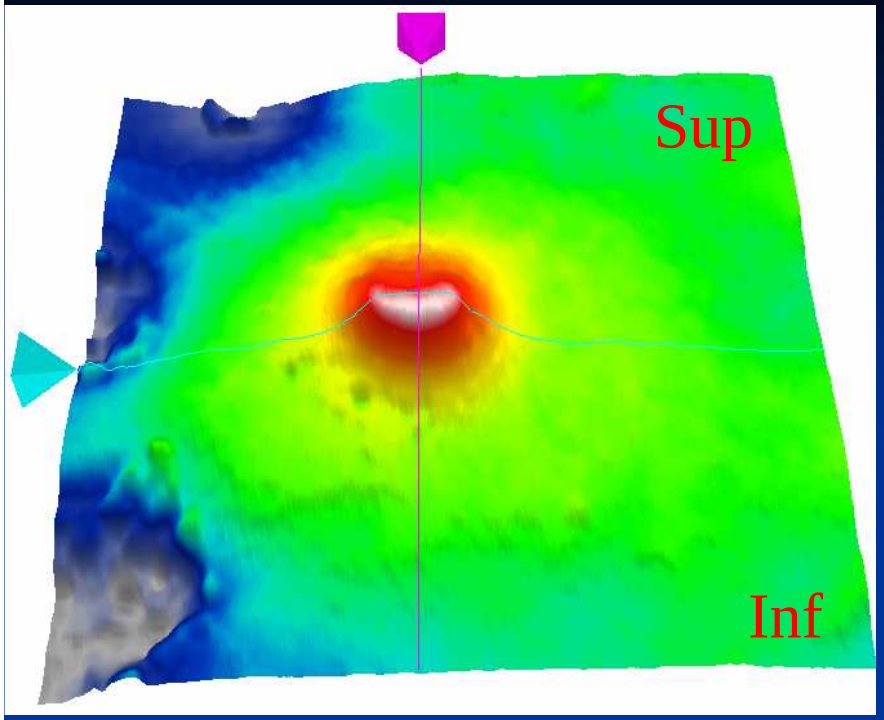


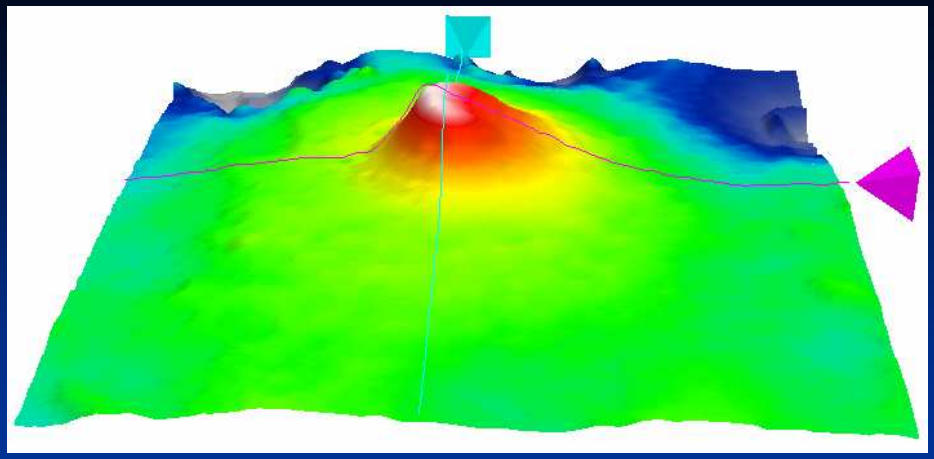
OM tractionnel

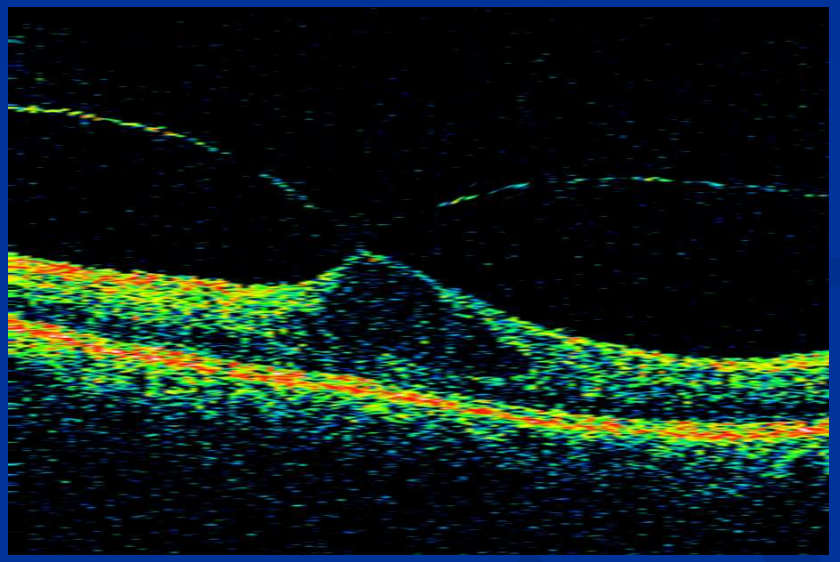


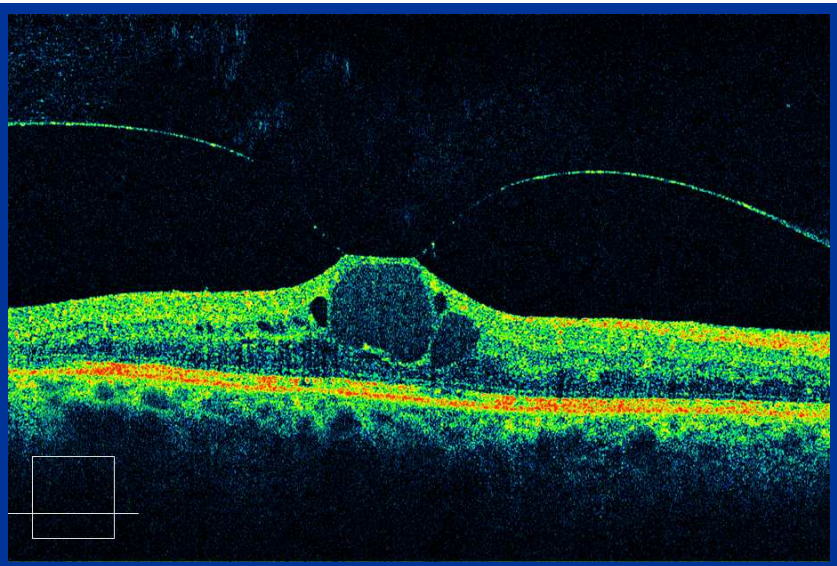


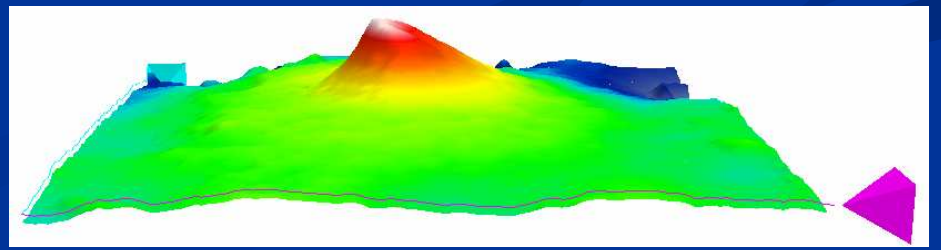


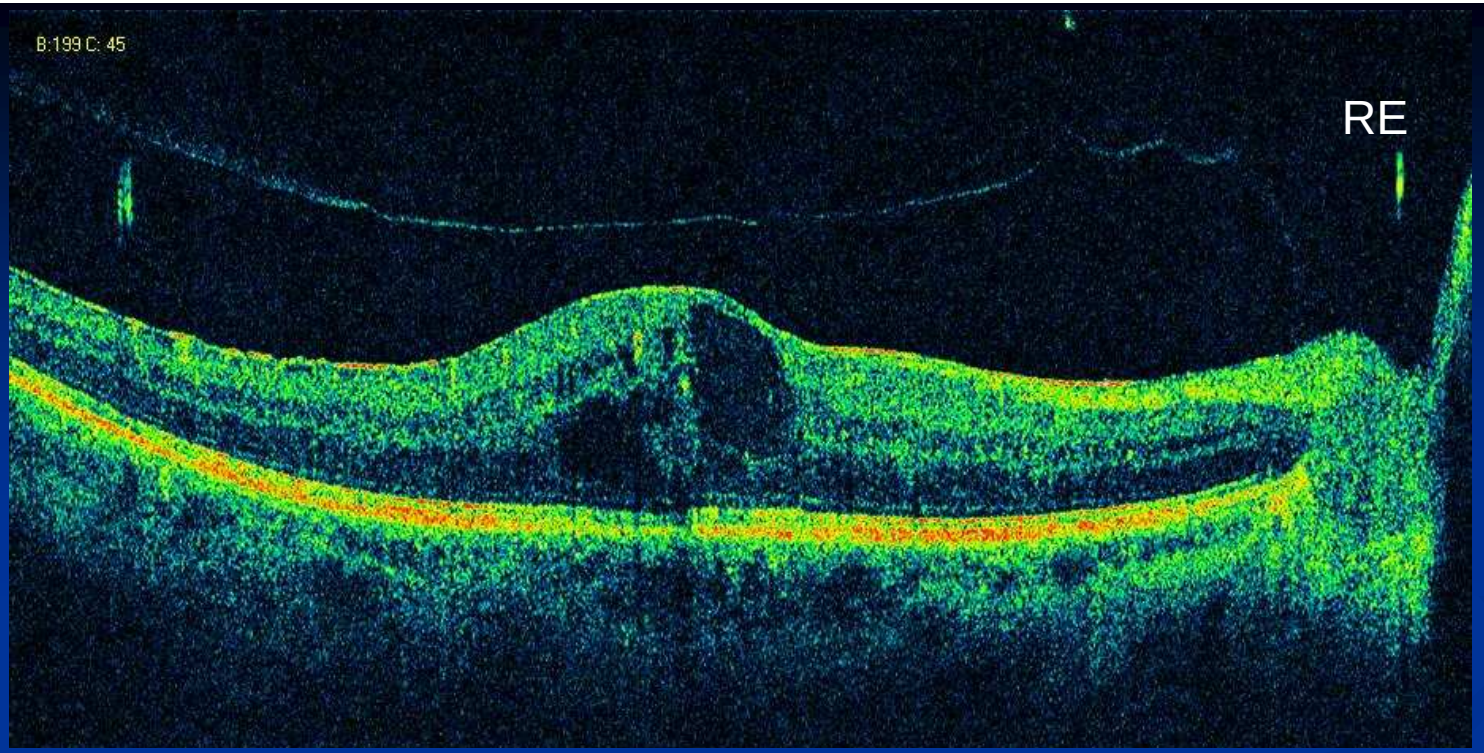

Sup
Inf

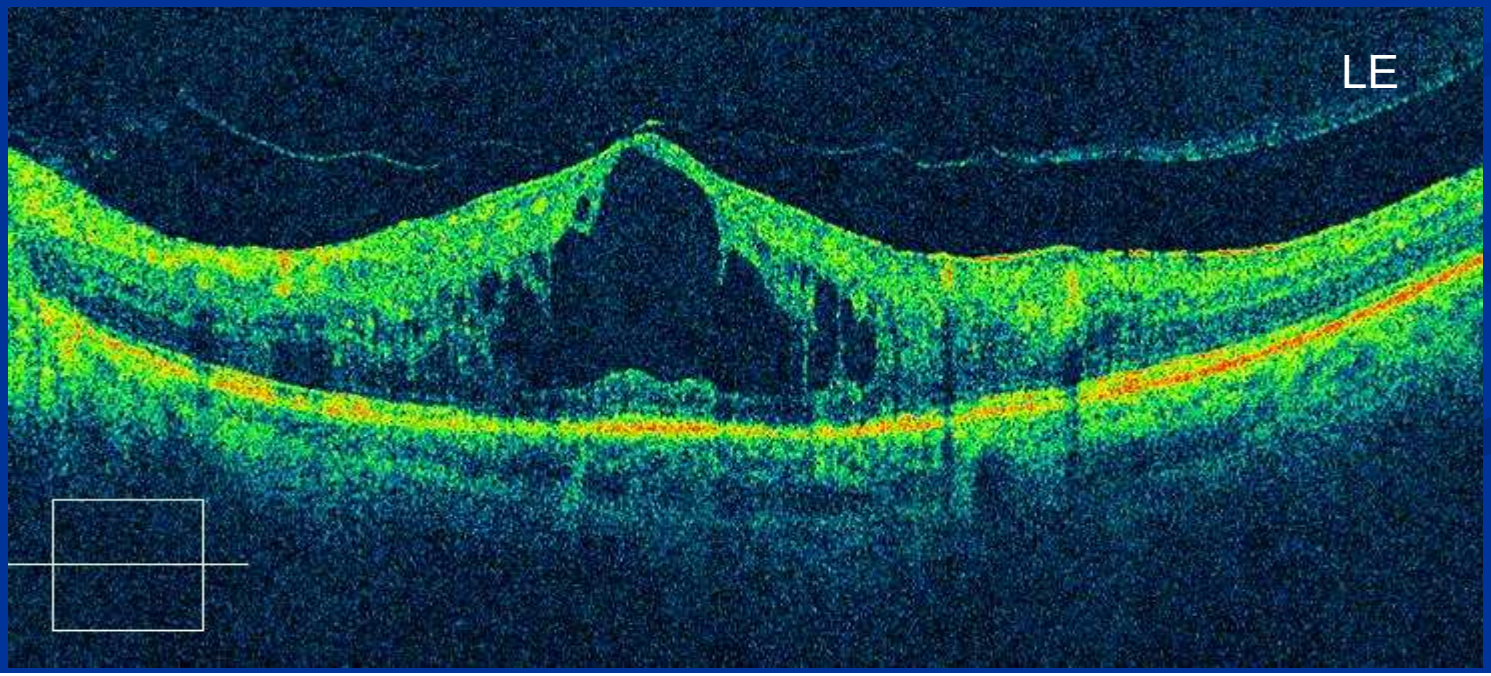









