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OMICS Group International is a pioneer and leading science event organizer, which publishes around 400 open access journals and conducts over 300 Medical, Clinical, Engineering, Life Sciences, Pharma scientific conferences all over the globe annually with the support of more than 1000 scientific associations and 30,000 editorial board members and 3.5 million followers to its credit.

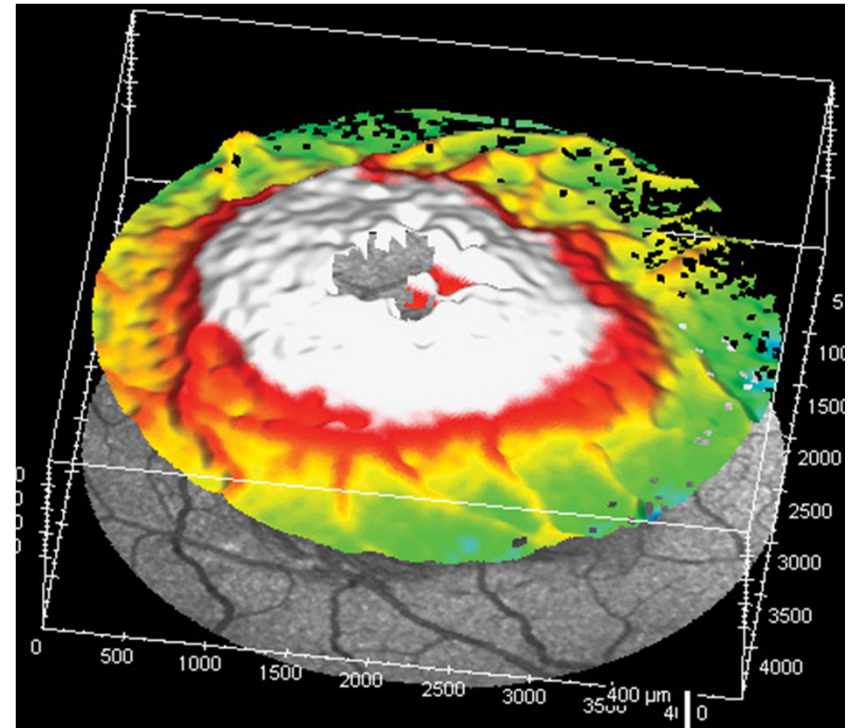
OMICS Group has organized 500 conferences, workshops and national symposiums across the major cities including San Francisco, Las Vegas, San Antonio, Omaha, Orlando, Raleigh, Santa Clara, Chicago, Philadelphia, Baltimore, United Kingdom, Valencia, Dubai, Beijing, Hyderabad, Bengaluru and Mumbai.

Nicholas J. Butler, MD
Wilmer Eye Institute
Clinical and Experimental Ophthalmology
4th International Conference
July 14-16, 2014

Interferon alpha-2b in the Treatment of Refractory Uveitic Cystoid Macular Edema

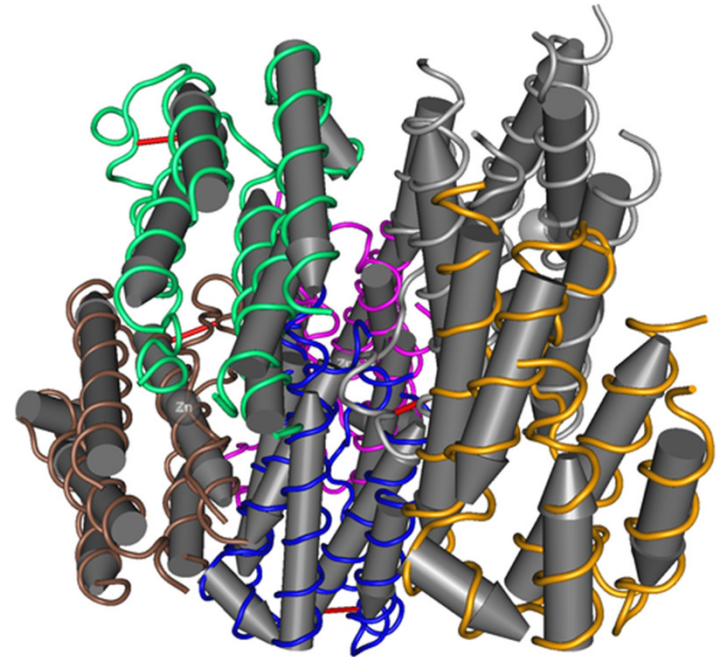
Introduction

- Burden of uveitic CME
 - >30%
 - Leading cause of LOV and legal blindness
 - Potentially irreversible LOV



Interferon alpha-2b

- IFN alphas
 - Species-specific cytokines
 - WBC produced
 - Antiviral, antiproliferative, immunomodulatory
 - Chronic hepatitis, leukemias/lymphomas, solid tumors



Ocular use of IFN α

CLINICAL SCIENCE

Human recombinant interferon alfa-2a for the treatment of Behçet's disease with sight threatening posterior or panuveitis

I Kötter, M Zierhut, A K Eckstein, R Vonthein, T Ness, I Günaydin, B Grimbacher, S Blaschke, W Meyer-Riemann, H H Peter, N Stübiger

Br J Ophthalmol 2003;**87**:423-431

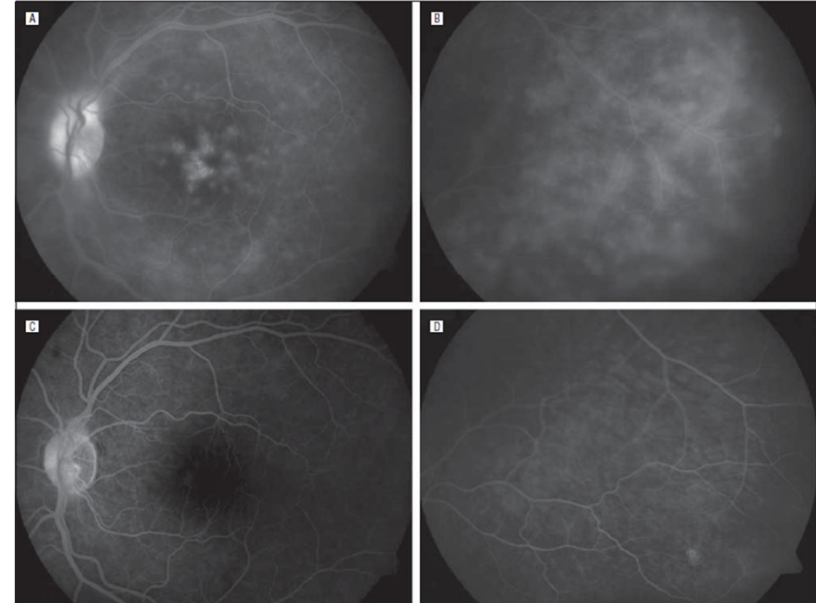
- 50 patients
- 92% response rate to IFN alfa s.c.
- Mean VA improved by wk 24
 - 0.56 to 0.84 (decimal); $p < 0.001$
- 58 eyes with CME → 100% resolution

Long-term Efficacy and Safety of Low-Dose and Dose-Escalating Interferon Alfa-2a Therapy in Refractory Behçet Uveitis

Sumru Onal, MD, FEBOphth; Haluk Kazokoglu, MD; Aylin Koc, MD; Mehmet Akman, MD, MPH; Tayfun Bavbek, MD; Haner Direskeneli, MD; Sule Yavuz, MD

Arch Ophthalmol. 2011;129(3):288-294

- 37 with refractory Behçet's PU
- 95% response rate



Interferon- α as an Effective Treatment for Noninfectious Posterior Uveitis and Panuveitis

JARKA PLSKOVA, KATHRIN GREINER, AND JOHN V. FORRESTER

- 12 patients, sight-threatening, refractory uveitis
- 9 idio, 1 sympathetic, 2 Behçet's
- 83% response rate
- 14 eyes with CME → 100% resolution
- SEs common

Am J Ophthalmol 2007;144:55–61.

TABLE 3. Uveitis Patients' Side Effects while Receiving IFN- α Therapy

Symptom	No	%
Tiredness	8	67
Lymphopenia	8	67
Transient increase in liver enzymes	7	58
Flu-like symptoms	6	50
Weight loss	4	33
Anemia	4	33
Depression	4	33
Mouth ulcers	4	33
Itching	3	25
Rash	3	25
Reddening at site of injection	3	25
Retinotoxicity	3	25
Nausea/vomiting	3	25
Worsening of psoriasis	2	16
Stingy tongue	2	16
Dry mouth	2	16
Mild forgetfulness	2	16
Dysmenorrhea	2	16
Loss of appetite	2	16
Fibromyalgia	1	8
Thyroid dysfunction	1	8
Suicidal tendency	1	8
Dry skin	1	8
Hair loss	1	8
Infection at injection site	1	8
Nose bleed	1	8
Breathlessness	1	8
Onychomycosis	1	8

All patients experienced at least one of the side effects.

Non- Behçet's CME??

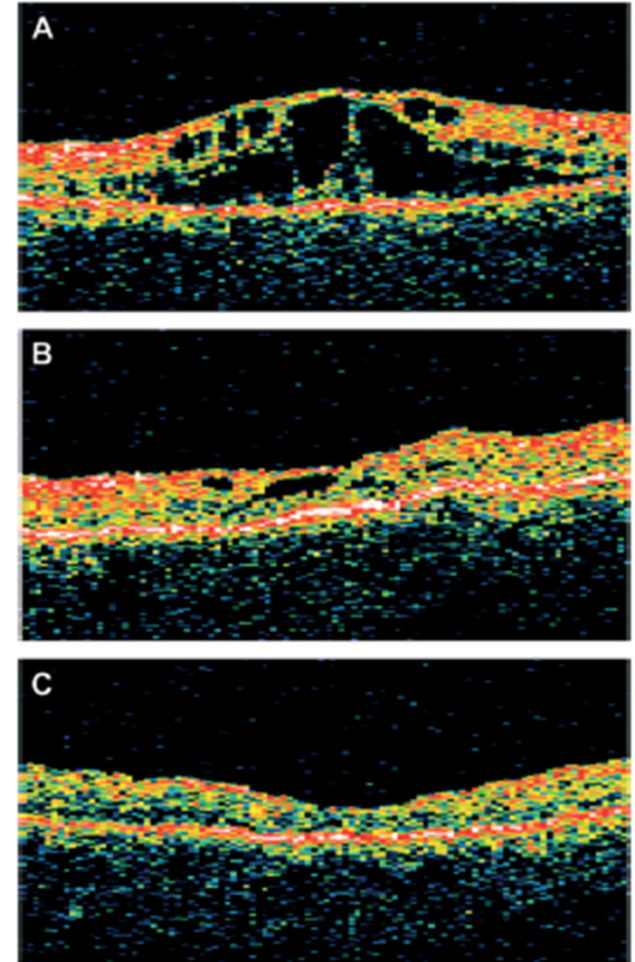
INTERFERON ALFA-2A: A NEW TREATMENT OPTION FOR LONG LASTING REFRACTORY CYSTOID MACULAR EDEMA IN UVEITIS?

