DR Barometer
Shifting the needle

Diabetic Retinopathy: The latest in treatment options and what the real world evidence is telling us

Francisco J. Rodríguez, MD
Fundacion Oftalmologica Nacional
Escuela de Medicina y Ciencias de la Salud
Universidad del Rosario
Bogotá, DC

IFA
IAPB
International Diabetes Federation
BAYER

Financial Disclosure

- Consultant
  - Novartis / Alcon, Allergan, Bayer
- Lecture
  - Novartis / Alcon, Allergan, Bayer
- Research Support
  - Novartis

Diabetic Retinopathy / DME

- DR is a major cause of blindness in the working-age group
- DME is the commonest cause of moderate visual loss.
- Wild et al estimated the worldwide prevalence of diabetes mellitus to be 2.8%
- Etiology and pathogenesis of macular edema is intricate and multifactorial
  - Hyperglycemic state induces a microangiopathy.
  - Pathologic changes in vascular endothelium through several inflammatory and vasogenic mediators
  - Breakdown of the blood retinal barrier
- The advent of medications targeting the VEGF pathway has led to great clinical improvements
- Reports have shown that patients have inadequate response, or are nonresponders or have no access to anti-VEGF therapy, demonstrating the need for additional therapies to more comprehensively treat this disease

Wild S, et al. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care 2004; 27:1047-53.

Imaging DR & DME

- Important for diagnosis and follow-up
- Multimodal imaging
  - Fluorescein angiography
    - Wide-field FA
- Fundus autofluorescence
- OCT-SD
- OCT angiography

Clinical Trials In DR & DME

DR Barometer
Shifting the needle

Laser Photocoagulation Trials	Intravitreal Pharmacotherapy Trials (DME)	Intravitreal Pharmacotherapy Trials (DR)	Vitreoretinal Surgery Trials	Medical Therapy Trials
DRS	DRCR (Protocol I)	CLARITY	DRVS	DCCT / EDIC
ETDRS	DRCR (Protocol T)	DRCR (Protocol S)	ETDRS Report 17	UKPDS
DRCR (Protocol A)	READ	DR-Pro-DEX Study	DRCR (Protocol D)	FIELD
DRCR (Protocol B)	RISE/RIDE		DRCR (Protocol N)	ACCORD
DRCR (Protocol F)	BOLT		CHAMPLAIN	DRCR (Protocol M)
DRCR (Protocol K)	FAME			
DRCR (Protocol S)	MEAD			
DRCR (Protocol V)	BEVERDEX			
	PLACID			
	VIVID / VISTA			

Clinical Trials with Anti-VEGF for DME

RISE & RIDE	RESOLVE	Protocol I	RESTORE	VIVID & VISTA	Protocol T
Ranibizumab 0.3 mg	Ranibizumab 0.3mg-0.6 mg	Ranibizumab 0.5 mg +PL	Ranibizumab 0.5 mg	Aflibercept 2 mg 2q4	Ranibizumab 0.3 mg
Ranibizumab 0.5 mg	Ranibizumab 0.5 mg-1mg	Ranibizumab 0.5 mg + DL	Ranibizumab 0.5 mg + Laser	Aflibercept 2 mg 2q8	Aflibercept 2 mg
Placebo (sham)	Sham	Laser	Laser	Laser	Bevacizumab 1.25 mg
		Triamcinolone 4 mg + PL			
Monthly	3 LD+ PRN L Monhly	4 LD + PRN every 4 w	3 LD + PRN monthly	5 LD+ 2q4 vs 2q8	1 LD + PRN Every 4 w

Results

RISE & RIDE[4]	RESOLVE[5]
BCVA gain of more than 15 letters after 36 months: 41.6 / 40.2% vs 22 / 19.2% Mean BCVA gain of 11 letters in RBZ 0.5 mg vs sham 4.3 Reduction in CFT: 269.1 /261µm vs 200.1 / 213 µm	Ranibizumab 0.3-0.6 mg y 0.5-1mg: BCVA (EDTRS) gain at 12 months: 8.8 letters ($p<0.001$ versus sham) vs 11.8 vs -1.4 letters
Delayed treatment in patients receiving sham did not lead to same extent of vision gain	IOP increase Ranibizumab 0.5 mg vs sham: 29% versus 2%