B:199 C: 45
RE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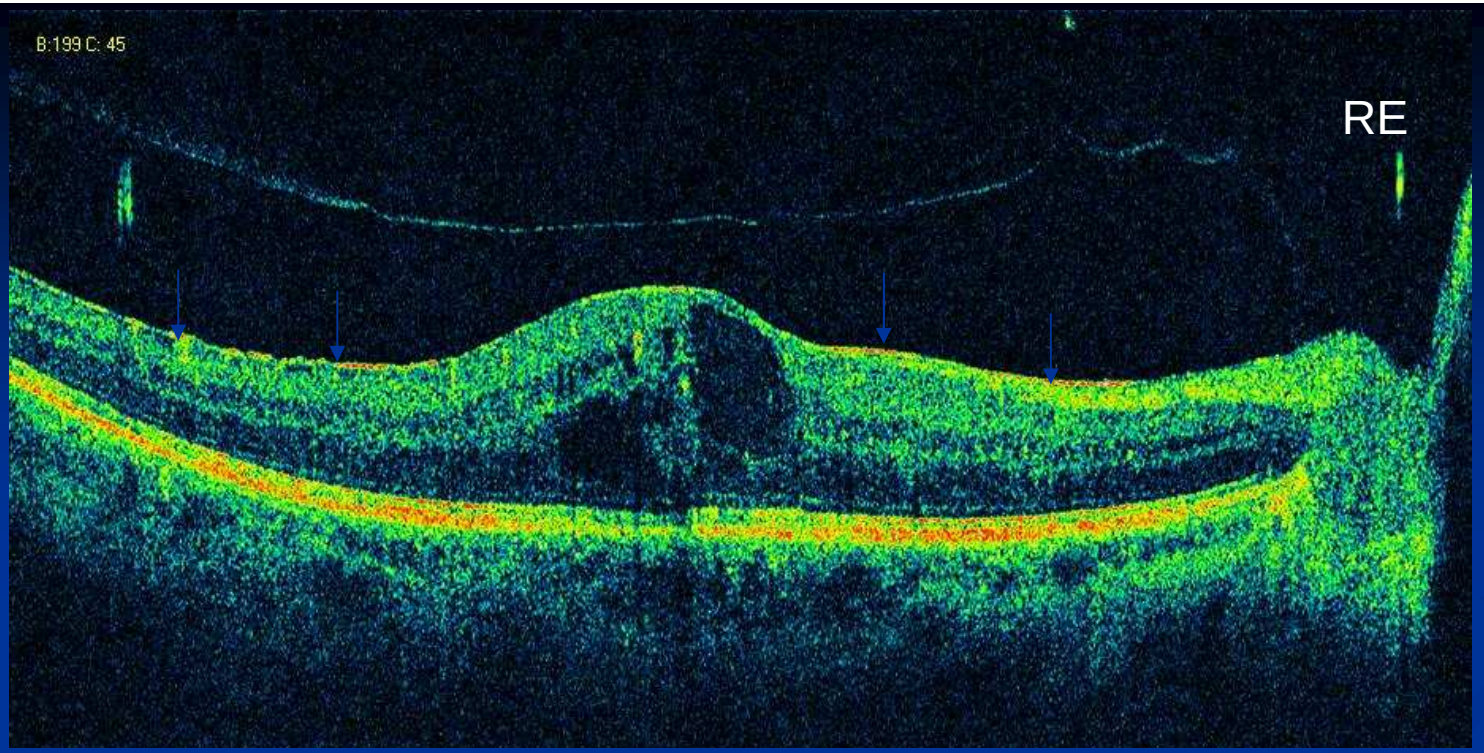
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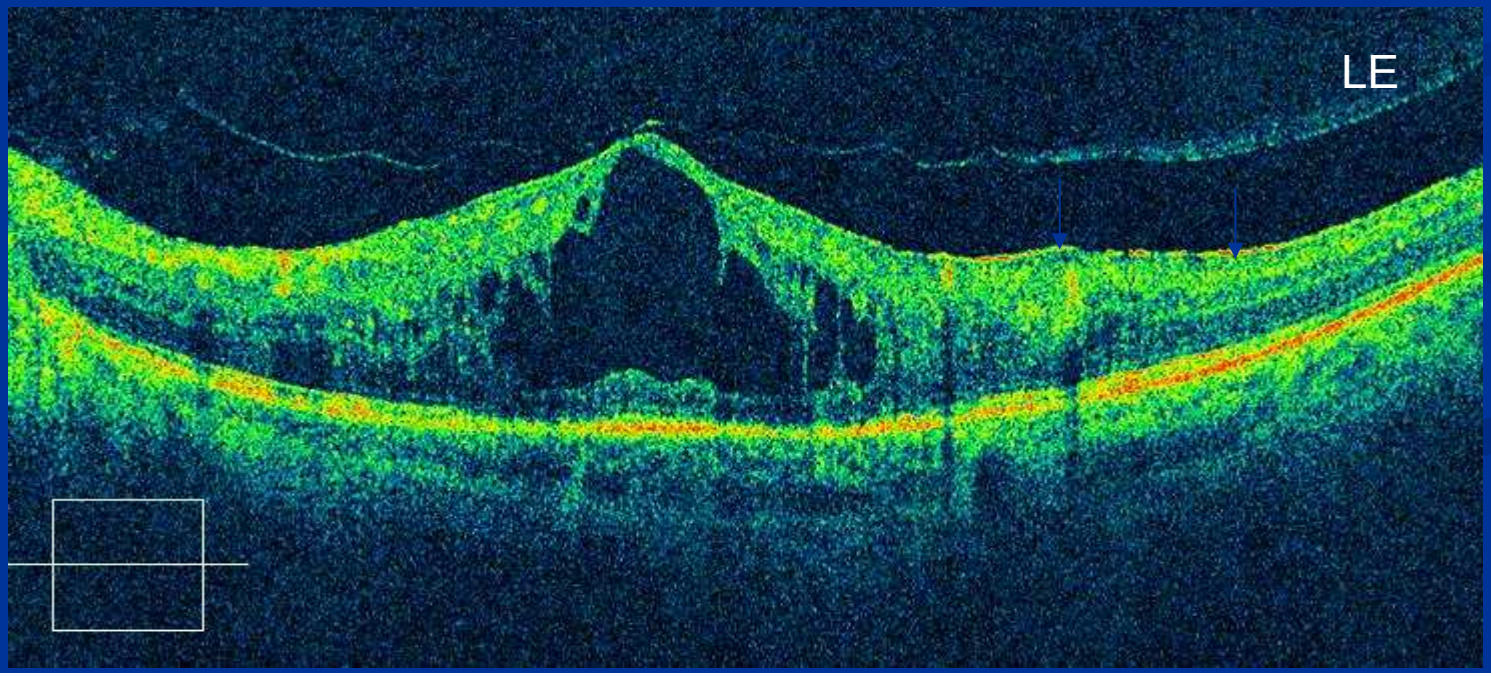
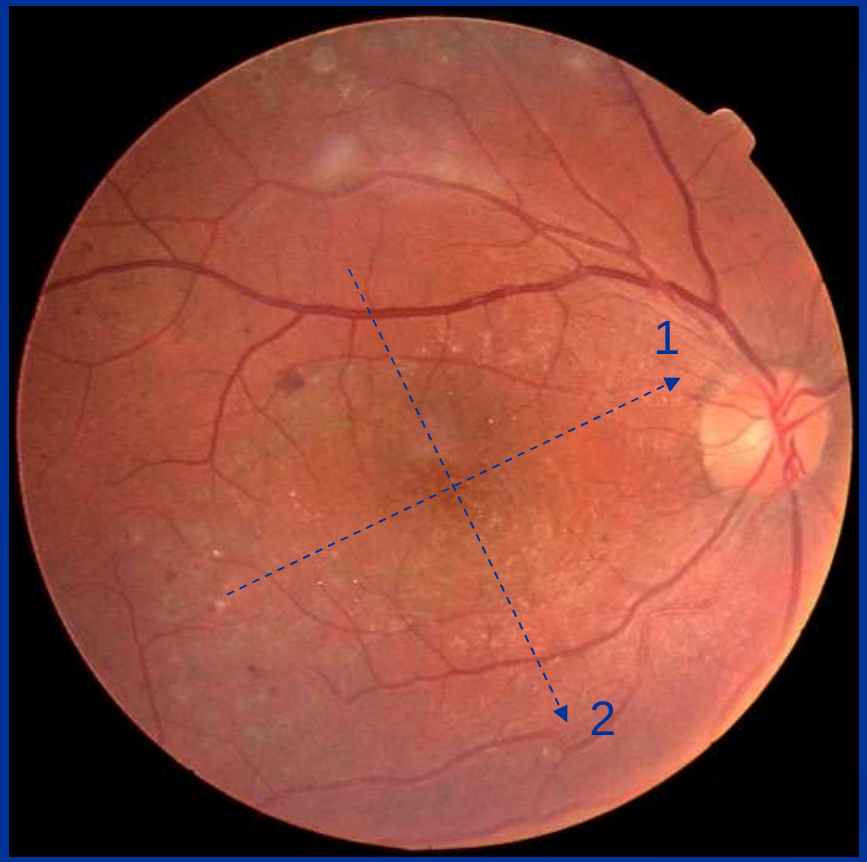
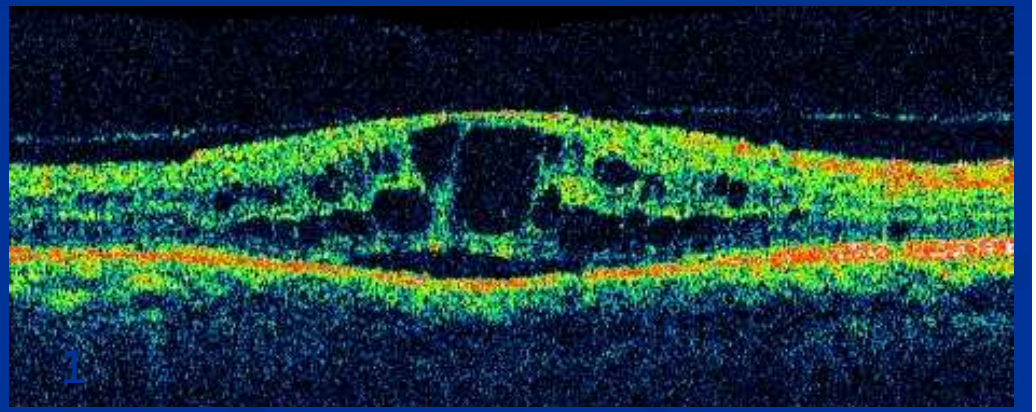
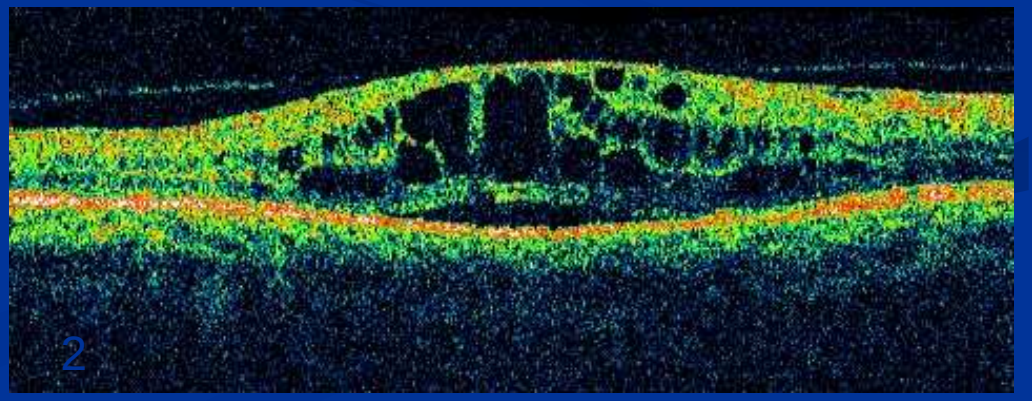