A Pilot Study

CHRISTOPH M. E. DEUTER, MD,* INA KOETTER, MD,†
ILHAN GUENAYDIN, MD,† NICOLE STUEBINGER, MD,*
MANFRED ZIERHUT, MD*

RETINA 26:786-791, 2006

- 15 eyes of 8 patients
- Mean duration: **52 mos.**
- 13/15 eyes → 100% resolution (2-4 wks)
- 1/8 (2 eyes) no response*; 1/7 lost response**
- Of 11 eyes treated over 6 mos.
 - mean CMT: 551 to 143 μm
 - mean BCVA (logMAR): +0.80 to +0.42



F/u Study

Efficacy and tolerability of interferon alpha treatment in patients with chronic cystoid macular oedema due to non-infectious uveitis

C M E Deuter,¹ I Kötter,² I Günaydin,² N Stübiger,¹ D G Doycheva,¹ M Zierhut¹ *Br J Ophthalmol* 2009;**93**:906–913.

- Interventional case series
- 24 consecutive pts (40 eyes)
- Mean duration: 36 mos.

Efficacy and tolerability of interferon alpha treatment in patients with chronic cystoid macular oedema due to non-infectious uveitis

C M E Deuter,¹ I Kötter,² I Günaydin,² N Stübiger,¹ D G Doycheva,¹ M Zierhut¹

Br J Ophthalmol 2009;**93**:906–913.

- “Effective”
 - 25 eyes of 15 pts (62.5%)
- “Partly effective”
 - 10 eyes of 6 pts (25%)
- “Not effective”
 - 5 eyes of 3 pts (12.5%)

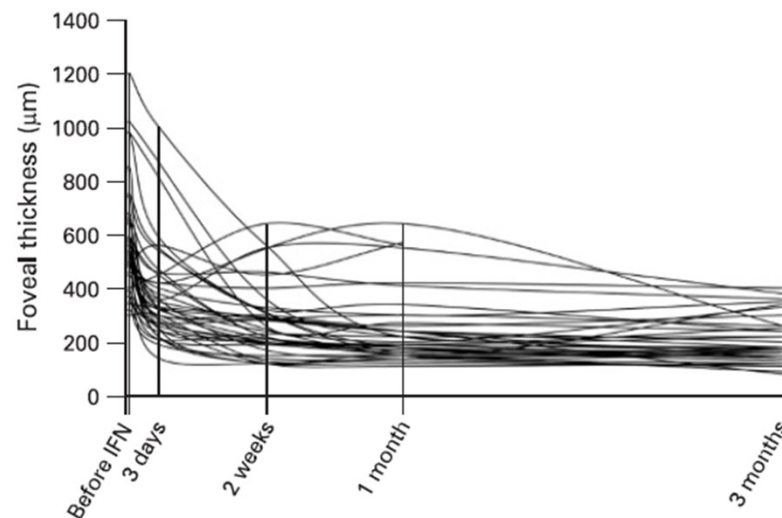


Table 2 Development of foveal thickness and visual acuity within the first 3 months of interferon (IFN) treatment and at the end of follow-up in relation to the grade of efficacy

	Mean foveal thickness and range (µm)					Change in visual acuity (no of eyes) compared with initiation of IFN treatment						
	Before IFN	3 days on IFN	2 weeks on IFN	1 month on IFN	3 months on IFN	End of follow-up	After 3 months on IFN			End of follow-up		
							↑ ≥3 lines	Unchanged	↓ ≥3 lines	↑ ≥3 lines	Unchanged	↓ ≥3 lines
“Effective” eyes, n = 25	571 (300 to 1020)	304 (140 to 590)	198 (120 to 360)	175 (110 to 270)	154 (90 to 240)	167 (90 to 250)	11	14	0	12	13	0
“Partly effective” eyes, n = 10	587 (340 to 850)	403 (270 to 550)	408 (300 to 550)	340 (160 to 640)	290 (80 to 380)	285 (190 to 470)	2	7	1	5	4	1
“Not effective” eyes, n = 5	571 (320 to 1200)	528 (210 to 1000)	456 (230 to 640)	398 (220 to 570)	400 (220 to 570)	NAP	0	5	0	NAP	NAP	NAP

NAP, not applicable.

Casey Eye Institute (OHSU)

- Collaborators:
 - James Rosenbaum, MD and Eric Suhler, MD, MPH
- Purpose:
 - Interferon alpha-2b (not -2a) available in U.S.
 - Is this also effective?

Methods

- Consecutive, interventional case series
- Retrospective
- Nov. 2009 thru Jan. 2011
 - IFN alpha-2b 6 million units s.c. daily
 - All patients treated included in analysis
- Stats: paired, one-tailed Student's t-test

Results (baseline characteristics)

Table 1. Baseline Characteristics, Prior Treatments, and Longitudinal Response to Interferon Alpha 2b.

Pt. No.	Age (start of IFN therapy)	Gender	Diagnosis	Treatment Failures
1	44	F	AU and IU; ? Sarcoid; idiopathic	pred, MTX, IVTA
2	58	F	PU; idiopathic	pred, FA-imp, Dex-imp, PPV, IVTA, IVMTX, IVB, MMF, FK-506, CSA, AZA
3	27	F	sclerouveitis; systemic vasculitis; idiopathic	CPP, m-pred, pred, IFXB, AZA, MMF, RTX
4	46	F	PU; ? Sarcoid; idiopathic	POK, pred, MTX, MMF, IVTA

Results (baseline characteristics)

- 4 patients; 8 eyes
- Mean duration of CME = 31 mos

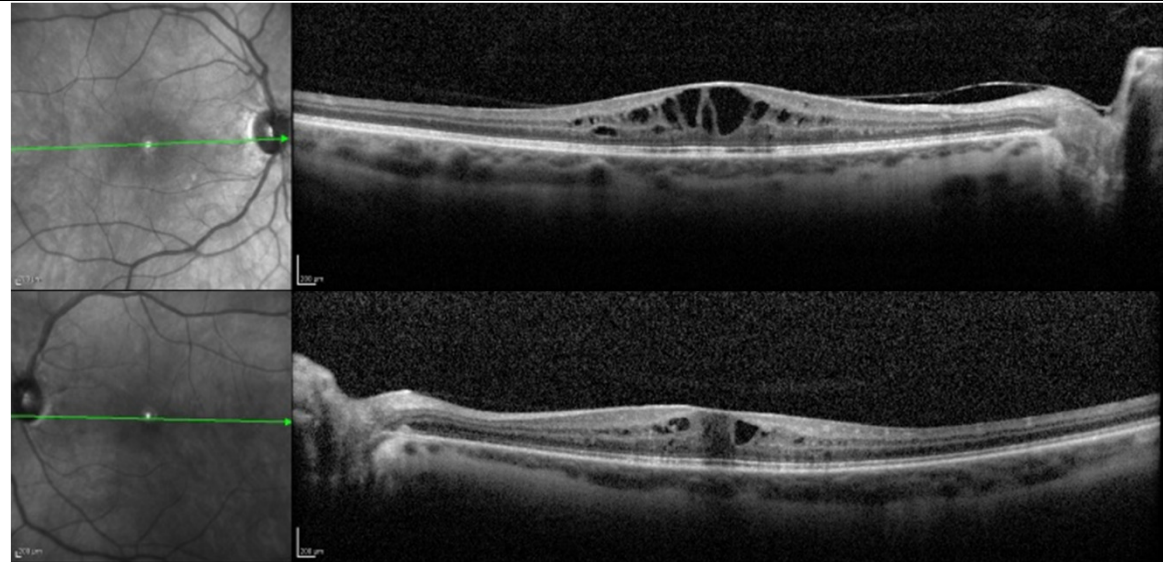
Table 1. (cont.) Longitudinal Response to Interferon Alpha 2b.

	Baseline		2-3 wks f/u		2 mos f/u		Last f/u*	
	CMT (μm)	logMAR	CMT (μm)	logMAR	CMT (μm)	logMAR	CMT (μm)	logMAR
Mean	563	0.81 (20/129)	299	0.70 (20/100)	273	0.60 (20/80)	267	0.45 (20/56)
SD	206	0.46	53	0.47	24	0.44	23	0.40
P-value			0.003	0.02	0.003	0.01	0.002	0.0004

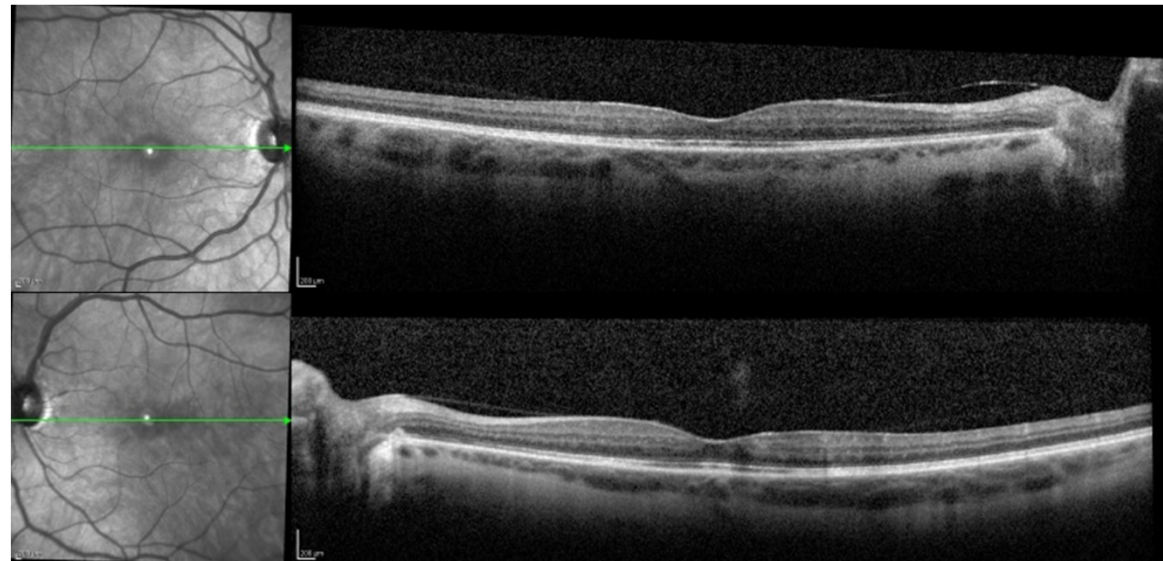
* Last followup in months: 17, 7, 5.5, 5 for patients 1-4 respectively.