4.Brown DM et al. Ophthalmology. 2013;120:2013–22.
5. Massin P, et al. Diabetes Care. 2010;33:2399–405

Results

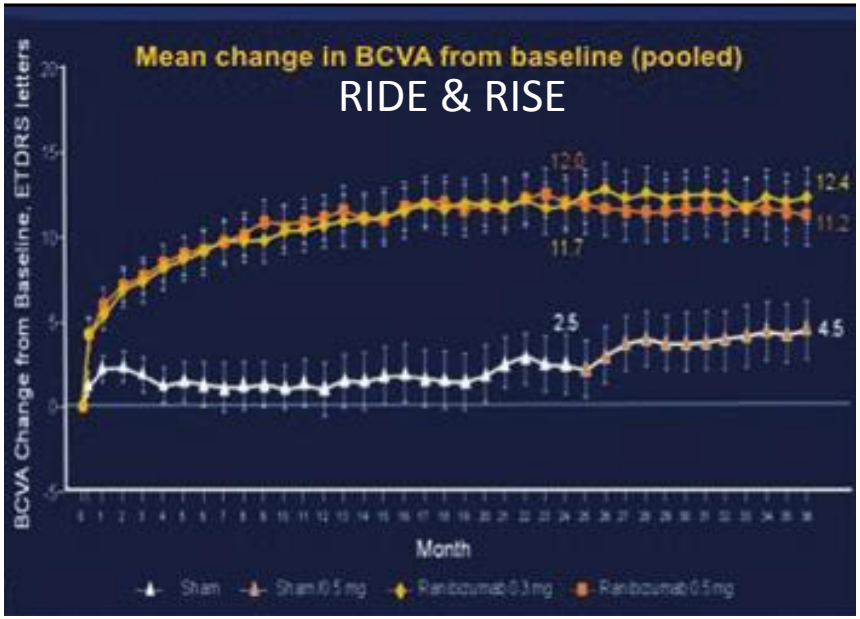
Protocol I[6]	RESTORE[7,8]
The mean change in VA from baseline through the 5-year visit: 7.2 letters versus 9.8 letters p=0.09) Improvement of ≥10 letters in 46% versus 58%, Improvement of >15 letters in 27% versus 38%	BCVA gain at 12 months: 6.1 letters (p<0.001 vs laser) vs 5.9 (p<0.001 vs laser) vs 0.8 letters CRT reduction 128 versus 119 versus 61 µm
Pseudophakia: Triamcinolone + PL more efective than laser alone. Risk of increased IOP	Mean number of injections: 6.5 from months 12–36 (Extension study)

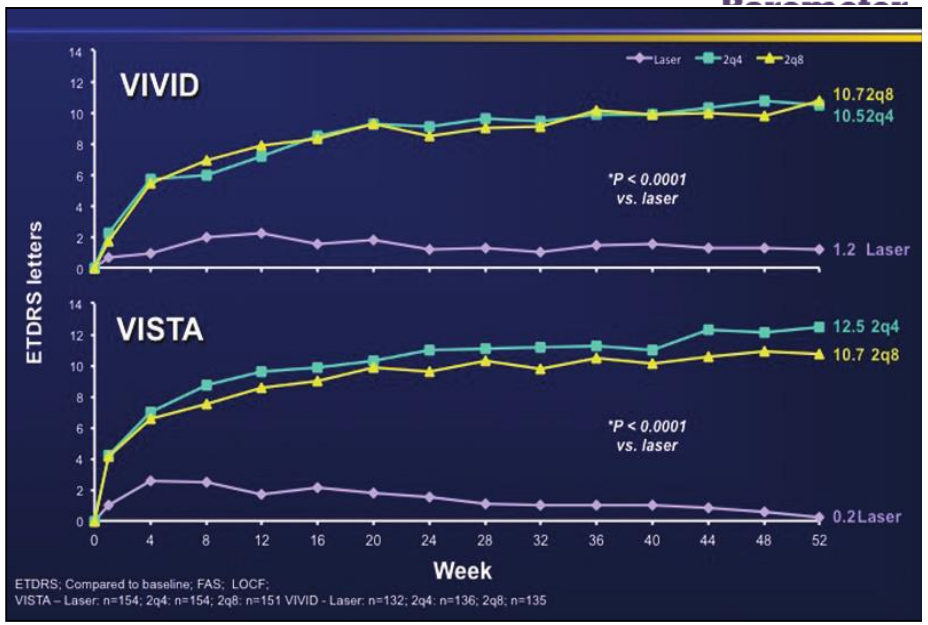
6. DRCR Network, Elman MJ, et al. Ophthalmology. 2010;117:1064–1077.e35
7. Mitchell P, et al. Ophthalmology. 2011;118:615–25.
8. Schmidt-Erfurth U, et al. Ophthalmology. 2014;121:1045–53.