LE

Que faire avec l'OMD diffus non tractionnel ?

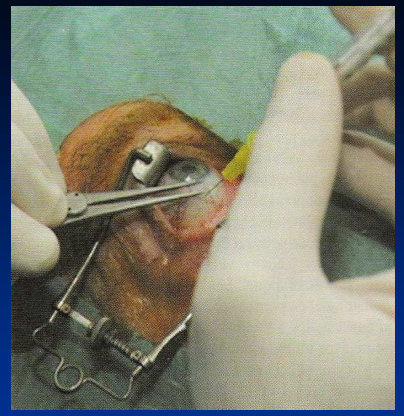
OM avec hyaloide posterieure complètement attachée, ou partiellement détachée, sans épaississement,



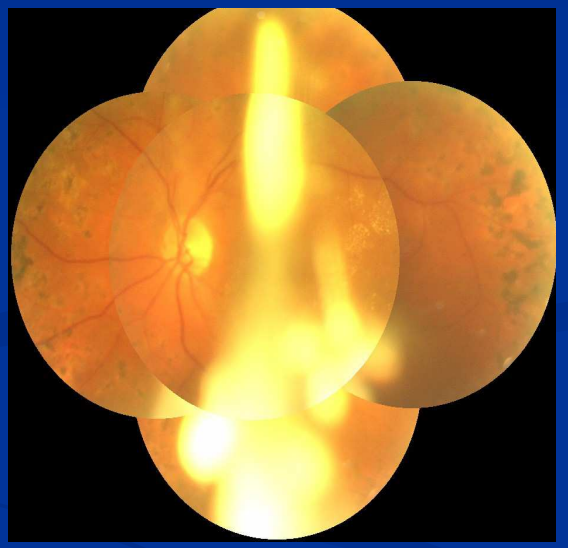




ACETONIDE DE TRIAMCINOLONE



- 4 mg (o.1 ml) d 'acétonide de triamcinolone (*Kenacort ®, Bristol-Myers Squibb, Paris*)
- Le choix de la dose est empirique
- Jonas : 25 mg TA, après filtration de l'alcool benzoïque
- Effet dose-dépendant ?
  - Plus longue durée d'action ? (Jonas, Audren 200)
  - Plus d'HTO ? (Lam 2008)



INDICATION: OM diabétique diffus , réfractaire au traitement par laser

IVT (ST) d'acétonide de triamcinolone

AVANTAGES

- Très grande efficacité
- Amélioration de l'acuité visuelle

INCONVENIENTS

- Pas d'AMM pour l'usage intraoculaire
- Durée d'action limitée (3 à 4 mois)
- HTO dans 50% des cas
- Cataracte
- Autres complications possibles: endophtalmies,DR

Traitement à réserver aux OM diabétiques réfractaires au laser, si l'AV < 0.5

POSURDEX (Allergan) DXM (300 ou 700 µg) inclus dans une matrice biodégradable (PLGA) en cours d'évaluation (phase III)

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

Diabetic Retinopathy Clinical Research Network

Objective: To evaluate the efficacy and safety of 1-mg and 4-mg doses of preservative-free intravitreal triamcinolone in comparison with focal/grid photocoagulation for the treatment of diabetic macular edema (DME).

Design: Multicenter, randomized clinical trial.

Participants: Eight hundred forty study eyes of 693 subjects with DME involving the fovea and with visual acuity of 20/40 to 20/320.

Methods: Eyes were randomized to focal/grid photocoagulation (n = 330), 1 mg intravitreal triamcinolone (n = 256), or 4 mg intravitreal triamcinolone (n = 254). Retreatment was given for persistent or new edema at 4-month intervals. The primary outcome was evaluated at 2 years.

Main Outcome Measures: Visual acuity measured with the electronic Early Treatment Diabetic Retinopathy Study method (primary), optical coherence tomography-measured retinal thickness (secondary), and safety.

Results: At 4 months, mean visual acuity was better in the 4-mg triamcinolone group than in either the laser group ($P<0.001$) or the 1-mg triamcinolone group ($P = 0.001$). By 1 year, there were no significant differences among groups in mean visual acuity. At the 16-month visit and extending through the primary outcome visit at 2 years, mean visual acuity was better in the laser group than in the other 2 groups (at 2 years, $P = 0.02$ comparing the laser and 1-mg groups, $P = 0.002$ comparing the laser and 4-mg groups, and $P = 0.49$ comparing the 1-mg and 4-mg groups). Treatment group differences in the visual acuity outcome could not be attributed solely to cataract formation. Optical coherence tomography results generally paralleled the visual acuity results. Intraocular pressure increased from baseline by 10 mmHg or more at any visit in 4%, 16%, and 33% of eyes in the 3 treatment groups, respectively, and cataract surgery was performed in 13%, 23%, and 51% of eyes in the 3 treatment groups, respectively.

Conclusions: Over a 2-year period, focal/grid photocoagulation is more effective and has fewer side effects than 1-mg or 4-mg doses of preservative-free intravitreal triamcinolone for most patients with DME who have characteristics similar to the cohort in this clinical trial. The results of this study also support that focal/grid photocoagulation currently should be the benchmark against which other treatments are compared in clinical trials of DME.

Table 4. Change in Visual Acuity at 2-Year Primary Outcome*

Change in Visual Acuity (Letters)	Laser (n = 330)	1 mg (n = 256)	4 mg (n = 254)
Mean±SD	1±17	−2±18	−3±22
Median (25th, 75th percentile)	4 (−6, 11)	1 (−11, 9)	2 (−11, 11)
Distribution of change at 2 yrs (%)			
≥15-letter improvement	18%	14%	17%
14- to 10-letter improvement	13%	11%	11%
9- to 5-letter improvement	16%	14%	15%
Same ±4 letters	24%	27%	23%
5–9 letters worse	10%	9%	6%
10–14 letters worse	5%	6%	8%
≥15 letters worse	14%	20%	20%

Table 4. Change in Visual Acuity at 2-Year Primary Outcome*

Change in Visual Acuity (Letters)	Laser (n = 330)	1 mg (n = 256)	4 mg (n = 254)
Mean ± SD	1 ± 17	−2 ± 18	−3 ± 22
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Same ±4 letters	24%	27%	23%
5–9 letters worse	10%	9%	6%
10–14 letters worse	5%	6%	8%
≥15 letters worse	14%	20%	20%