Patient 1

- Baseline

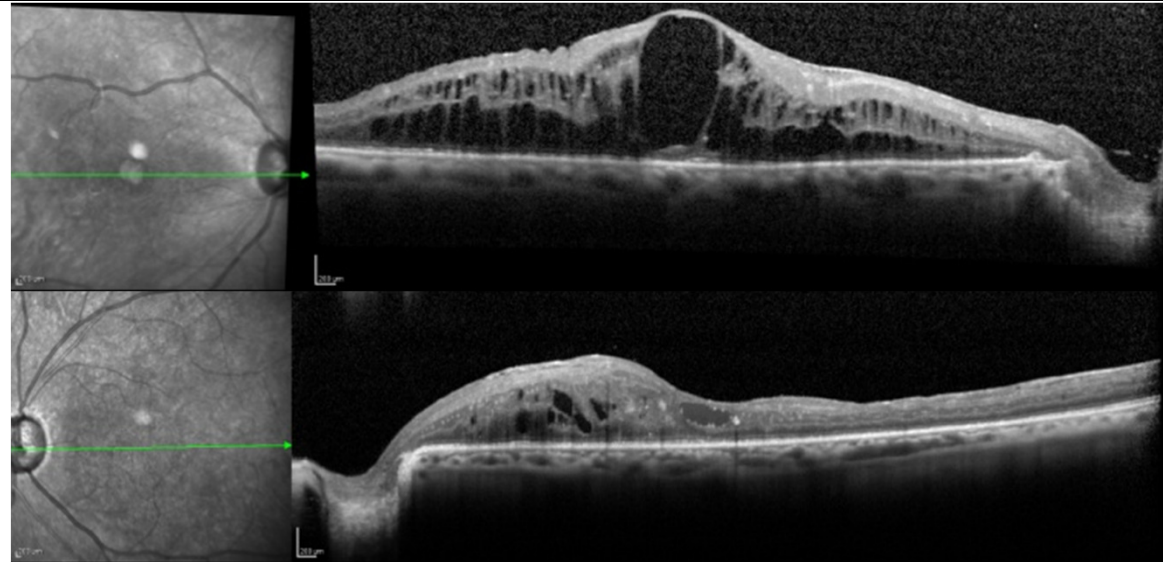


- 3 wk f/u

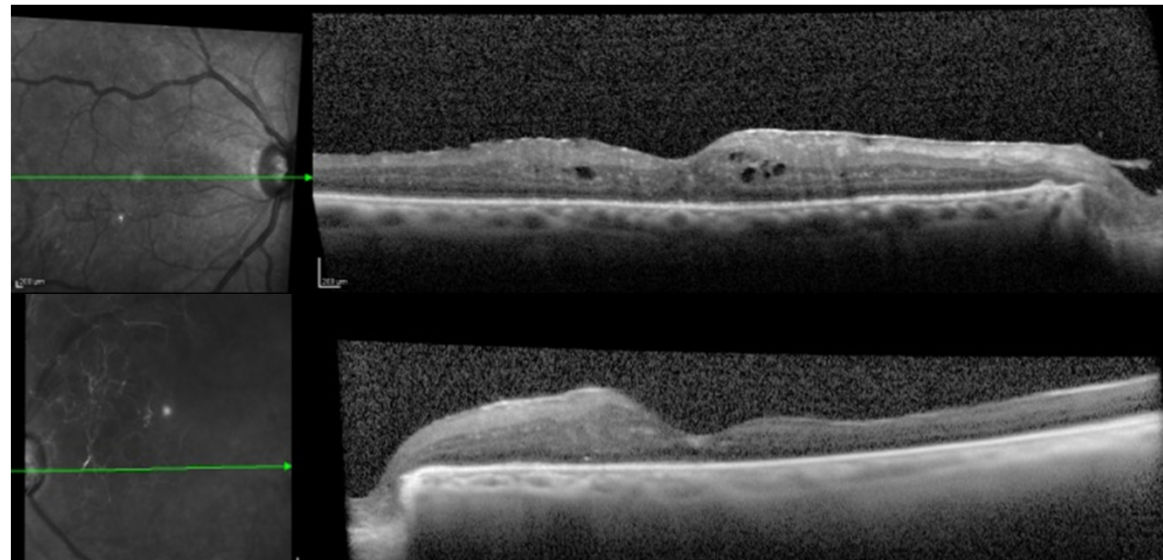


Patient 2

- Baseline

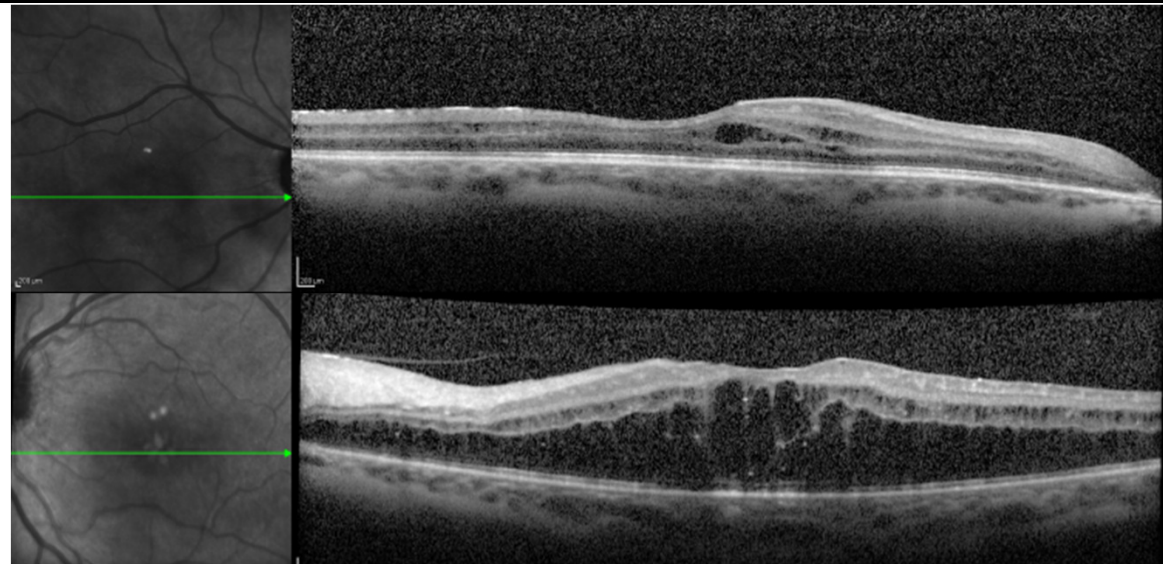


- 2 wk f/u

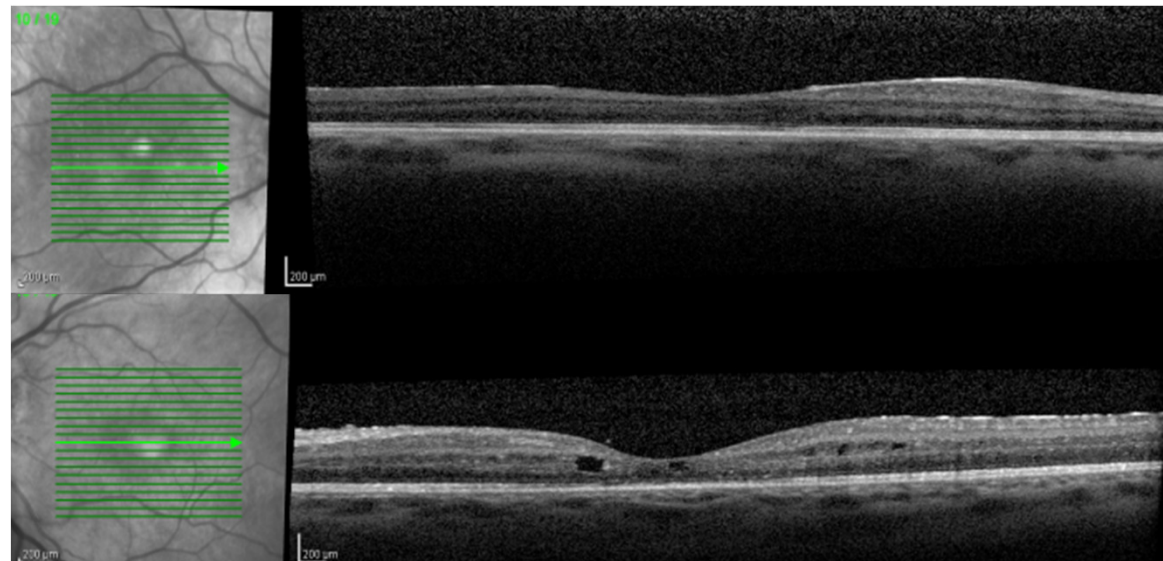


Patient 3

- Baseline

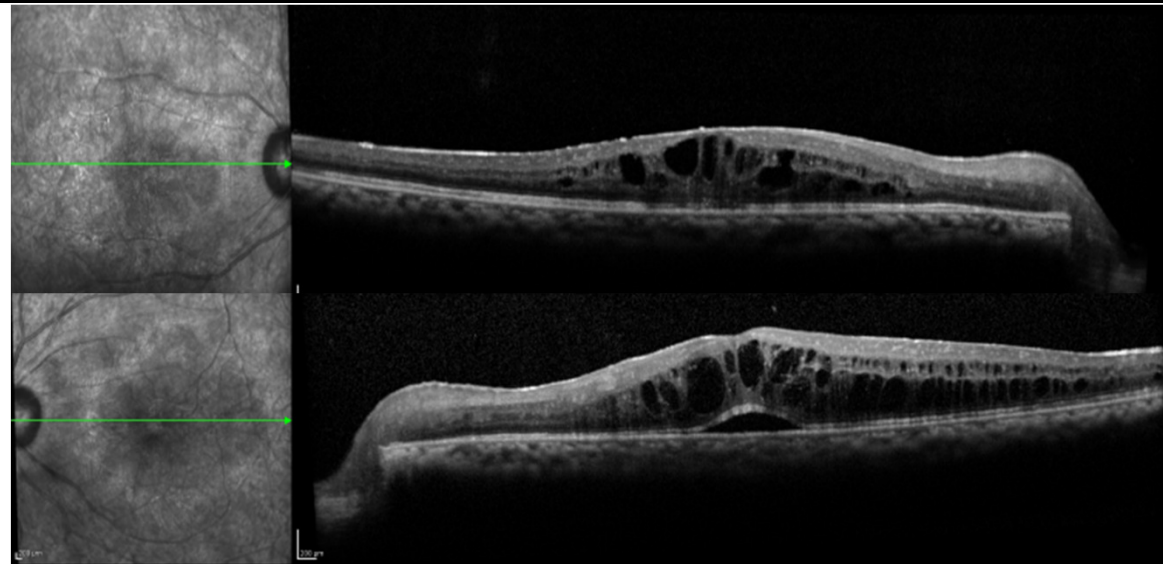


- 2 wk f/u

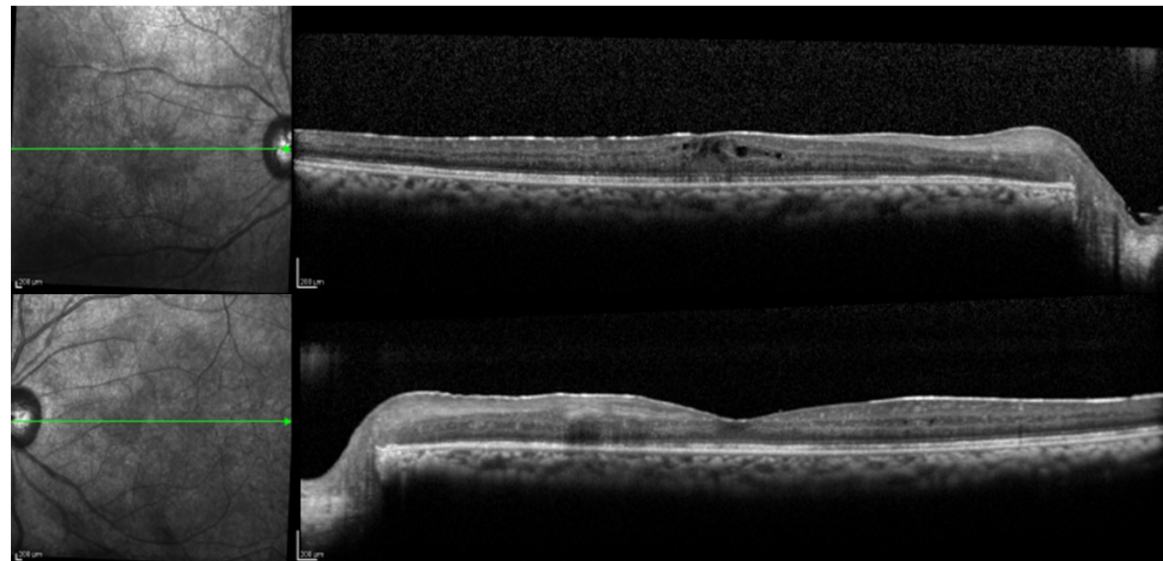


Patient 4

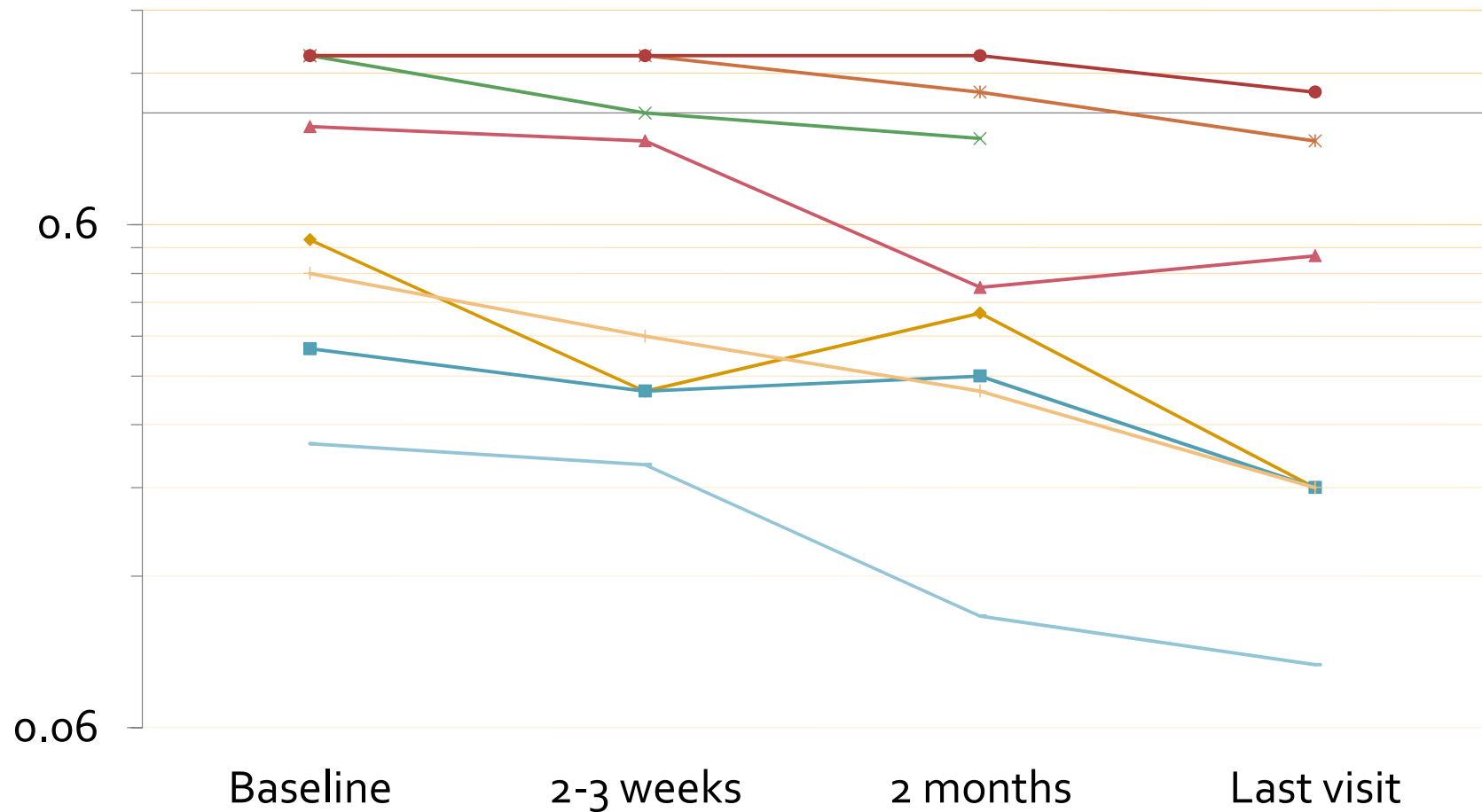
- Baseline



- 3 wk f/u



LogMAR VA with time (8 eyes)



Wonder drug??

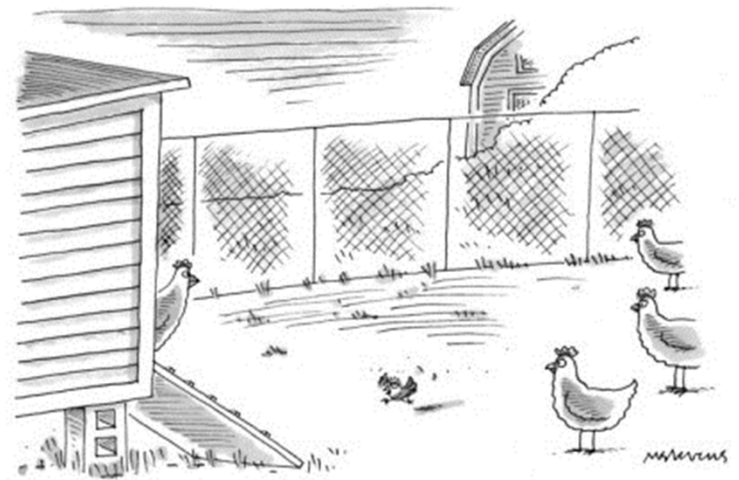
- Gen: fatigue, influenza-like symptoms
- Cardio: hypotension, arrhythmias, tachycardia, cardiomyopathy, and myocardial infarction
- Skin: alopecia, erythema multiforme, injection site necrosis, psoriasis, rash, Stevens-Johnson syndrome, toxic epidermal necrolysis
- Endo: diabetes mellitus, disorder of thyroid gland, gynecomastia, hyperglycemia, hyperkalemia, hypertriglyceridemia, hypocalcemia, hypopituitarism, lipids abnormal, SIADH, virilization, weight loss
- GI: diarrhea, disorder of taste, loss of appetite, nausea and vomiting, pancreatitis
- Heme: anemia, neutropenia, and thrombocytopenia
- Liver: AST/SGOT level raised, biliary cirrhosis, hepatic encephalopathy, hepatotoxicity, increased liver enzymes, jaundice, liver failure
- Immune: antibody development, autoimmune disease, immune hypersensitivity reaction, lupus erythematosus, rhabdomyolysis, viral disease
- MSK: musculoskeletal pain, myasthenia gravis, myositis, rhabdomyolysis, rheumatoid arthritis
- Neuro: asthenia, cerebrovascular accident, confusion, headache, somnolence
- Psych: aggressive behavior, depression, suicidal
- Renal: nephrotic syndrome, polyuria, proteinuria, renal failure, renal impairment
- Repro: abnormal spermatogenesis, fertility problem
- Pulm: bronchitis, epistaxis, pneumonia, pneumonitis, pulmonary hypertension, pulmonary infiltrate, dyspnea, cough, pharyngitis, sinusitis, and nasal congestion, sarcoidosis

Ocular Effects?