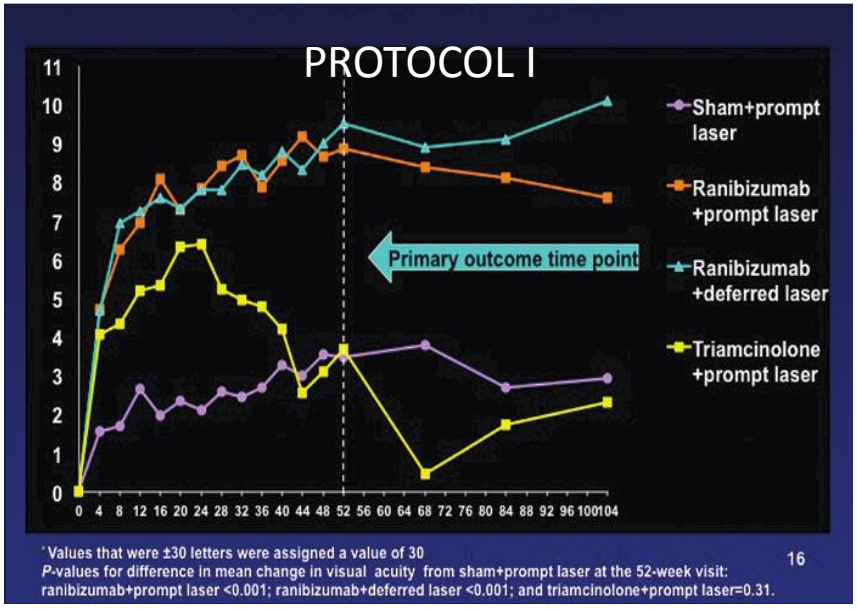
Results

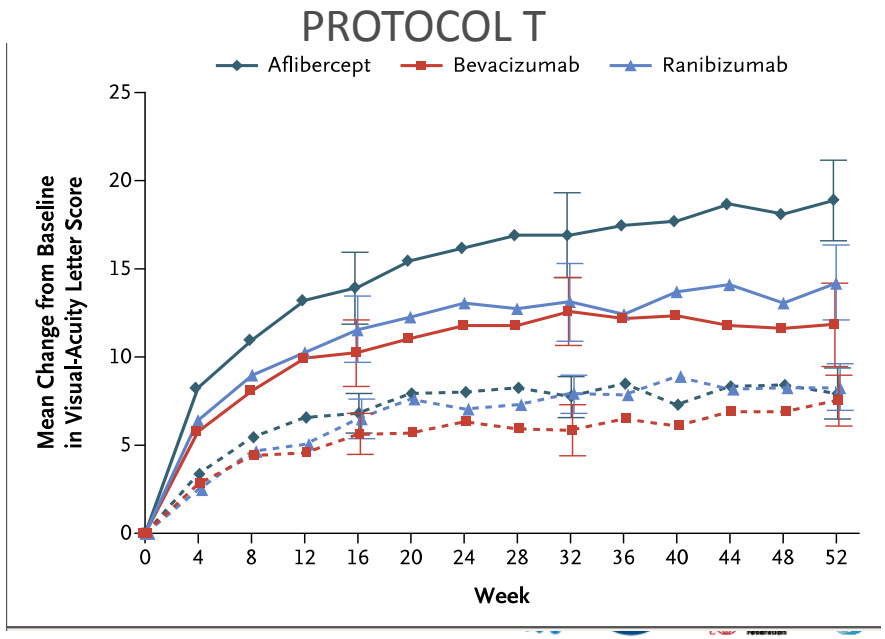
VIVID & VISTA[9]	Protocolo T[10]
Mean change in BCVA (letters) at month 12: 10.5/12.5 vs10.7/10.7 vs 1.2/0.2 Mean BCVA gain at 100 weeks: 11.4, 9.4 and 0.7 letters (p<0.0001)	Mean VA gain at 2 years: Ran 12.3, Bev 10.0, AFL12.8 VA gains in patients with VA 20/32 to 20/40: RBZ 8.6, BEV 6.8, AFL 7.8
Proportion of eyes with >15 letter gain at week 100: 38.2/38.3, 31.1/33.1 and 12.1/13.0% (p≤0.0001)	VA worst than 20/40, AFL shows greater VA gain. Treated with AFL requiered less number of laser treatments.

9. Korobelnik JF, et al. Ophthalmology. 2014;121:2247–54.
10. DRCR Network, Wells JA, et al. N Engl J Med. 2015; 372:1193–203.


Mean change in BCVA from baseline (pooled)
RIDE & RISE
BCVA Change from Baseline, ETDRS letters
Month
12.0
12.4
11.2
11.7
2.5
4.5
Sham
Sham/0.5 mg
Ranibizumab 0.3 mg
Ranibizumab 0.5 mg


VIVID
Laser
2q4
2q8
10.72q8
10.52q4
*P < 0.0001
vs. laser
1.2 Laser
VISTA
12.5 2q4
10.7 2q8
*P < 0.0001
vs. laser
0.2Laser
ETDRS letters
Week
ETDRS; Compared to baseline; FAS; LOCF;