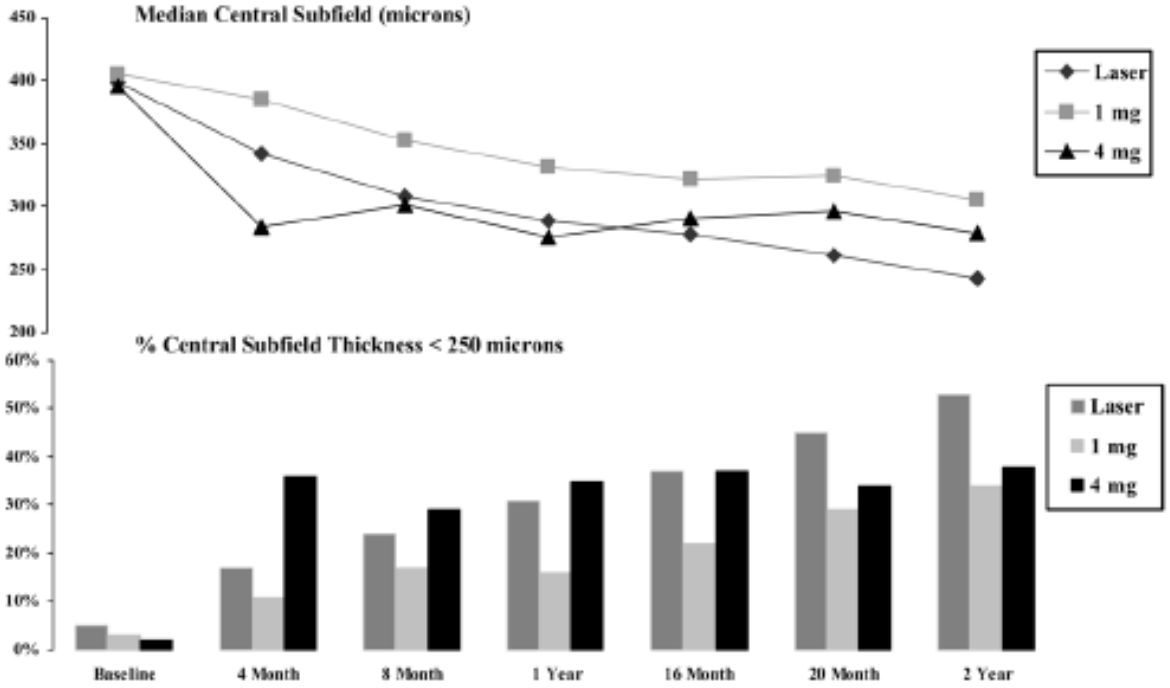


Figure 3. Graph showing the effect of treatment on the central subfield thickness, measured with optical coherence tomography (OCT), at each visit according to treatment group. The top portion of the figure displays the median thickness in each treatment group. The bars in the bottom portion represent the proportion of eyes in each treatment group with thickness of less than 250 μm.

Table 6. Change in Central Subfield Retinal Thickening* at Follow-up Visits

	Laser	1 mg	4 mg
4 Mos	n = 304	n = 234	n = 242
Thickness (μm), median (25th, 75th percentile)	342 (279, 470)	385 (295, 488)	284 (236, 387)
Change from baseline (μm), mean±SD	−39±109	−16±111	−98±130
Change from baseline (μm), median (25th, 75th percentile)	−33 (−90, 13)	−13 (−62, 41)	−77 (−145, −19)
Thickening decreased by ≥50%	23%	15%	46%
Thickness <250 μm	17%	11%	36%
8 Mos	n = 288	n = 221	n = 220
Thickness (μm), median (25th, 75th percentile)	308 (252, 411)	353 (279, 455)	301 (244, 397)
Change from baseline (μm), mean±SD	−73±136	−35±133	−78±130
Change from baseline (μm), median (25th, 75th percentile)	−60 (−147, 4)	−23 (−101, 38)	−76 (−134, −7)
Thickening decreased by ≥50%	40%	27%	45%
Thickness <250 μm	24%	17%	29%
1 Yr	n = 278	n = 225	n = 213
Thickness (μm), median (25th, 75th percentile)	289 (235, 396)	331 (270, 449)	276 (231, 390)
Change from baseline (μm), mean±SD	−98±144	−55±142	−93±146
Change from baseline (μm), median (25th, 75th percentile)	−85 (−167, −14)	−31 (−137, 25)	−74 (−152, −13)
Thickening decreased by ≥50%	48%	33%	48%
Thickness <250 μm	31%	16%	35%
16 Mos	n = 255	n = 208	n = 191
Thickness (μm), median (25th, 75th percentile)	278 (225, 362)	322 (260, 433)	290 (229, 436)
Change from baseline (μm), mean±SD	−105±149	−62±152	−69±150
Change from baseline (μm), median (25th, 75th percentile)	−100 (−184, −15)	−57 (−141, 10)	−69 (−160, 23)
Thickening decreased by ≥50%	54%	35%	48%
Thickness <250 μm	37%	22%	37%
20 Mos	n = 240	n = 198	n = 179
Thickness (μm), median (25th, 75th percentile)	261 (213, 326)	325 (239, 439)	296 (234, 453)
Change from baseline (μm), mean±SD	−132±143	−69±160	−60±175
Change from baseline (μm), median (25th, 75th percentile)	−119 (−211, −36)	−56 (−155, 23)	−65 (−163, 26)
Thickening decreased by ≥50%	64%	40%	45%
Thickness <250 μm	45%	29%	34%
2 Yrs	n = 261	n = 207	n = 193
Thickness (μm), median (25th, 75th percentile)	243 (197, 326)	305 (231, 406)	279 (228, 430)
Change from baseline (μm), mean±SD	−139±148	−86±167	−77±160
Change from baseline (μm), median (25th, 75th percentile)	−131 (−217, −49)	−74 (−168, −3)	−76 (−175, 11)
Thickening decreased by ≥50%	67%	46%	48%
Thickness <250 μm	53%	34%	38%

	Visit					
P Value§	4 Mos	8 Mos	1 Yr	16 Mos	20 Mos	2 Yr
Laser vs. 1 mg	.01†	<0.001†	<0.001†	<0.001†	<0.001†	<0.001†
Laser vs. 4 mg	<0.001‡	0.98	0.97	0.004†	<0.001†	<0.001†
1 mg vs. 4 mg	<0.001‡	<0.001‡	<0.001‡	0.33	0.86	0.91

Baseline Data DRCR net….

- Ip et al, Retina 2008
- CSME on retinal photographs
- FA chez 51% patients, dont 75% d'interprétables
- 64% présentaient des diffusions provenant de microanévrysmes (>33%) ….
- 81% des patients étaient hypertendus (aucune PA n'a été mesurée pendant les 2 ans…!)

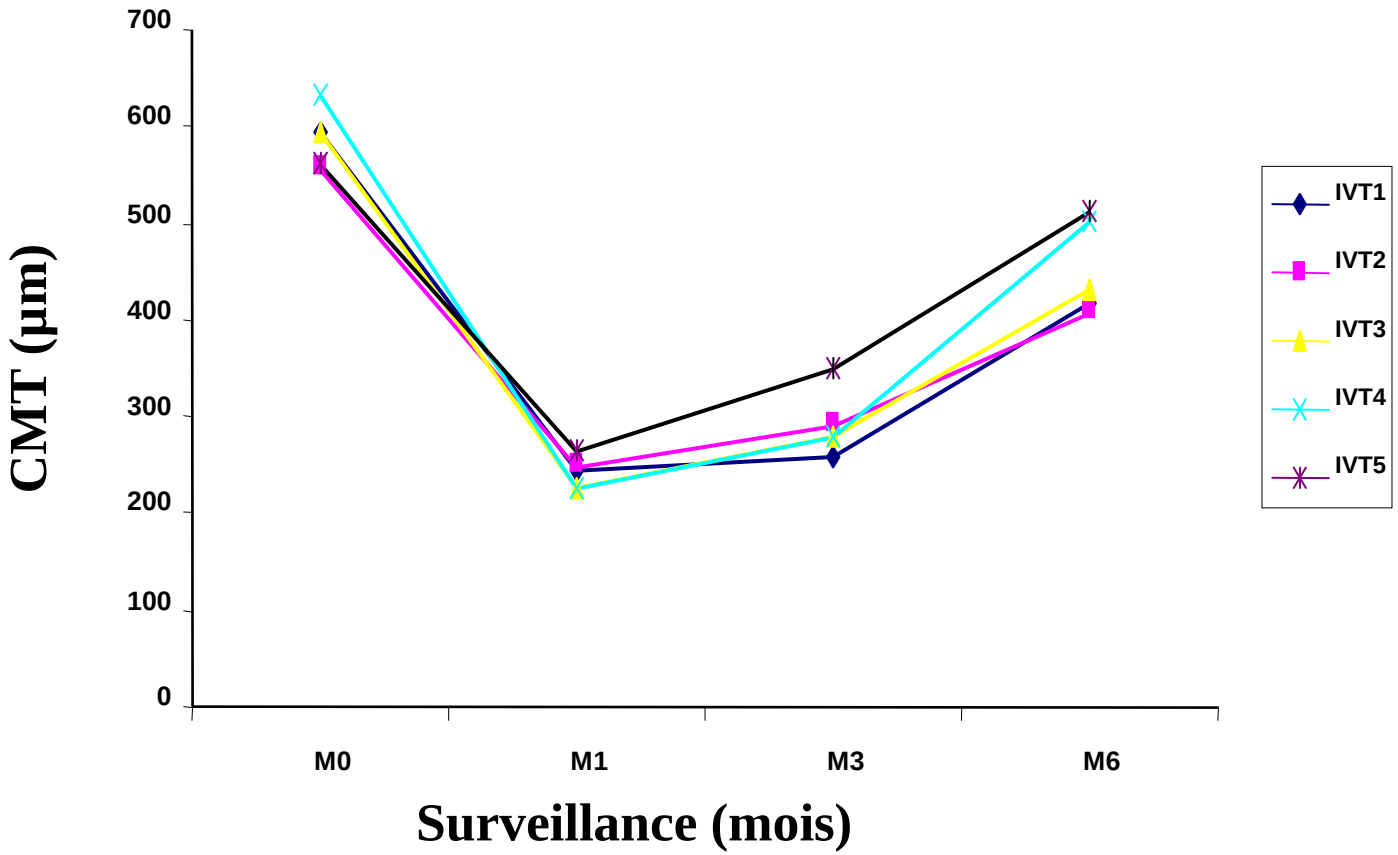
L'effet de la TA est-il reproductible?