- Case Reports abound
- Cotton wool spots, functional visual loss, optic disc edema, optic neuritis, retinal hemorrhage, **macular edema**, retinopathy, CRAO, CRVO, AION
- No ocular side effects in uveitis literature

Our Patients

- Flu-like illness, na/vo (4)
- Joint and muscle aches (4)
- LFT elevation (2)
- Hair loss (2)
- Hives (2)
- WBC suppression (1)
- Weight loss, anorexia (1)



"The flu is coming! The flu is coming!"

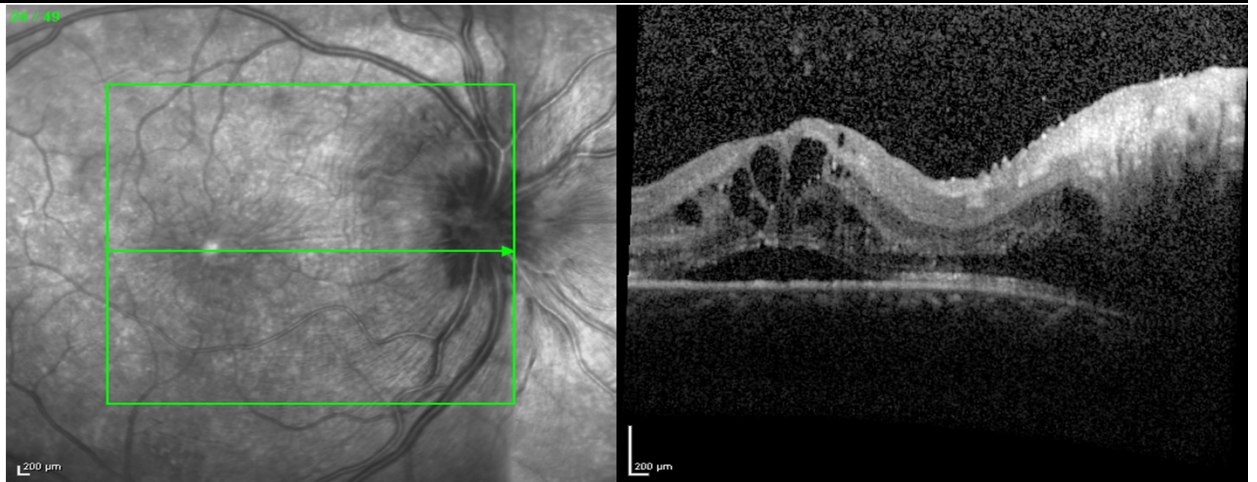
* None were treatment limiting.

Experience at Wilmer

- 30 year-old AAM with intermediate uveitis and retinal vasculitis (non pars planitis)
 - Workup non-contributory
- Prior to referral
 - 15 month h/o chronic uveitis with CME OU and optic nerve swelling
- CME refractory to high dose prednisone and local steroid injections (*and Avastin*)

On presentation...

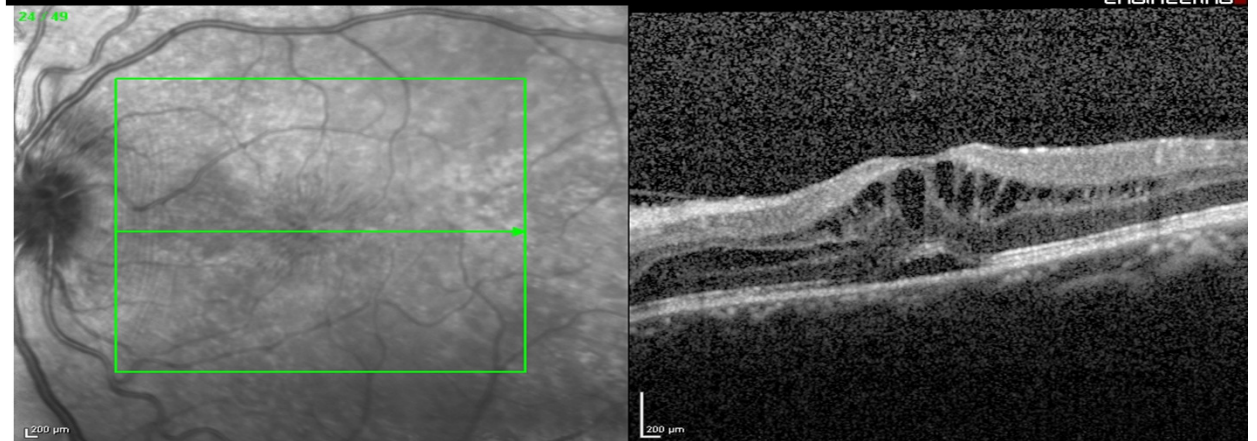
- VA
 - 20/80-2 (OD)
 - 20/50 (OS)



4/10/2012, OD
IR&OCT 30° [HS] ART(18) Q: 18

HEIDELBERG
ENGINEERING

- CFT
 - 634 µm (OD)
 - 560 µm (OS)

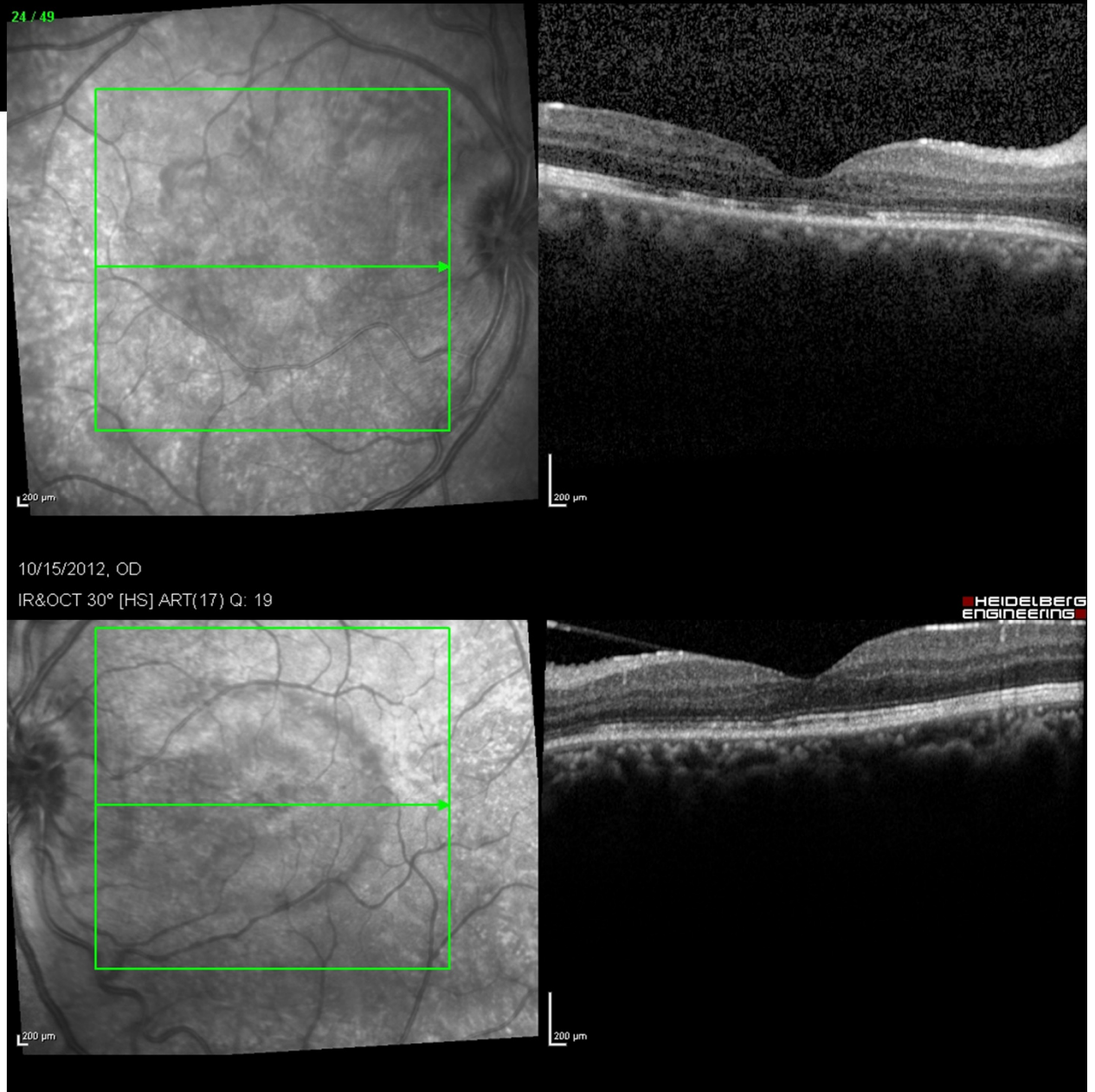


4/10/2012, OS
IR&OCT 30° ART [HS] ART(17) Q: 15

HEIDELBERG
ENGINEERING

After one month of IFN 6mu s.c. daily...

