

## **Treatment of Vascularly Active Familial Exudative Vitreoretinopathy with Pegaptanib Sodium (Macugen)**

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Precis

Treatment of vascularly active FEVR resistant to cryotherapy, intravitreal steroids, and photocoagulation with Macugen provides visual and anatomical stabilization of the disease.

**Abstract**

**Purpose:** To report the treatment of vascularly active Familial Exudative Vitreoretinopathy (FEVR) with pegaptanib sodium (Macugen) injection.

**Design:** Retrospective, case series

**Participants:** Four patients treated with Macugen injection for FEVR

**Methods:** Four patients with vascularly active FEVR, as demonstrated by increasing subretinal exudation despite photocoagulation, cryotherapy and/or intravitreal steroid injection, received a single intravitreal injection of Macugen. Pre- and post-injection fundus photography, fluorescein angiography (FA) and optical coherence tomography (OCT) were performed in order to evaluate the effect of therapy.

**Main outcomes:** Changes in visual acuity, vascular activity and amount of exudation.

**Results:** The mean follow up period was 11.2 months (range 8.1-15.5) after the first intravitreal injection. All 4 patients demonstrated a decrease in exudation following treatment with Macugen, documented by a decrease in subretinal exudate by fundus photography and decreased leakage on FA. Following reduction of exudation, two patients required vitrectomy to relieve vitreoretinal traction. Visual acuity improved in two patients, stabilized in one patient and worsened in one patient secondary to tractional retinal detachment. No injection-associated systemic or ocular complications were observed in any of the treated patients.

**Conclusions:** Intravitreal injection of pegaptanib sodium is a potential treatment option for patients with FEVR and worsening exudation despite treatment with standard therapy.

Vitreoretinal traction may develop with rapid resolution of subretinal exudate and require surgical intervention. However, visual acuity can improve after retinal traction is released.

Further studies using anti-vascular endothelial growth factor agents are needed to better understand the treatment of FEVR.

## Introduction

Familial exudative vitreoretinopathy (FEVR) is an inherited disease that is characterized by aberrant retinal development that includes peripheral avascular retina, abnormal vascularization with retinal neovascularization, subretinal exudation, formation of an abnormal vitreoretinal interface, and retinal detachment (1,2). The presentation, course and inheritance pattern of FEVR may be variable (3-9). The clinical classification of FEVR is based upon five stages (Table 1). Mild cases (Stage 1 and 2B) are frequently asymptomatic, and clinical findings may be missed on routine clinical examination. Likewise, severe cases (Stage 5) with total retinal detachment may be difficult to distinguish from advanced Norrie's disease, Coats' disease, retinopathy of prematurity (ROP) (if birth history is not available), and persistent fetal vasculature syndrome (PFVS).

The vitreoretinal abnormalities in FEVR are due to aberrant vasculogenesis and subsequent abnormal angiogenesis (10). The Wnt-receptor: $\beta$ -catenin pathway has been implicated in retinal development and mutations in proteins involved in activation and regulation of this pathway have been linked to FEVR (11-13). In addition, dysregulation of the Wnt-receptor: $\beta$ -catenin pathway has been associated with increased levels of VEGF, potentially explaining the life-long, chronic nature of FEVR, which is characterized by exacerbations in exudation secondary to upregulated vascular activity (14,15).

We hypothesized that anti-VEGF therapy may offer a unique treatment in patients with vascularly active FEVR characterized by persistent exudation despite therapy. Four patients with persistent vascular activity and increasing exudation despite aggressive treatment with photocoagulation, cryotherapy and/or intravitreal steroid injection were offered treatment with

Macugen. This report summarizes the clinical course and visual outcomes following anti-VEGF therapy in patients with vascularly active FEVR resistant to standard therapy.

### **Methods**

The study received institutional board approval and informed signed consent was obtained prior to therapy. Four patients with Stage 3 or greater FEVR (Table 1), who have been followed by our practice for many years, were noted to have extensive exudation with decreased vision despite standard therapies. Each patient received a single intravitreal injection of Macugen (0.3mg in 90 microliters) and was examined one week after injection and then monthly for 6 months. Both pre- and post-injection best-corrected visual acuities, fundus photos and OCT were obtained.