- Gillies et al 2006
  - Résultats à 2 ans d'une étude randomisée (TA vs placebo)
  - 68 eyes, 82% ≥ 2 injections
  - **Amélioration AV ≥ 5 lettres: 56% (TA) vs 26% (placebo)**
  - **Réduction de 74% de l'épaisseur maculaire**

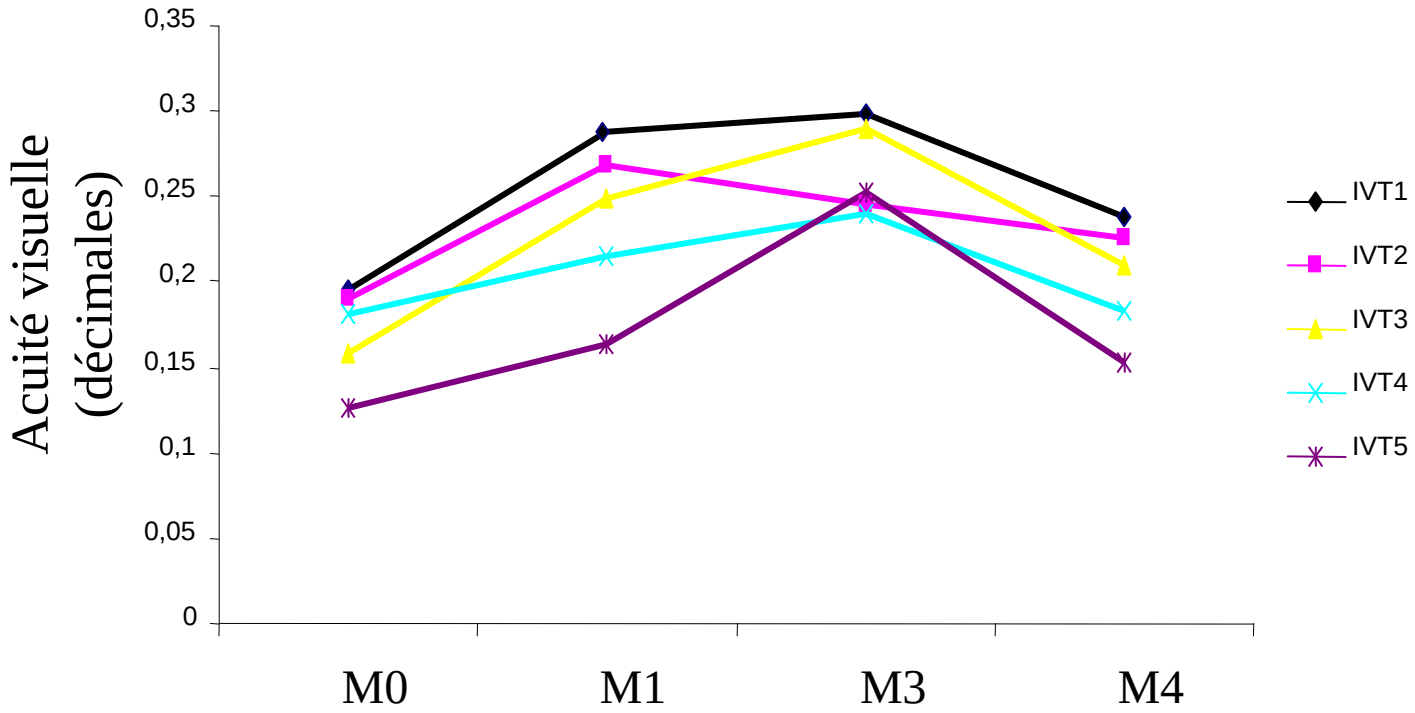
- Lariboisière, 2007 (L Malvitte, D Gaucher, A Catier, A Collet, C Mazit, R Benosman, F Audren)
  - 47 yeux de 36 patients, ayant reçu au moins 2 IVTs
  - OM diffus chronique, réfractaire au laser
  - Suivi : 22 ± 12 mois
  - Nb moyen d'IVTs: 3.3 ± 1.2

Nombre IVT	2	3	4	5 et +
Nombre d'yeux	17	10	8	12

Évolution de l’épaisseur maculaire



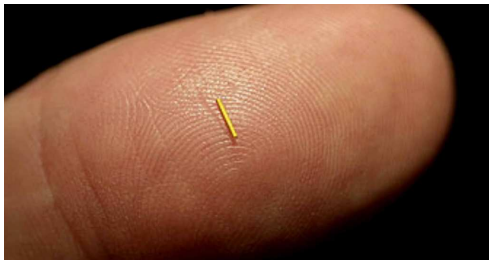
Évolution de l’acuité visuelle



En cours d'évaluation …

- Posurdex ® (Allergan): dexamétasone dans un implant biodégradable, phase III

- Medidur ®: implant de fluocinolone (Amilera), phase III



- I-VAtion TA (Surmodics): Matrice polymère libérant de la Triamcinolone (925 µg) pendant durée ≤ 2 ans, phase II

- Nova 63035 (Novagali Pharma) Emulsion lipidique sans conservateur et sans solvant libérant une prodrogue de la DXM injecté dans le vitré, phase II

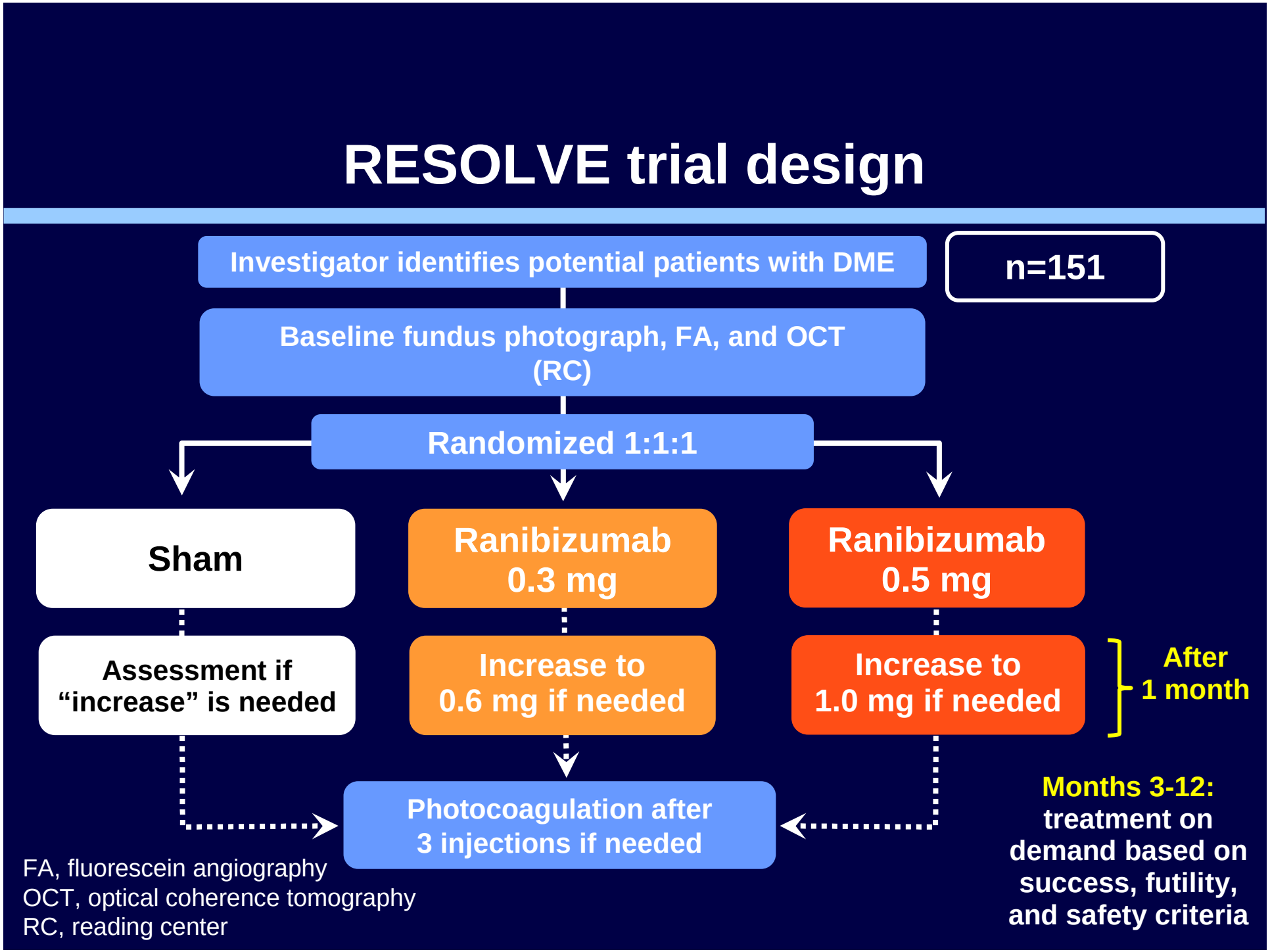
Phase II RESOLVE trial: twelve-month analysis of ranibizumab in diabetic macular edema

Pascale G Massin, on behalf of the RESOLVE Study Group

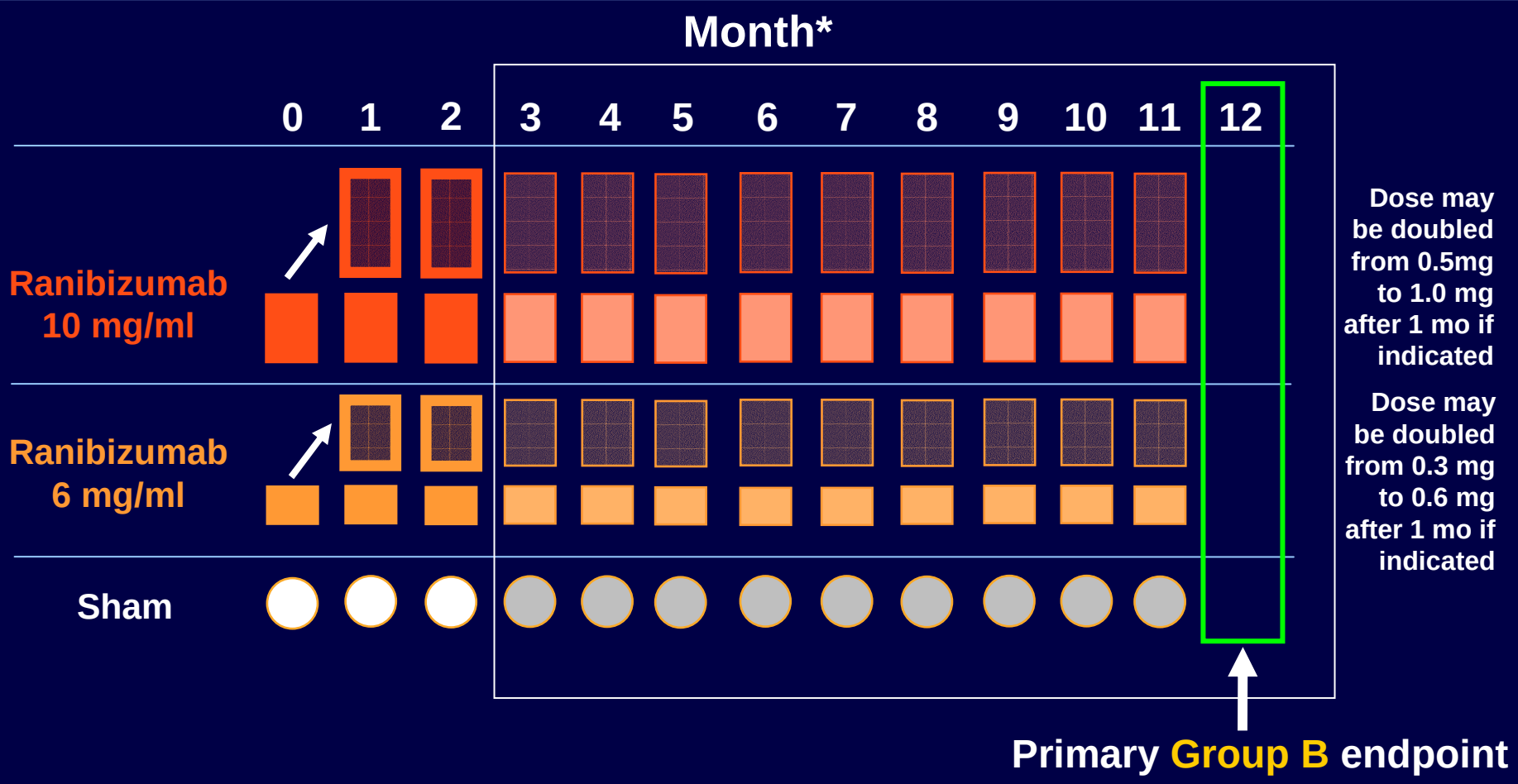
Université Paris VII

Paris, France

RESOLVE trial design



RESOLVE treatment dosing schedule



*Months 3-12 treatment on demand based on success, futility and safety criteria.