- VA
 - 20/80 (OD)
 - 20/32 (OS)
- CFT
 - 171 μm (OD)
 - 211 μm (OS)

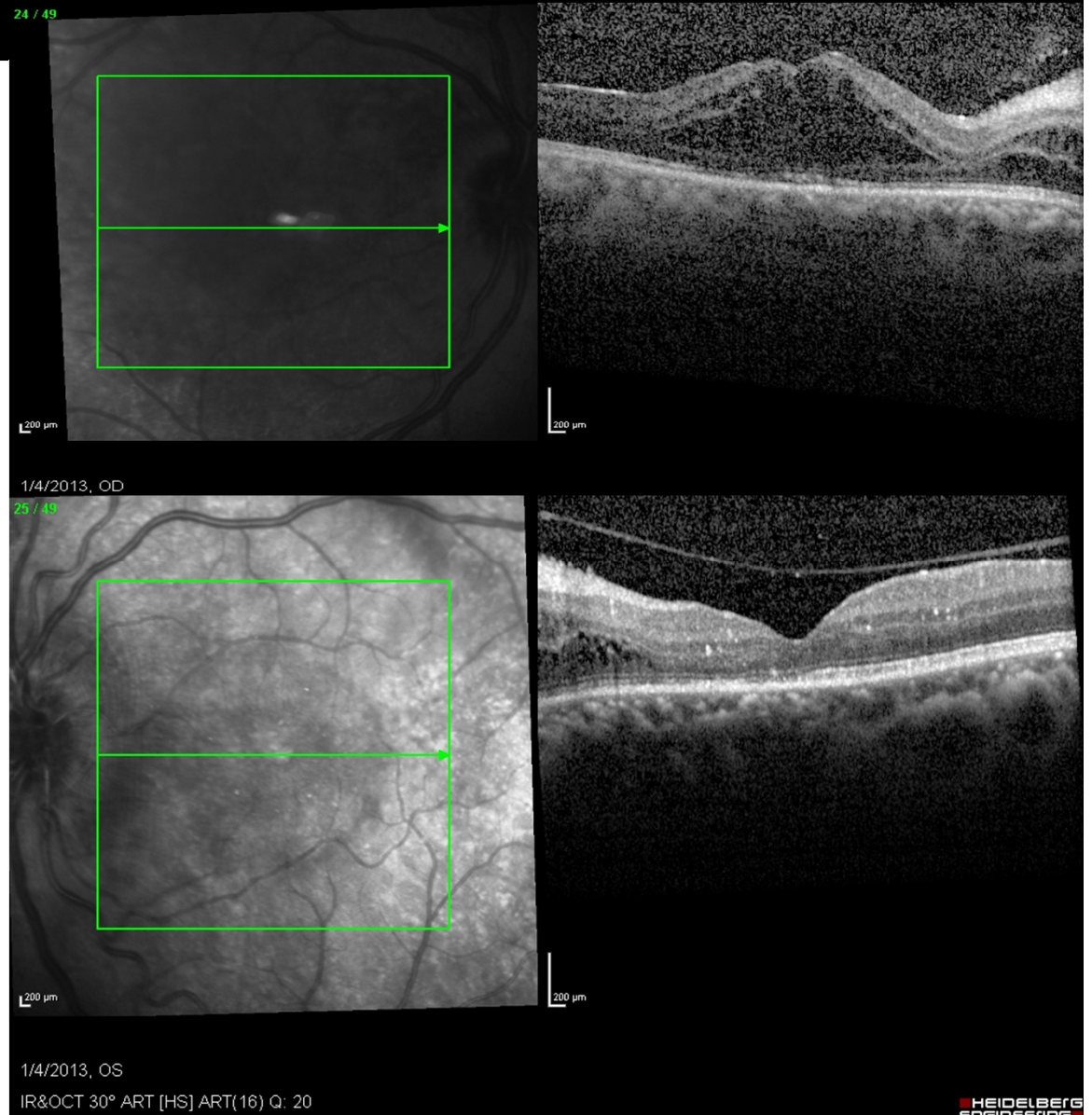


But, hospitalized 3 days prior...

- Neutropenia (ANC 900 and WBC ~2000), hypokalemia, platelets 70K
- 15 lb. weight loss
- Hematemesis
- IFN stopped abruptly

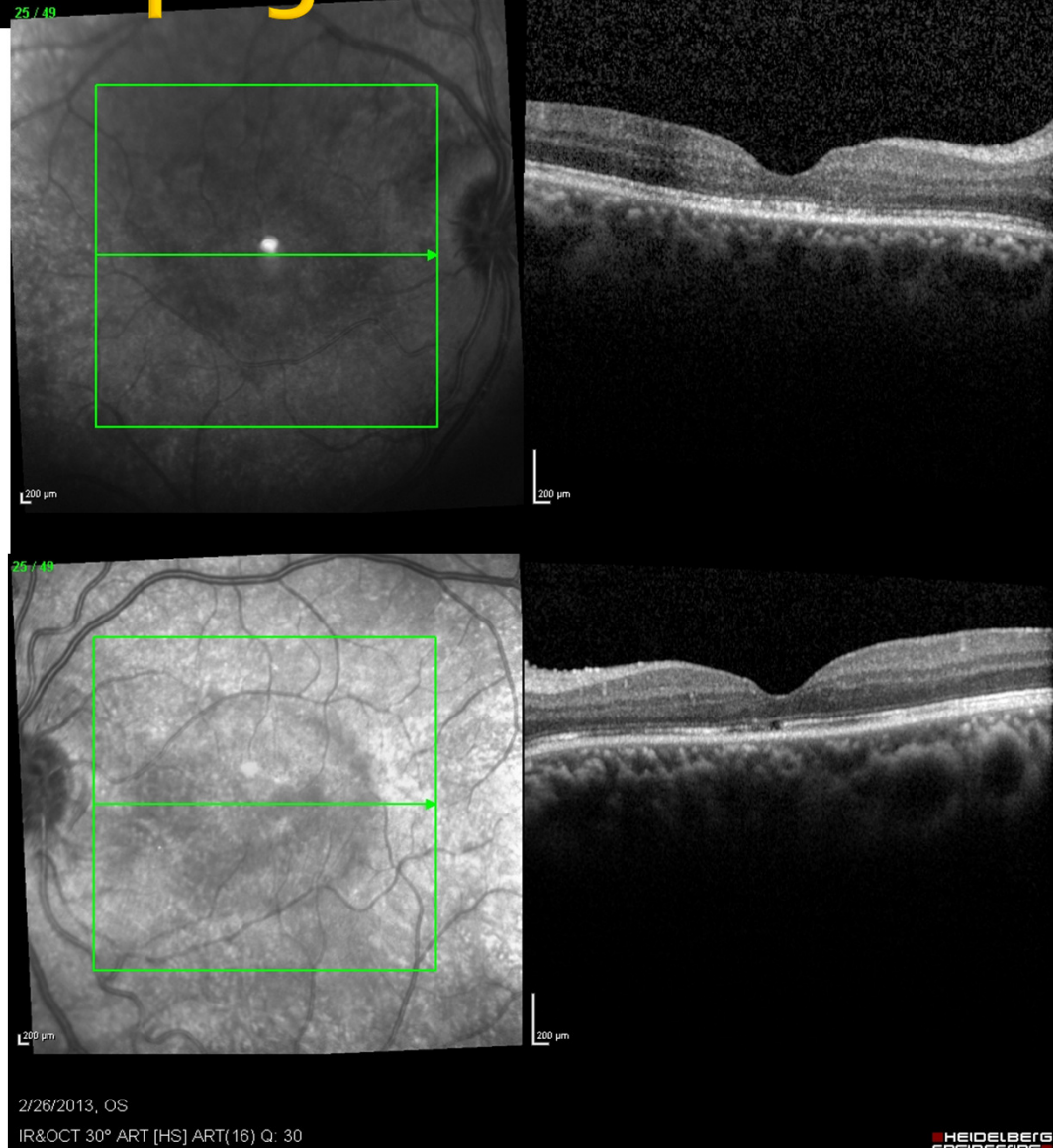
Three months later with spotty therapy (Durezol, retrial of IFN, one month of CellCept)...

- VA
 - 20/260 (OD)
 - 20/80 (OS)
- CFT
 - 566 μm (OD)
 - 187 μm (OS)



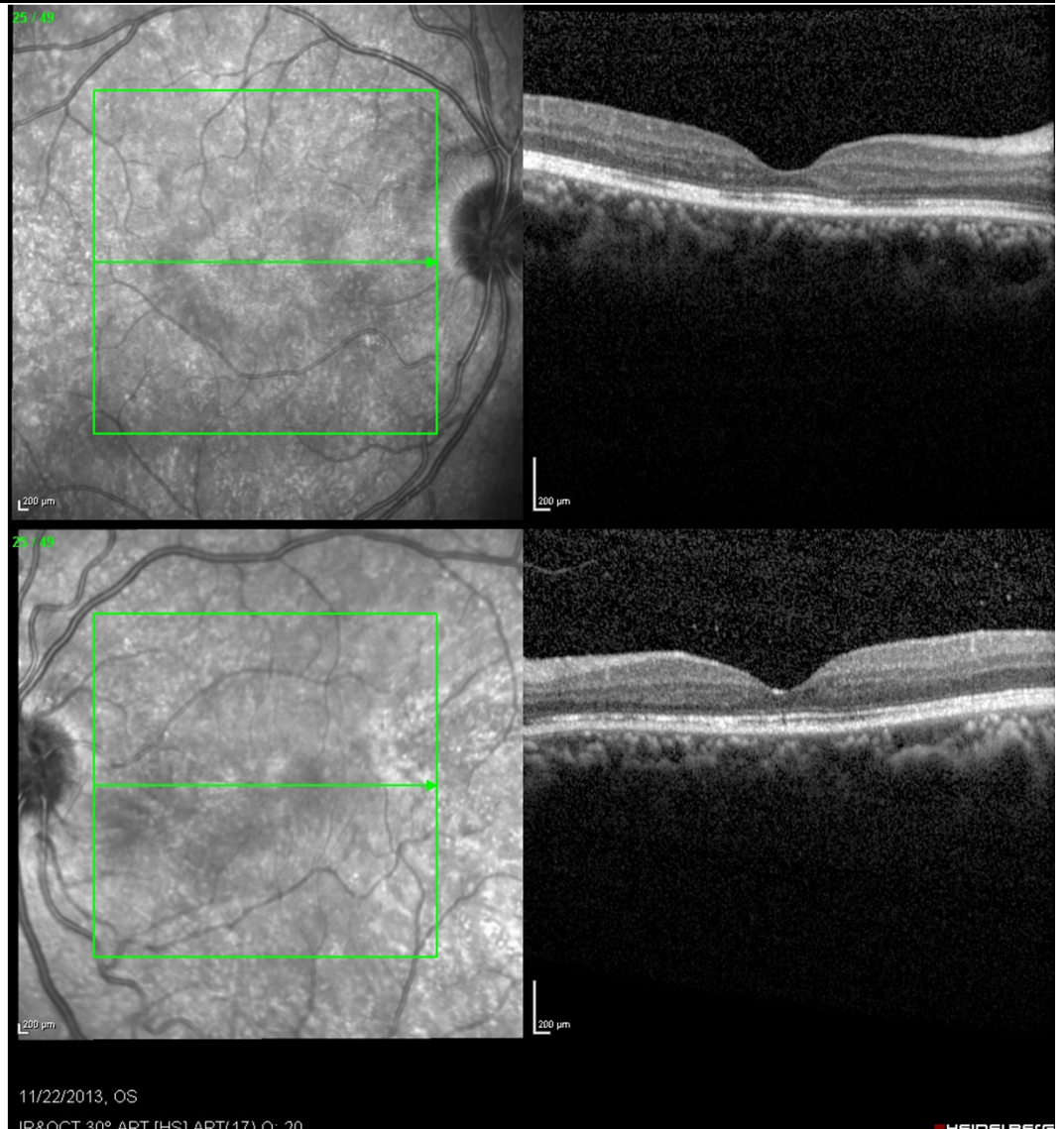
After 6 weeks of IFN 3mu s.c. every other day *plus* Neupogen...