### **Results**

Six weeks after injection with pegaptanib sodium, subretinal exudation had decreased in all four patients. Exudation initially decreased peripherally with subsequent reduction of exudation toward the posterior pole in all 4 eyes. The reabsorption of exudate was identified as a graying and flattening within the underlying subretinal space (Figure 1a/1c). Decreased leakage was also noted by fluorescein angiography (not shown). Following an initial improvement in both clinical appearance and visual acuity, two patients developed vitreous hemorrhage secondary to vitreoretinal traction (Patient 2 and 4) as shown in Table 2. Following pars plana vitrectomy with membrane peeling visual acuity and exudation improved.

Patient 1

Patient 1 is a 6 year-old female born at full term. At one year of age she was noted to have bilateral temporal dragging and exudate and diagnosed with FEVR. Bilateral laser photocoagulation was performed. Three years later an increase in exudation and retinal hemorrhages were noted OD>OS and laser photocoagulation was performed followed by intravitreal kenalog OD. Despite standard therapy of laser photocoagulation and kenalog, vascular activity persisted OD with exudate and hemorrhage (Figure 1a/b). An intravitreal injection of Macugen (0.3mg) was given and the patient was examined 6 weeks later. Upon examination, decreased exudation and reduction of vascular activity was noted (Figure 1c/d). To date, no additional therapy has been required OU in the follow up period of nine months.

#### Patient 2

Patient 2 is a 14 year old Caucasian male born at full-term. At the age of 7, he was noted to have exotropia and amblyopia OS. Examination revealed exudate and temporal dragging and he was diagnosed with FEVR. At initial retinal consultation, his best-corrected visual acuity was 20/30 OD and 20/70 OS. He underwent laser photocoagulation OU upon diagnosis. Over the following two years he required two additional laser treatments for vascular activity OU. Following three years of quiescence, the left eye developed exudation and vascular activity that persisted despite three sessions of laser photocoagulation and an intravitreal kenalog injection as illustrated by FA and OCT (Figure 2a/3a). Four weeks following intravitreal injection of Macugen, reabsorption of subretinal fluid and exudate was noted on exam (not shown). Two months later, the patient presented with a decrease in vision (counting fingers), vitreous hemorrhage and a tractional retinal detachment OS. Following successful pars plana vitrectomy

and retinal detachment repair, visual acuity improved to 20/200 and exudation decreased (Figure 2b/3b).

#### Patient 3

Patient 3 is a 23 year-old Caucasian male who initially presented with stage 4 FEVR at the age of 9. He underwent scleral buckling and pars plana vitrectomy OU at the age of 11 in addition to multiple sessions of laser photocoagulation and cryotherapy. Exudation and vascular activity persisted despite two injections of intravitreal kenalog OS. Macugen was injected OS with decreased in exudation with an increase in vision (20/200). No additional therapy has been required during the follow up period of 12 months.

#### Patient 4

Patient 4 is a 13 year old Caucasian male who underwent pars plana vitrectomy and lensectomy OS at the age of 3 months. At the age of 3 years he underwent enucleation for a blind, painful eye OS and laser photocoagulation OD for vascular activity secondary to FEVR. He presented over a year ago with visual acuity of 20/80 OD with exudation and vascular activity which persisted despite two sessions of photocoagulation and intravitreal kenalog. Following injection with Macugen, exudation had decreased at the one month follow up exam. Approximately one month later, the patient returned complaining of decreased vision following jumping on a trampoline. He was noted to have a dense vitreous hemorrhage and a tractional retinal detachment on B-scan. Following pars plana vitrectomy and membrane peeling his visual acuity was 20/60 and he has remained without vascular activity since last follow up of 15 months.