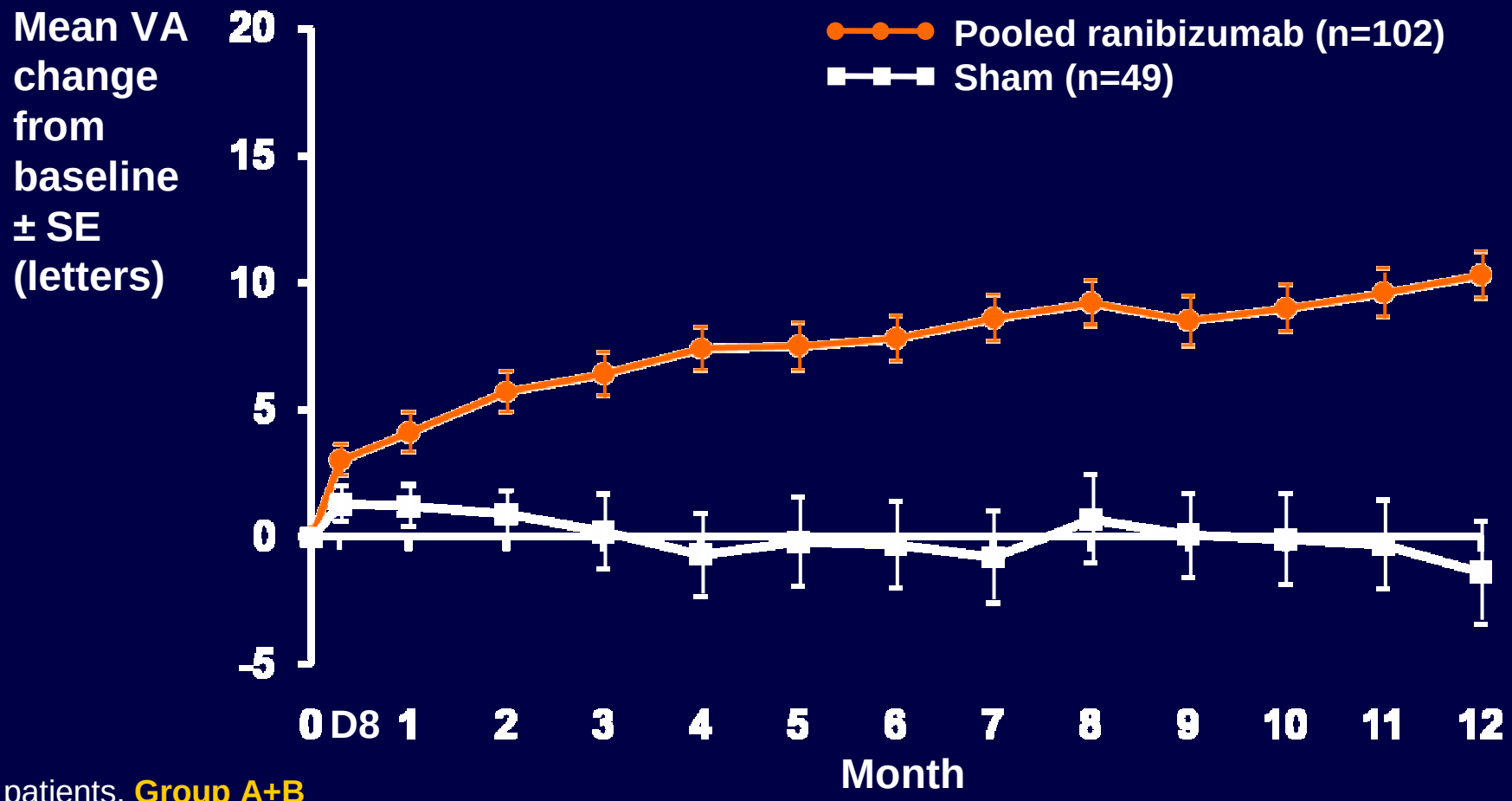
All patients were permitted to receive rescue laser treatment after the 3rd injection

Primary endpoint:
Mean average BCVA change* from baseline to Month 1 through Month 12

	Ranibizumab 6 mg/mL (n=37)	Ranibizumab 10 mg/mL (n=40)	Ranibizumab pooled (n=77)	Sham (n=32)
Baseline BVCA				
Mean (SD)	58.8 (10.74)	63.4 (8.06)	61.2 (9.66)	60.2 (8.52)
Average BCVA from Month 1 through Month 12				
Mean (SD)	68.2 (10.35)	69.4 (11.79)	68.8 (11.29)	61.4 (11.52)
Average change from baseline				
Mean (SD)	9.4 (5.82)	6.0 (9.86)	7.6 (8.29)	1.2 (8.38)
95% CI for mean	(7.4, 11.3)	(2.9, 9.2)	(5.7, 9.5)	(-1.8, 4.2)
Comparison vs Sham				
Diff in LS means	8.1	5.5	6.7	
95% CI for diff	(4.7, 11.5)	(1.0, 9.9)	(3.2, 10.1)	
p-value	<0.0001	0.0067	0.0002	

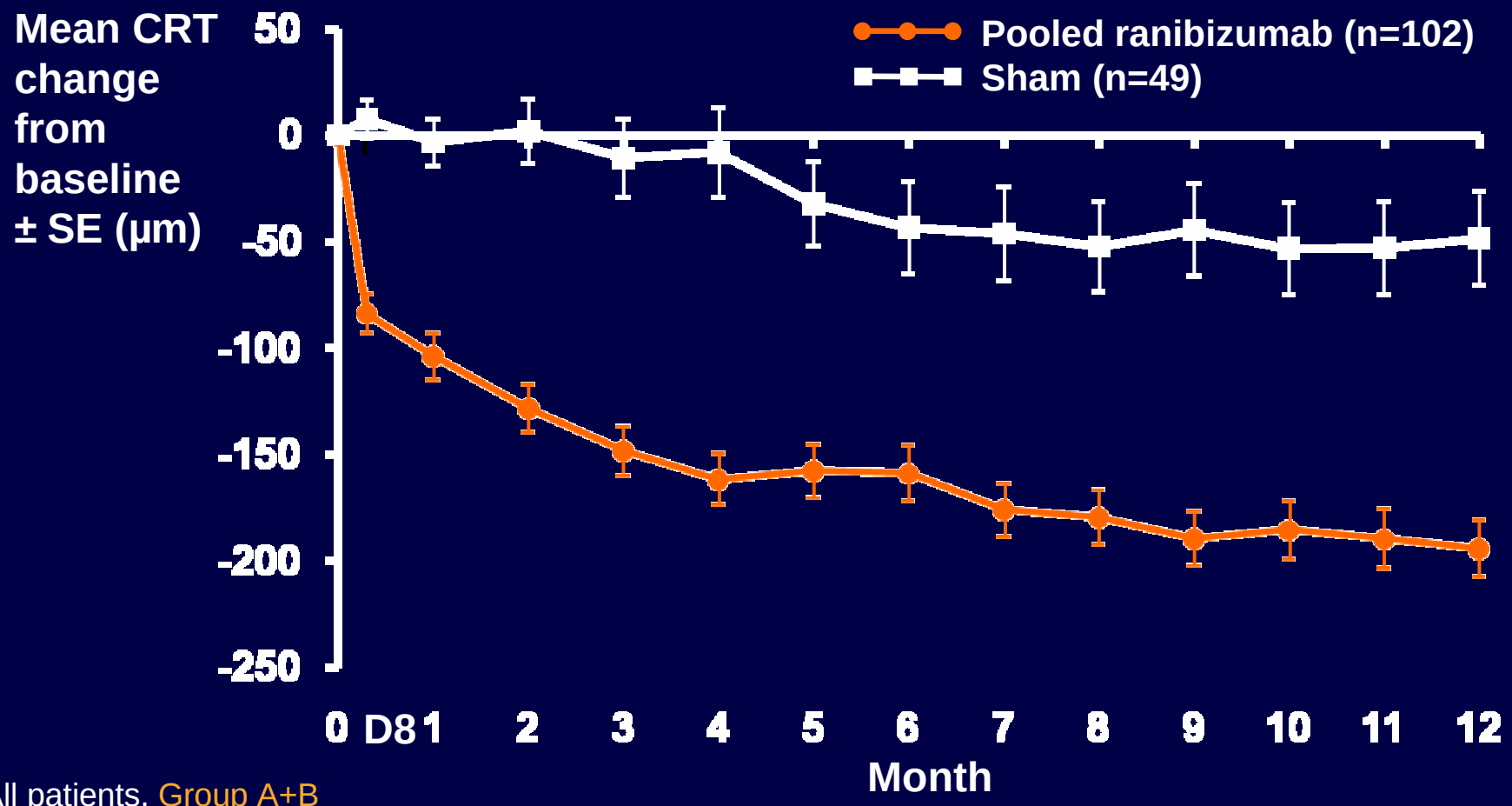
*Confirmatory hypothesis testing, Group B
Full analysis set; last observation carried forward

Secondary endpoint: Mean BCVA change* from baseline



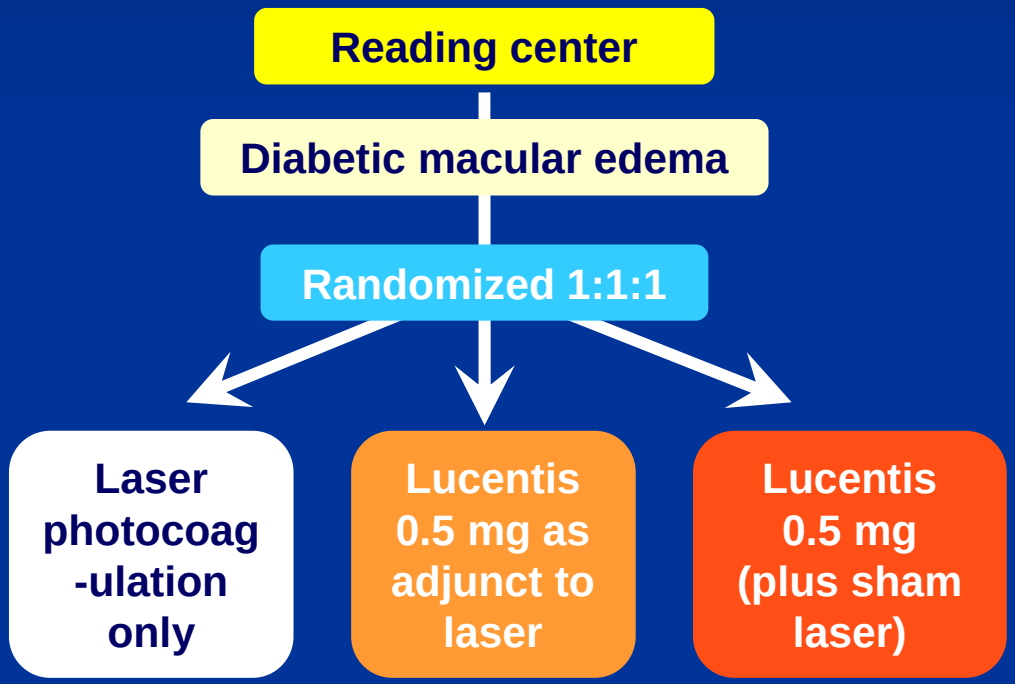
*All patients, **Group A+B**
Full analysis set, last observation carried forward
First VA value post-baseline was assessed at Day 8
SE, standard error of the mean