- VA
 - 20/130+ (OD)
 - 20/40 (OS)
- CFT
 - 167 μm (OD)
 - 172 μm (OS)
- 2 months later
 - 20/63 (OD)
 - 20/50 (OS) and
 - No CME OU on IFN 3mu s.c. q 3 days



Last f/u: ~1 year of therapy; down to IFN 3m units q7 days*

- VA
 - 20/40-2 (OD); PCIOL
 - 20/50-2 (OS); 1+ PSC
- CMT (μm)
 - 205 (OD)
 - 214 (OS)



Patient JM: case 2

- RFC: ?? Steroid sparing therapy for retinal vasculitis with CME OU (1/2013)
- HPI:
 - 70 WF s/p CEIOL OU (11-12/2011)
 - Floaters and LOV OU within weeks (no associated symptoms)
 - Dx'd: retinal vasculitis with CME
 - Workup: undifferentiated

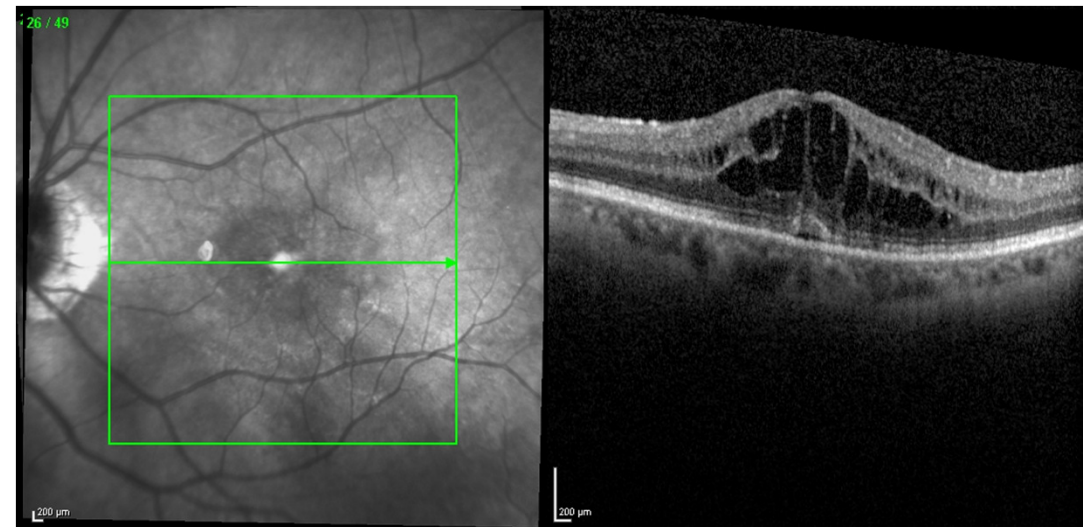
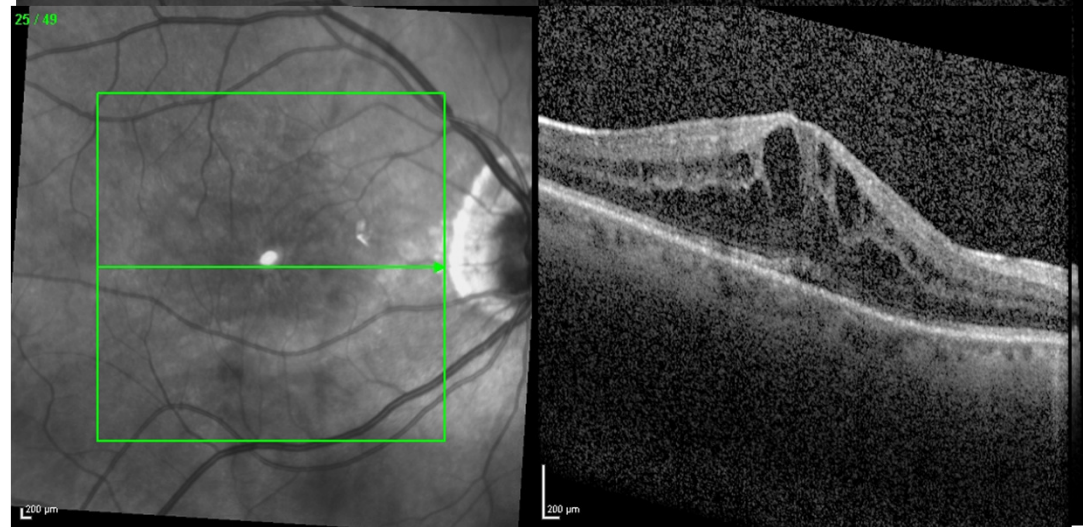
Patient JM: case 2

- Tx failures/AEs:
 - Prior to referral
 - IVTA- resolved CME but IOP in 40s
 - Avastin- no benefit
 - Diamox- fatigue, no clear benefit
 - Prednisone- CME recurred at 20mg
 - After referral
 - Methotrexate 20mg sc weekly- incomplete effect
 - Durezol- IOP issues

Patient JM: case 2

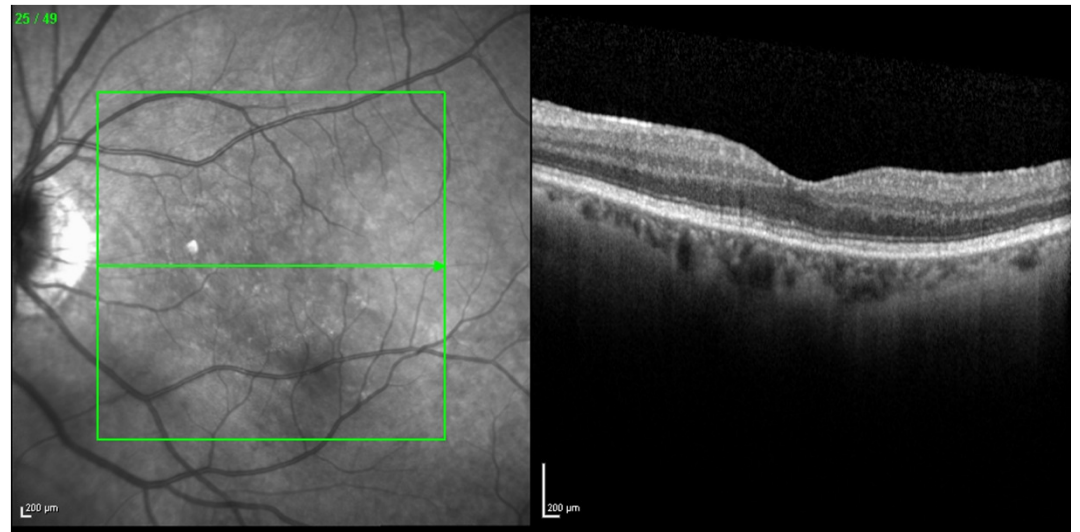
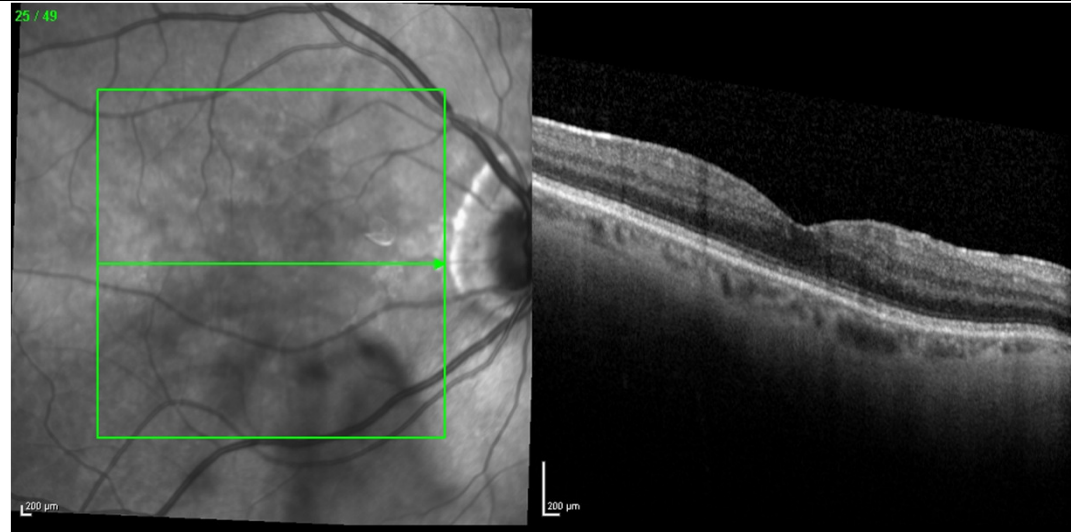
6/2013

- Worsening vision OU
 - 20/65 OD
 - 20/50 OS
- Tx unchanged
- ???