## Discussion

Familial exudative vitreoretinopathy is a lifelong disease with recurrent episodes of abnormal vascular activity and exudation (1). Although many patients will be controlled with standard treatment options, a subset will have persistent vascular activity with worsening exudation and progressive blindness. Anti-VEGF therapies offer a unique opportunity to inhibit the underlying pathophysiology. In this study we examine the efficacy and safety of using intravitreal pegaptanib sodium in patients with FEVR that is not responsive to traditional therapies. We find that intravitreal pegaptanib sodium reduces exudation and vascular activity in patients with FEVR.

Many patients with FEVR have a mutation affecting the Wnt-receptor: $\beta$ -catenin pathway. Dysregulation of this pathway appears to result in upregulation of VEGF which is an indirect marker of eye pathology that increases during times of vascular dysgenesis. In addition, TGF- $\beta$  levels are elevated in times of increased VEGF which can result in vitreous organization and fibrosis (15). The presence of this dysregulated signal transduction pathway with subsequent increases in VEGF and TGF- $\beta$  levels may cause the lifelong chronic disease seen in these patients. Whereas in some patients retinal ablation can address areas of active exudation and injection of intravitreal triamcinolone may produce both anti-angiogenesis and anti-permeability effects, some patients may develop recalcitrant disease with a worsening clinical course and persistent exudation which may require intravitreal Macugen therapy.

In this study, we treated 4 FEVR patients with Macugen after they continued to worsen despite multiple treatments with current methods. All 4 patients were noted to have decreased exudation and vascular activity within the first 4 weeks following injection (Figures 1 and 2). Two patients developed vitreous hemorrhage secondary to vitreoretinal traction (Patient 2 and 4).

The mechanism of tractional detachment may be related to the rapid reabsorption of subretinal exudates or to the upregulation of TGF- $\beta$  which occurs during episodes of vascular activity in response to the increased levels of VEGF. Also, vitreoretinal fibrosis and organization are known complications of FEVR. Following surgical repair, both patients had stabilization of vision with decreased subretinal exudates. Interestingly, none of the 4 patients have required additional therapy following treatment with Macugen for the follow up period of 9-15 months. We noted no ocular or systemic side effects using selective VEGF blockage in children (16). Further follow up will determine if VEGF blockade will result in stable long term control or if periodic treatment will be required for maintenance of FEVR. In patients with vascularly active FEVR, anti-VEGF therapy with Macugen offers a viable therapeutic option when traditional interventions fail.