VISTA – Laser: n=154; 2q4: n=154; 2q8: n=151 VIVID - Laser: n=132; 2q4: n=136; 2q8; n=135


PROTOCOL I
Sham+prompt laser
Ranibizumab +prompt laser
Primary outcome time point
Ranibizumab +deferred laser
Triamcinolone +prompt laser
*Values that were ±30 letters were assigned a value of 30
P-values for difference in mean change in visual acuity from sham+prompt laser at the 52-week visit:
ranibizumab+prompt laser <0.001; ranibizumab+deferred laser <0.001; and triamcinolone+prompt laser=0.31.
16


PROTOCOL T
Aflibercept
Bevacizumab
Ranibizumab
Mean Change from Baseline in Visual-Acuity Letter Score
Week

Vision improvement

	RIDE & RISE	RESOLVE	Protocol I	RESTORE	VISTA & VIVID	Protocol T
Prportion of eyes with > 15 letter gain	R 0.3mg RIDE: 36.8% RISE: 51.2%	R 0.5mg 32.4%	R 0.5 mg +PL 30%	R 0.5 mg 22.6%	AFL 2q4 VISTA: 41.6% VIVID: 32.4%	R 0.3 mg >20/40: 16% <20/50: 50%
	R 0.5 mg RIDE: 40.2% RISE: 41.6%		R 0.5 mg + DL 28%	R 0.5 mg + Laser 22.9%	AFL2q8 VISTA: 31.1% VIVID: 33.3%	A 2 mg >20/40: 18% <20/50: 67%
	(sham) RIDE: 19.2% RISE: 22.0%	Laser 5%	Laser 15%	Laser 8.2%	Laser VISTA: 7.8% VIVID: 9.1%	B 1.25 mg >20/40: 15% <20/50: 41%
			T 4 mg + PL 21%			