3 weeks post IFN 3m units sc daily 8/2013

- *Improving* vision OU
 - 20/65 → 20/40 OD
 - 20/50 → 20/35 OS
- CMT (μm)
 - 647 → 228 (OD)
 - 570 → 252 (OS)

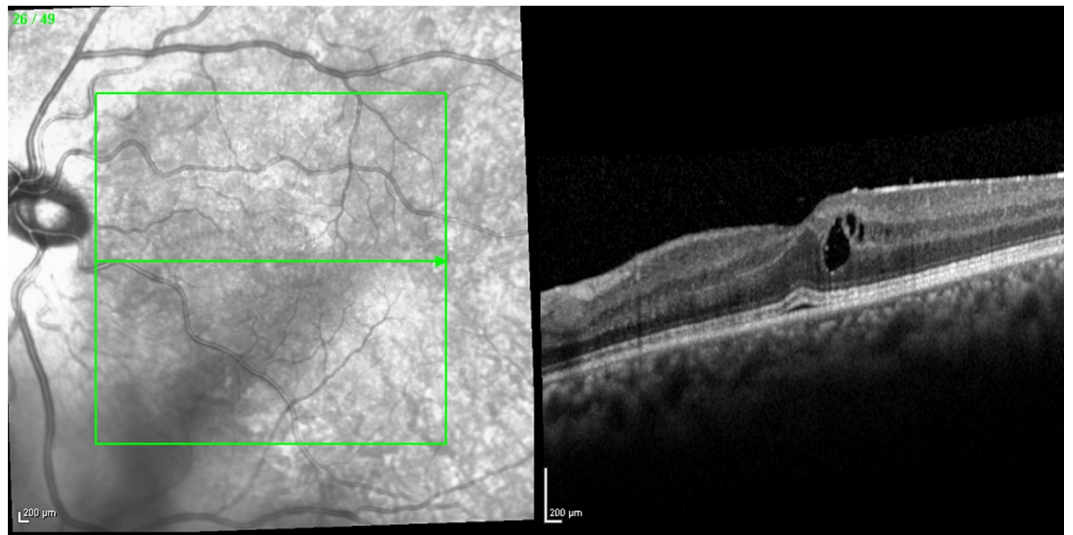
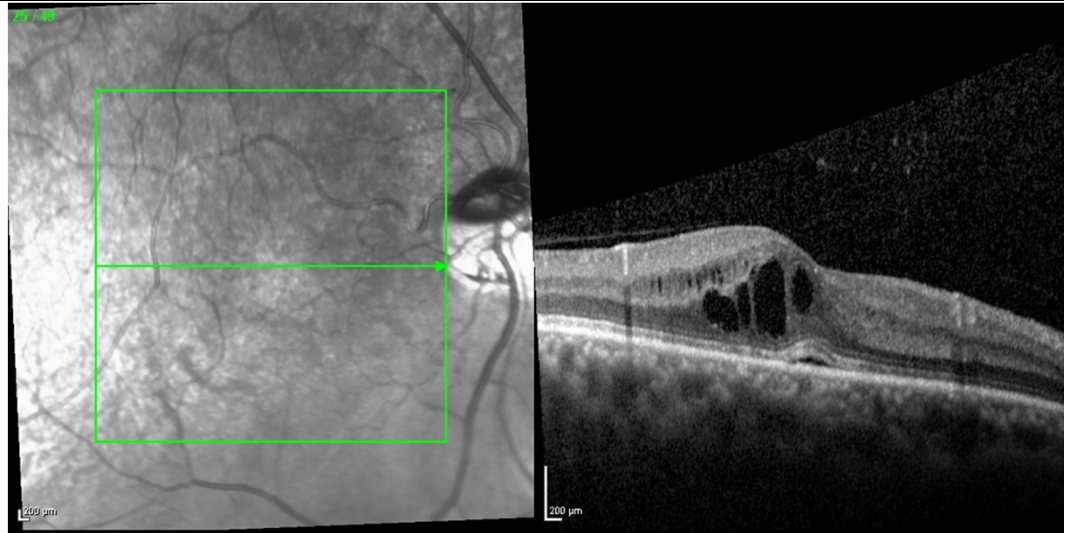


9/2013

- Hospitalized for pulmonary embolism
- Rare association
- Hematologist opinion
 - “other systemic RFs”
 - “cannot prove causality”
 - continue if R/B/A analysis in favor
- Last f/u (5/2014): down to IFN 3m sc q4 days
 - 20/40+2 OD and 20/25+ OS
 - OCT stable/no fluid

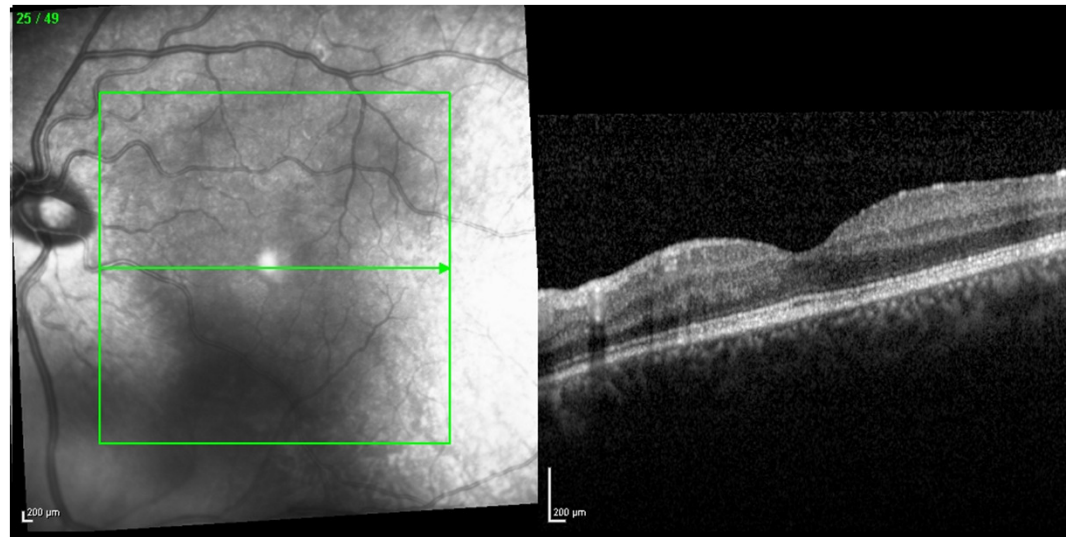
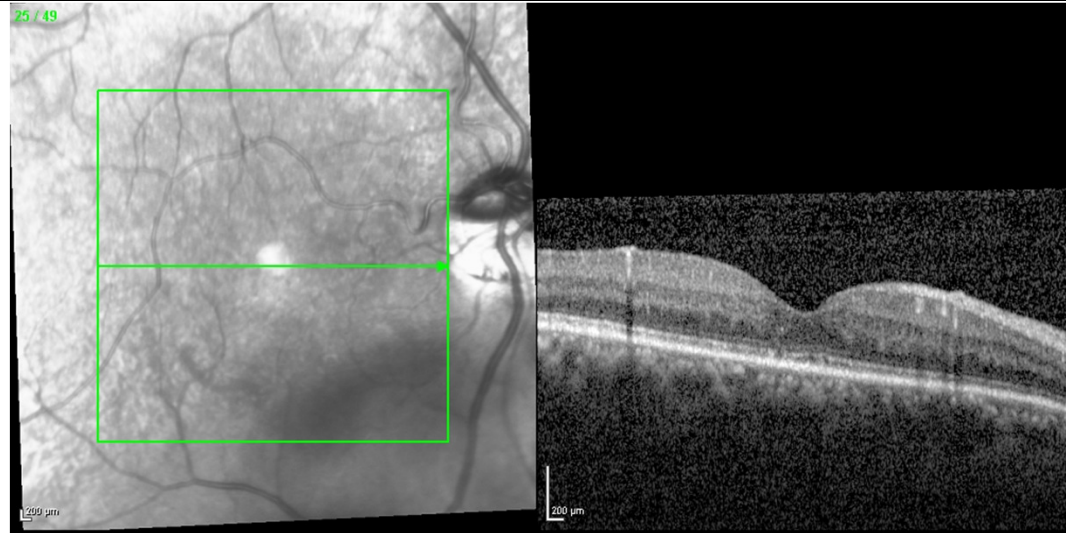
Patient AS: case 3

- 51 AAM w/ “possible” sarcoidosis
- Pars planitis and chronic CME
 - 8 steroid injections annually per eye



2 weeks post IFN alpha-2b 3m units sc daily

- CMT (μm)
 - 451 \rightarrow 275 (OD)
 - 391 \rightarrow 290 (OS)
- SEs??
 - Significant neutropenia



Mechanism

- Unknown
- Chronic CME; inflammation “burnt out”

MICROVASCULAR RESEARCH **49**, 277–288 (1995)

Interferon- α 2b Enhances Barrier Function of Bovine Retinal Microvascular Endothelium *in Vitro*

MARK C. GILLIES AND TAO SU

Department of Ophthalmology, Prince of Wales Hospital and Pediatric Research Laboratories, Prince of Wales Childrens' Hospital, Randwick, NSW 2031, Australia

“We conclude that **interferon- α 2b can enhance the barrier function** of retinal microvascular endothelium *in vitro*. ~~This is consistent with the hypothesis that interferon- α is an effector of a mechanism which actively promotes tissue homeostasis and suggests that it might have~~ **therapeutic potential in diseases characterized by leakage** of the vascular endothelium.”

Conclusions

- Interferon alpha-2b appears effective
- Side effects considerable
 - Careful risk:benefit analysis
 - Rarely treatment limiting
- Select patients with limited options
- Refractory to intravitreal steroid (or contraindicated)
- Refer for tx as indicated

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