Secondary endpoint: Mean CRT change* from baseline



*All patients, Group A+B
Full analysis set, last observation carried forward
First CRT value post-baseline was assessed at Day 8
CRT, central retinal thickness

Lucentis DME Phase III: RESTORE



- Evaluation of the efficacy and safety of Lucentis (0.5 mg) as adjunctive therapy when added to laser photocoagulation and/or monotherapy in patients with visual impairment due to DME
- Monthly treatment for 12 months

Primary endpoint

Mean change from baseline in BCVA over 12 months

Larib, Paris
Nantes (Pr Weber)
Dijon (Pr Creuzot)
Grenoble (Pr Romanet

READ II, Phase II, ranibizumab

- READ I, Phase 1: résultats encourageants
- 126 patients , diabétiques, ayant un OMD touchant le centre de la macula,
  - Épaisseur centrale > 250 microns
  - AV comprise entre 20/320 et 20/40
- Critère principal: pourcentage de patients ayant un gain d'AV d'au moins 3 lignes à 6 mois

Randomisation 3 mois

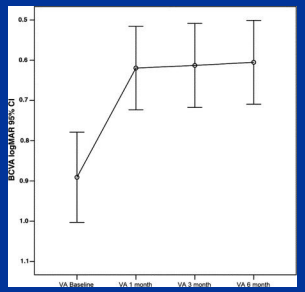
- Groupe I: 4 injections de 0,5 mg ranibizumab à 0, 1, 3 et 5 mois
- Groupe II: Laser + ranibizumab 0,5 mg à 0 et 3 mois
- Groupe III: laser à 3 mois et si besoin à 6mois

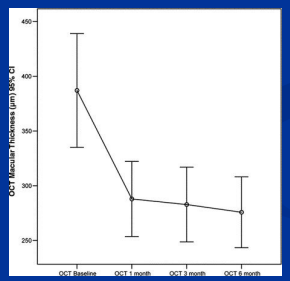
A 6 mois	I 4 Injections RNBZM	II Laser +2 inj 1 et 3 mois	III Laser
AV ≥ 3 lignes	24%	12%	0%
AV ≥ 2 lignes	49%	30%	15%
Score ETDRS	+7.6	+3.8	-1.7
Baisse EMC	57%	42%	11%

Bevacizumab (Avastin®)

- DRCR Net, Ophthalmology 2007
  - Etude randomisée, 5 bras, 1,25mg, 2,5mg, laser sham
  - Pas d'effet bénéfique à 6 semaines
- Pan-American Collaborative Sudy Group, 2007
  - Etude rétrospective (88 patients), Suivi: 6 mois
  - 1 à 3 injections de 1,25 ou 2,5 mg Avastin

Acuité visuelle
55% amélioration
de l'AV





Epaisseur maculaire
Ep Maculaire initiale: 387 ± 183
Ep Maculaire finale: 288 ± 102, 4

- Etude IBEME (Université de Sao Paolo), BJO 2008
  - 2 bras: bevacizumab / Triamcinolone
  - 701 patients randomisés, injections/4 semaines
  - Résultats préliminaires (26 yeux): *meilleurs résultats AV et OCT avec TA*

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

L Paccola, R A Costa, M S Folgosa, J C Barbosa, I U Scott and R Jorge

Br. J. Ophthalmol. 2008;92:76-80; originally published online 26 Oct 2007; doi:10.1136/bjo.2007.129122

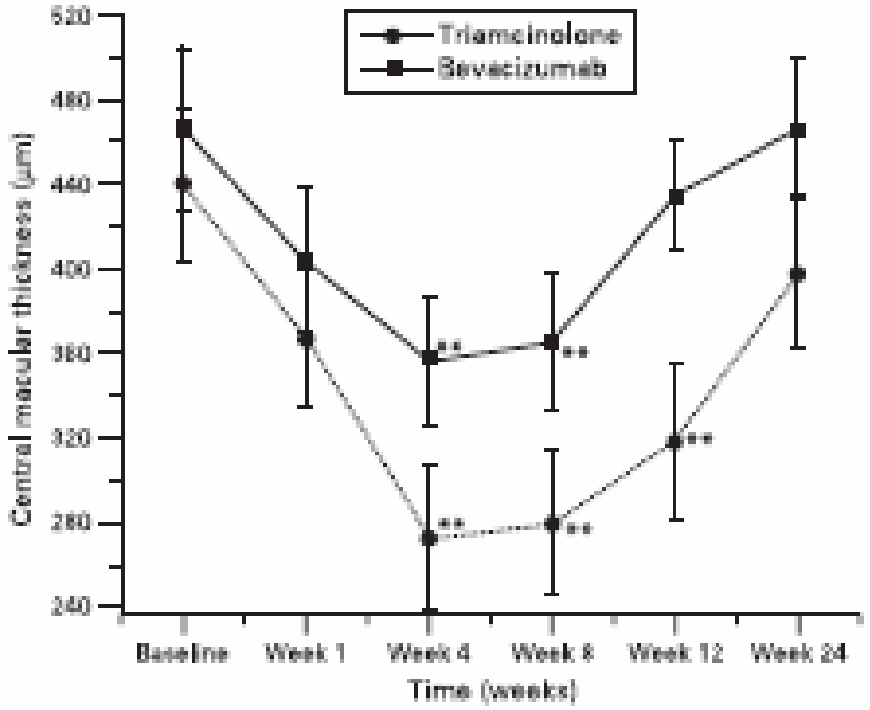


Figure 1 CMT (µm) after intravitreal bevacizumab and triamcinolone treatments by visit. **p<0.01 for within-group changes from baseline values.

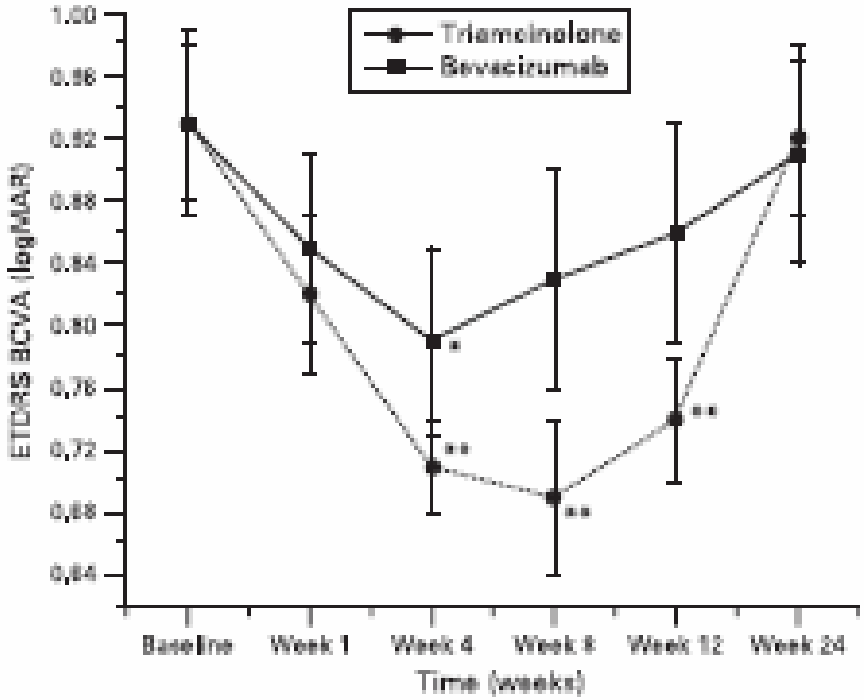
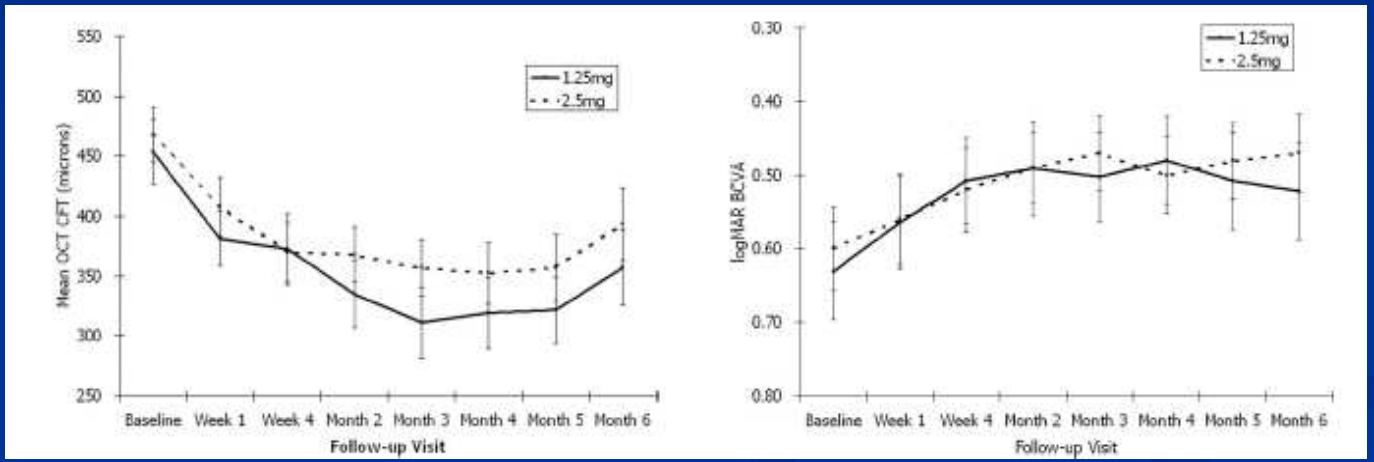


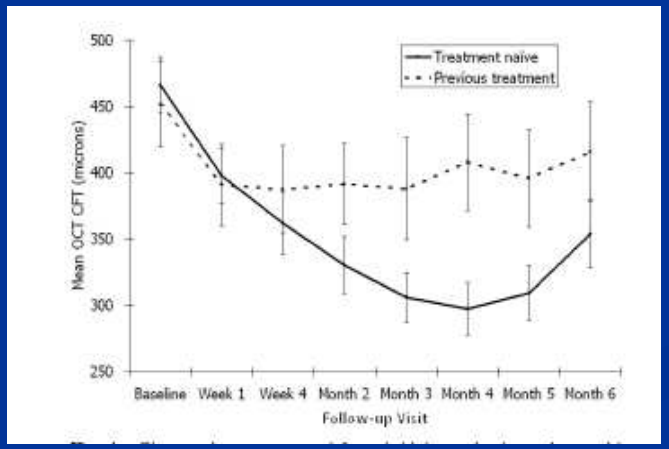
Figure 2 BCVA (LogMAR) after intravitreal bevacizumab and triamcinolone treatments by visit. *p<0.05, **p<0.01 for within-group changes from baseline values.