Intravitreal Corticosteroids

TRIAMCINOLONE[6]	DEXAMETASONE[12]	FLUCINOLONE[13]
Protocol I /J Subgroup analysis: Similar VA gains as Ranibizumab in pseudophakic	Ozurdex (MEAD study) 0.7-0.35 mg BCVA % patients ≥ 15 letters at month 36: DEX 0.7 mg: 22; Sham: 12 (p<0.018) Mean average reduction over 36 months versus baseline: DEX 0.7 mg: -111.6 µm; Sham: -41.9 µm Similar effect of DEX 0.7 mg in subgroups defined by DME duration.	Fluocinolone (FAME): non-degradable implant. (0.2-0.5ug/día) > 15 letras, 28.7%
Risk of cataract and increased IOP.	Cataract surgery rate: DEX: 59%, Sham: 7.2% Increased IOP: DEX: 36%, Sham 5%	82%: cataract 20% IOP > 30 mmHg.

6. DRCR Network, Elman MJ, et al. Ophthalmology. 2010;117(6):1064–1077.e35
12. Boyer DS, et al. Ophthalmology. 2014 Oct;121(10):1904–14.
13. Cunha-Vaz J, et al. Ophthalmology. 2014 Oct;121(10):1892–903.

Diabetic Retinopathy Progression

Severity

RISE & RIDE[11,12]	VIVID & VISTA[9,10]
Ranibizumab 0.3 or 0.5mg showed substantial >2 and >3 step improvement in retinopathy severity.	Significant more eyes in AFL 2q4 and 2q8 vs laser had 2> step improvement in DRSS score: VISTA (37.0% and 37.1% vs. 15.6%; P < 0.0001) and VIVID (29.3% and 32.6% vs. 8.2%; P ≤ 0.0004)
Fewer patients developed PDR or underwent PRP. Therapy modifies natural course of the disease	

9. Korobelnik J-F, et al. Ophthalmology. 2014;121:2247–54
10. Brown DM et al. Ophthalmology 2015;122:2044-52
11. Ip MS, et al. Ophthalmology. 2015;122:367–74.
12. Nguyen DQ et l. Opthalmology 2012;119:789-801.

Clinical Trials with Anti-VEGF for DR

Study Population / F/U (m)	Inclusion Criteria	Treatment Arms	Mean Vision Change (letters)	Mean CMT Change (um)	Regression on Neovascularization At Last Follow Up
Protocol S [13] 394 / 24	VA≥ 20/320	Ranibizumab (0.5 mg q4 PRN) PRP	2.8 (95% CI, 0.4 to 5.2) 0.2 (95% CI,−1.9 to 2.3)	-47 (95% CI -61 to -33) -3 (95% CI -15 to 9)	35% 30%
Clarity [14] 232 / 12	VA≥20/80	Aflibercept (2 mg q4, PRN after 3 loading q4 doses) PRP	1.3 (0.6 SE) -2.9 (0.7 SE)	-8.9 (2.3 SE) 24.0 (5.5 SE)	64% 34%

13. Writing Committee for the Diabetic Retinopathy Clinical Research Network, Gross JG, Glassman AR, et al. JAMA 2015;314:2137-2146.
14. Sivaprasad S et al. Lancet, 2017.

Real World Evidence for DME Ranibizumab

Menchini [14] (PRIDE Study)	Patrao[15] RWO of Ranibizumab for DME in UK
Ranibizumab 0.5 mg, laser as needed in 515 patients (unilateral and bilateral treatment); 10% naïve patients.	Ranibizumab 3 monthly injection and PRN in 164 patients/200 eyes, F/U at least 6 months.
Mean VA gain in decimal scores (±SD) at month 5: Unilateral: 1.5 ± 2.38 Bilateral: 1.22 ± 1.67	At 12 months: Mean VA change: +6.6 (± 13.35) letters (P=.0003). 40.3% of patients gained > 10 letters 25.1% gained > 15 letters 8.9% lost >10 letters / 6.3% los >15 letters. Mean change CST -133.9 (± 160.12)um Mean change MV -1.5 (± 1 Average of 7.2 (± 2.3) injections
Eye disorders: 3.18%/4.18% respectively Cardiac disorders:1.27%/1.23% Vascular disorders: 0.64%/0.66%	Outcomes comparable with clinical trials

14. Menchini U, et al. J Ophthalmol 2015
15. Patrao NV, et al. AJO 2016;172:51-57

Real World Evidence for DME

Ciulla [16]	Willis[17] IRIS
EMR – Vestrum Health Retina Database -5872 patients -3 cohorts on F/U: 6, 12, 24 m -At least 3 m injections anti-VEGF -No exclusive criteria	13.410 patients (July 1, 2013 – March 31 2016) Newly diagnosed treatment-naive DME Mean age 66 years old 51% bilateral, 2/3 from public insurance 58% received care from retina specialists
-6 m: 2503 patients, age 62, mean # 5.2 injections. 6.1 letter improvement (VA was 6.9 letters with AFL, 4.9 with RBZ, 6.1 with BEV) **-12 m**: 2315 patients, age 62, mean # 8.5 injections. 6.3 letter improvement (VA was 7.4 letters with AFL, 6.1 with RBZ, 6.0 with BEV) **-24 m**: 1041 patients, age 61, mean # 14.8 injections. (VA was 6.2 letters with RBZ, 6.5 with BEV).	Time points 1 m/ 1 year: 74.5% received no treatment during the first 28 days after diagnosis and only 15.6% started anti-VEGF therapy. A year after diagnosis, more than half (60.4%) remained untreated, including 81% of those who were only observed during the first month. Preferred agent BEV / AFL/ RBZ # injections 4.2
Under treatment may supersede the VEGF agent used. VA of 20/40 or better did not show improvements in vision.	

16. Ciulla TA, Williams DF. “Real-World” Outcomes for Anti-VEGF Therapy of Diabetic Macular Edema in USA. Presented at: 35th Annual Meeting of the ASRS; August 11-15, 2017; Boston.
17. Willis JR. IRIS. AAO, November 131-14, 2017, New Orleans.

Conclusions

- Management of DME is complex and often multiple treatment approaches are needed
- Treatment for DME /DR
  - First line: Anti-VEGF
  - Second line:
- Multiple injections are required in the first year with diminishing injections in subsequent years
- Anti-VEGF have a disease modifying effect on DR

Conclusions

- Major limitations to comparing pivotal trials with clinical practice data
  - Differing, mostly shorter study periods
  - Different reporting of efficacy endpoints:
    - Visual acuity
    - Smaller patient numbers
    - Less clearly defined patient populations,
      - especially in respect to duration of DME.
- Based on the pivotal trial findings, the current assumptions should be that delayed treatment of patients results in lower overall vision gains.