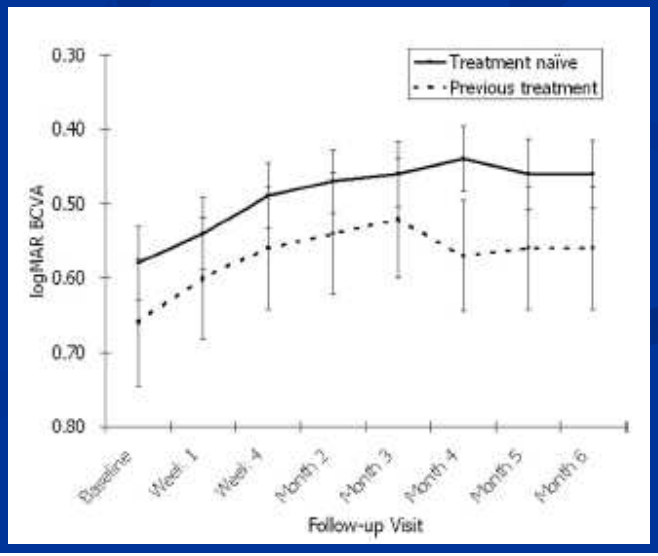
EFFICACY OF 1.25 MG VERSUS 2.5 MG INTRAVITREAL BEVACIZUMAB FOR DIABETIC MACULAR EDEMA

Six-Month Results of a Randomized Controlled Trial

DENNIS S. C. LAM, MD, FRCOPHTH,*† TIMOTHY Y. Y. LAI, MD, FRCS,*†
VINCENT Y. W. LEE, FRCS,*‡ CARMEN K. M. CHAN, MRCP, FRCS,*†
DAVID T. L. LIU, FRCS,*‡ SHAHEEDA MOHAMED, MRCS, MRCOPHTH,*†
CHI-LAI LI, MRCS*‡



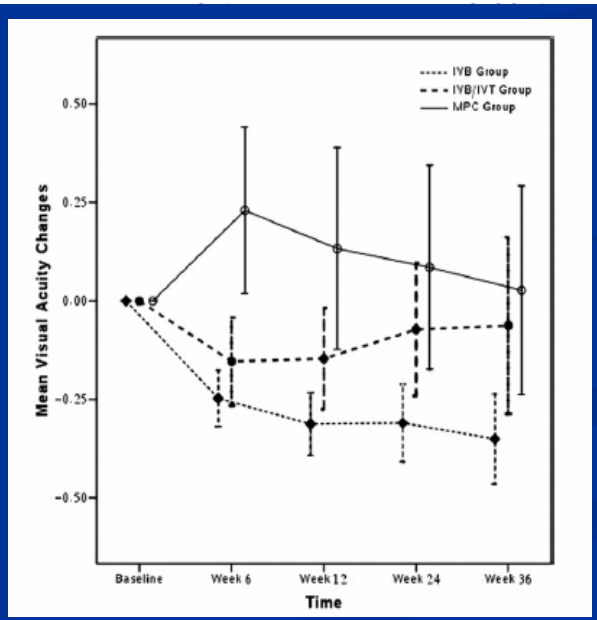




Randomized Trial of Intravitreal Bevacizumab Alone or Combined with Triamcinolone versus Macular Photocoagulation in Diabetic Macular Edema

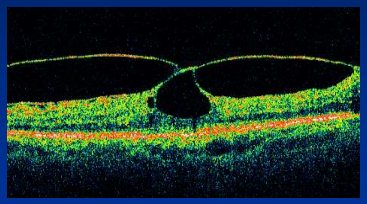
Masoud Soheilian, MD,[1,2] Alireza Ramezani, MD,[1,2] Arash Obudi, MD,[1,2] Bijan Bijanzadeh, MD,[1,2] Masoud Salehipour, MD,[1,2] Mehdi Yaseri, PhD,[3] Hamid Ahmadieh, MD,[1,2] Mohammad H. Dehghan, MD,[1,2] Mohsen Azarmina, MD,[1,2] Siamak Moradian, MD,[1,2] Gholam A. Peyman, MD[4]

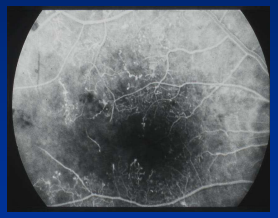
Conclusions: Intravitreal bevacizumab injection in patients with DME yielded a better visual outcome at 24 weeks compared with macular photocoagulation. A change in CMT beyond the 6-week time point that corresponded to the vision change was not detected. No adjunctive effect of IVT was demonstrated.



OM diffus ou mixte

Eliminer un OM tractionnel et une ischémie maculaire





S'acharner à obtenir les objectifs glycémiques et tensionnels +++

Type 1

Traitement par laser
(2-3 sessions)
+ suivi tous les 4 mois

Anti VEGFs ?

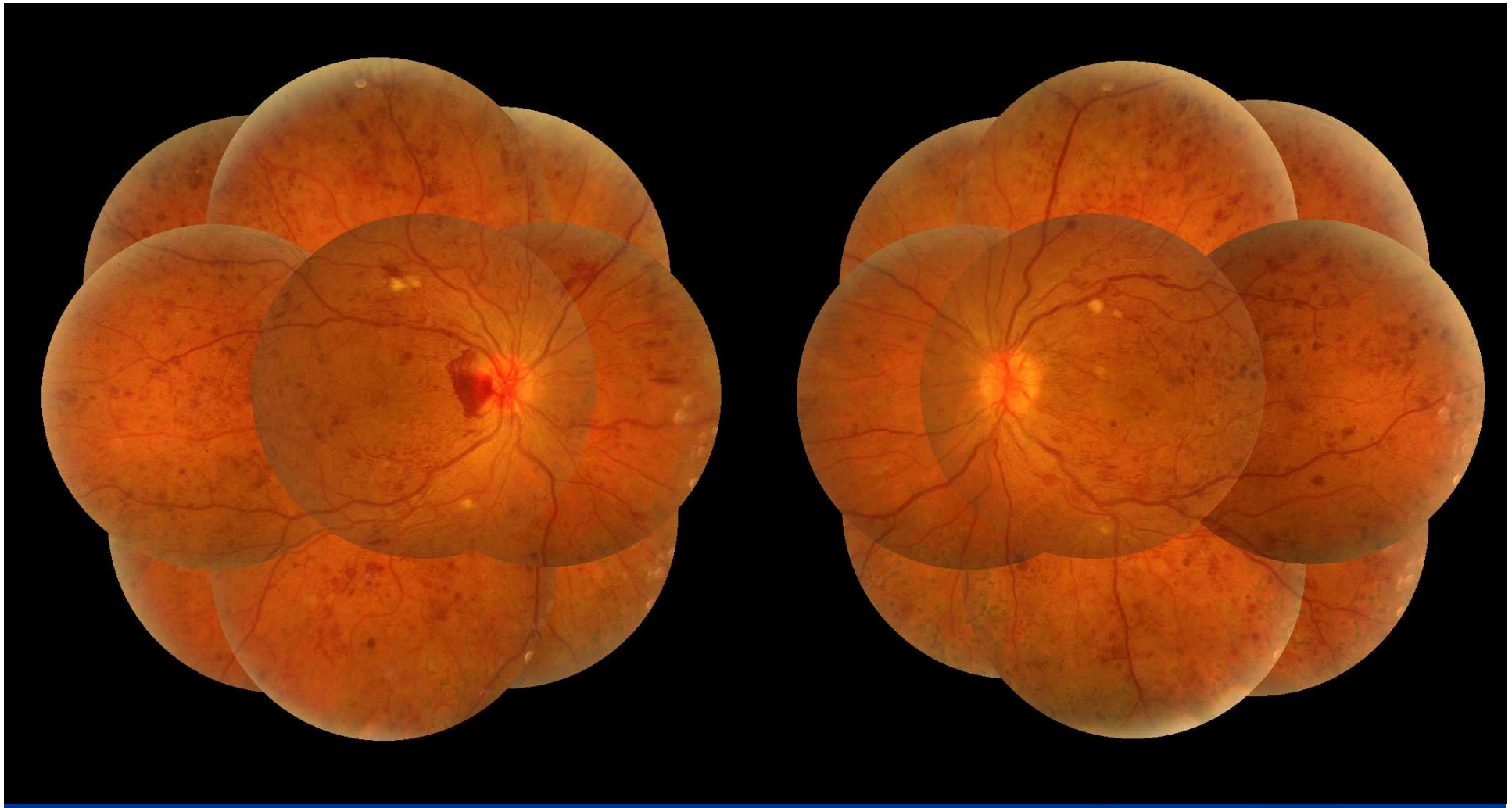
Si échec

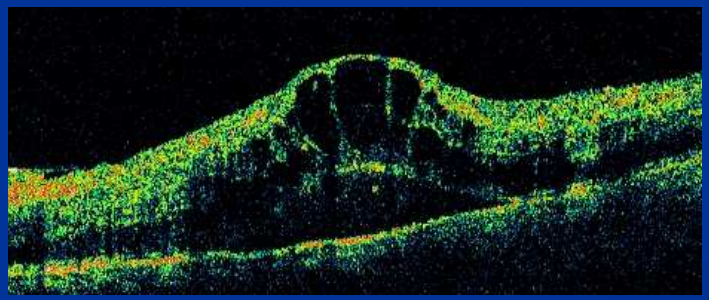
(Vitrectomie)
Injection Triamcinolone

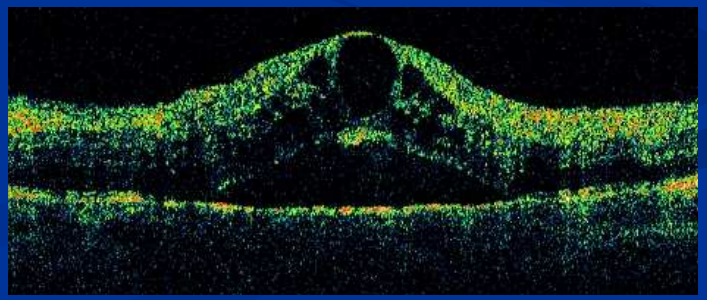
Type 2

Stabilisation de l 'AV

Rééducation Basses Visions







Une indication de première intention:: OM diffus majeur associée à une indication de PPR urgente