DR Barometer

Shifting the needle

IFA

IAPB

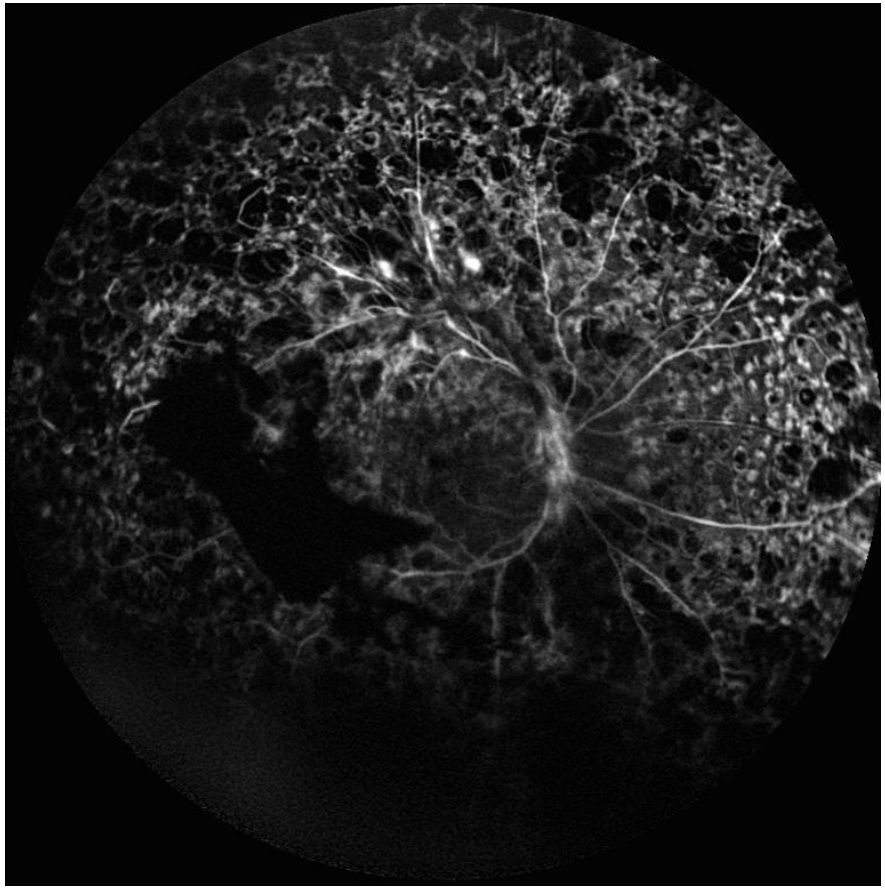
International Diabetes Federation

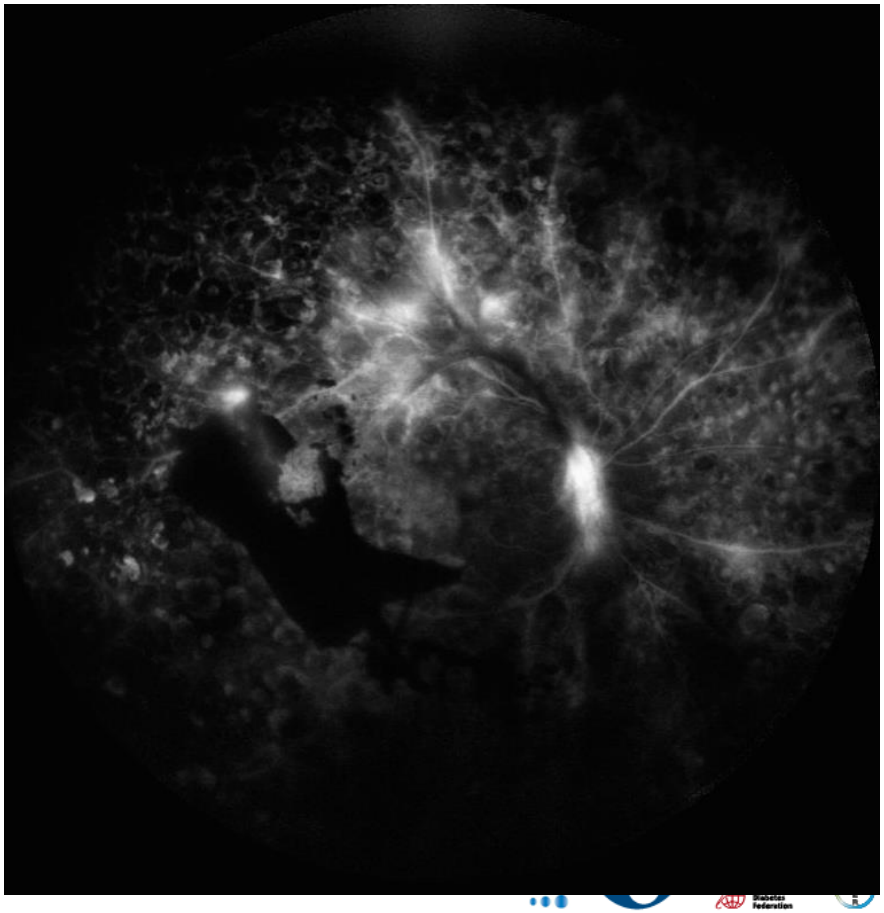
BAYER

Estudios en RD

Severidad

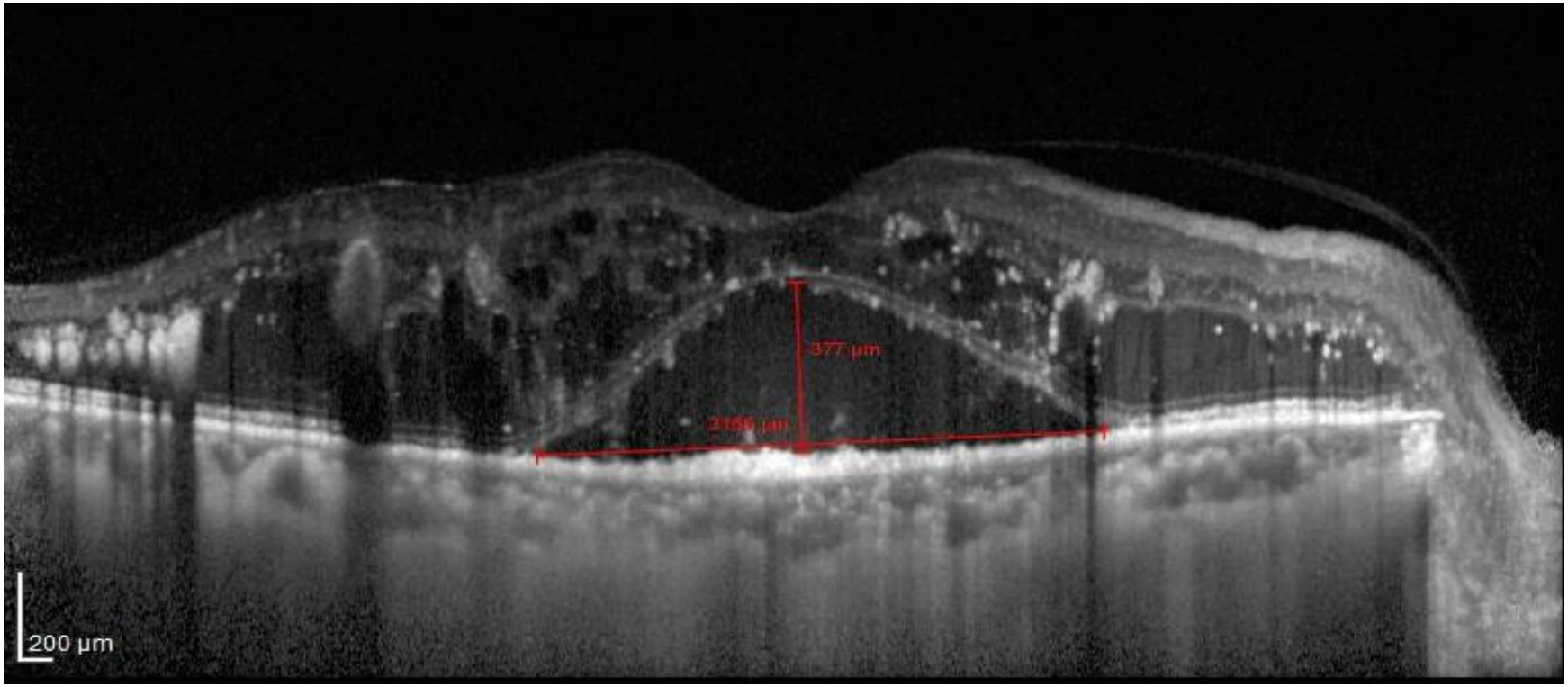
- Angiografía Fluoresceínica Panorámica





Diagnosis & F/U in DR and DME

- Optical Coherece Tomography
  - OCT



Seguimiento en RD y EMD

- Fluoresecein Angiography