## References:

1. Trese MT, Capone A. Familial Exudative Vitreoretinopathy. In Pediatric Retina ed. Hartnett MA, Lippincott, Philadelphia, PA, 2005, 425-428
2. Shastry BS, Trese MT. Cosegregation of two unlinked mutant alleles in some cases of autosomal dominant familial exudative vitreoretinopathy. *Eur J Hum Genet.* 2004;12:79-82.
3. Shastry BS, Liu X, Hejtmancik JF, Plager DA, Trese M.T. Evidence for genetic heterogeneity in X-linked familial exudative vitreoretinopathy. *Genomics.*1997; 44:247-8.
4. Jiao X, Ventruto V, Trese MT, Shastry BS, Hejtmancik JF. Autosomal recessive familial exudative vitreoretinopathy is associated with mutations in LRP5. *Am J Genet.* 2004; 75:878-84.
5. De Crecchio G, Simonelli F, Nunziata G, Mazzeo S, Grecco GM, Rinaldi E, Ventruto V, Ciccodicola A, Miano MG, Testa F, Curci A, D'Urso M, Rinaldi MM, Cavaliere ML, Casteluccio P. Autosomal recessive familial exudative vitreoretinopathy: evidence for genetic heterogeneity. *Clin Genet.* 1998;54:315-20.
6. Flaxel CJ, Zhang K, Black GC, Fryer A, Downey LM, Ingelhearn CF. Spectrum and frequency of FZD4 mutations in familial exudative vitreoretinopathy. *Invest Ophthalmol Vis Sci.* 2004; 45:2083-90
7. Qin M, Hayashi H, Oshima K, Tahira T, Hayashi K, Kondo H, Complexity of the genotype-phenotype correlation in familial exudative vitreoretinopathy with mutations in the LRP5 and/or FZD4 genes. *Hum Mutat.* 2005. 26:104-12
8. Toomes C, Downey LM, Bottomley HM, Mintz-Hittner HA, Ingelhearn CF. Further evidence of genetic heterogeneity in familial exudative vitreoretinopathy; exclusion of EVR1, EVR3, and EVR4 in a large autosomal dominant pedigree. *Br J Ophthalmol.* 2005;89:194-7.
9. Toomes C, Bottomley HM, Jackson RM, Towns KV, Scott S, Mackey DA, Craig JE, Jiang L, Yang Z, Trembath R, Woodruff G, Gregory-Evans CY, Gregory-Evans K, Parker MJ, Black GC, Downey LM, Zhang K, Ingelhearn CF. Mutations in LRP5 or FZD4 underlie the common familial exudative vitreoretinopathy locus on chromosome 11q. *Am J Hum Genet.* 2004; 74:721-30.
10. Zhou S, Overbeek PA. Elevated TGF beta signaling inhibited ocular vascular development. *Dev Biol* 2001;237:45-53.
11. Moon RT. Wnt/beta-catenin pathway. *Sci STKE.* 2005 15;2005.
12. Wu C, Nusse R. Ligand receptor interactions in the Wnt signaling pathway in *Drosophila.* *J Biol Chem.* 2002; 277: 41762-69
13. Van Raay TJ, Vetter ML. Wnt/frizzled signaling during vertebrate retinal development. *Dev Neurosci.* 2004;26(5-6):352-8
14. Weis S, Cui J, Barnes L, Cheresch D.. Endothelial barrier disruption by VEGF-mediated Src activity potentiates tumor cell extravasation and metastasis. *J Cell Biol.* 2004 25;167:223-9.

15. Nakagawa T, Lan HY, Zhu HJ, Kang DH, Schreiner GF, Johnson RJ. Differential regulation of VEGF by TGF-beta and hypoxia in rat proximal tubular cells. *Am J Physiol Renal Physiol* 2004;287:F658-64.
16. D'Amico DJ VISION Clinical Trial Group. Pegaptanib sodium for neovascular age-related macular degeneration: two-year safety results of the two prospective, multicenter, controlled clinical trials. *Ophthalmology*. 2006 113:992-1001.

Table 1

Table 1. Stages of Familial Exudative Vitreoretinopathy (FEVR)

Stage	Clinical Features
Stage 1	Avascular retinal periphery without extraretinal vascularization
Stage 2	Avascular retinal periphery with extraretinal vascularization A - with exudate B - without exudate
Stage 3	Retinal detachment- subtotal not involving fovea A - with exudate B - without exudate
Stage 4	Retinal detachment- subtotal involving fovea A - with exudate B - without exudate
Stage 5	Retinal detachment- total A - with exudate B - without exudate

Table 2

Table 2. Patient Characteristics

	Patient 1	Patient 2	Patient 3	Patient 4
Age (years)	6	14	23	13
Sex	Female	Male	Male	Male
Eye	OD	OS	OS	OD
Stage	3	3	4	3
Previous laser therapy	3	7	6	3
Previous cryotherapy	0	0	1	0
Previous intravitreal kenalog	1	1	2	1
Previous vitrectomy	0	0	1	0
Visual acuity pre-Macugen	CSM	20/80	CF	20/70
Visual acuity post-Macugen	CSM	20/200	20/200	20/60
Vitrectomy post-Macugen	no	yes	no	yes
Visual acuity last F/U	20/125	20/200	20/200	20/60
Complications	none	TRD/VH	none	TRD/VH
Time to last F/U (months)	9.2	8.1	12.2	15.5

F/U= follow up; CSM= Constant, steady, maintained; TRD=tractional retinal detachment; VH= vitreous hemorrhage, CF=counting fingers

Figure 1  
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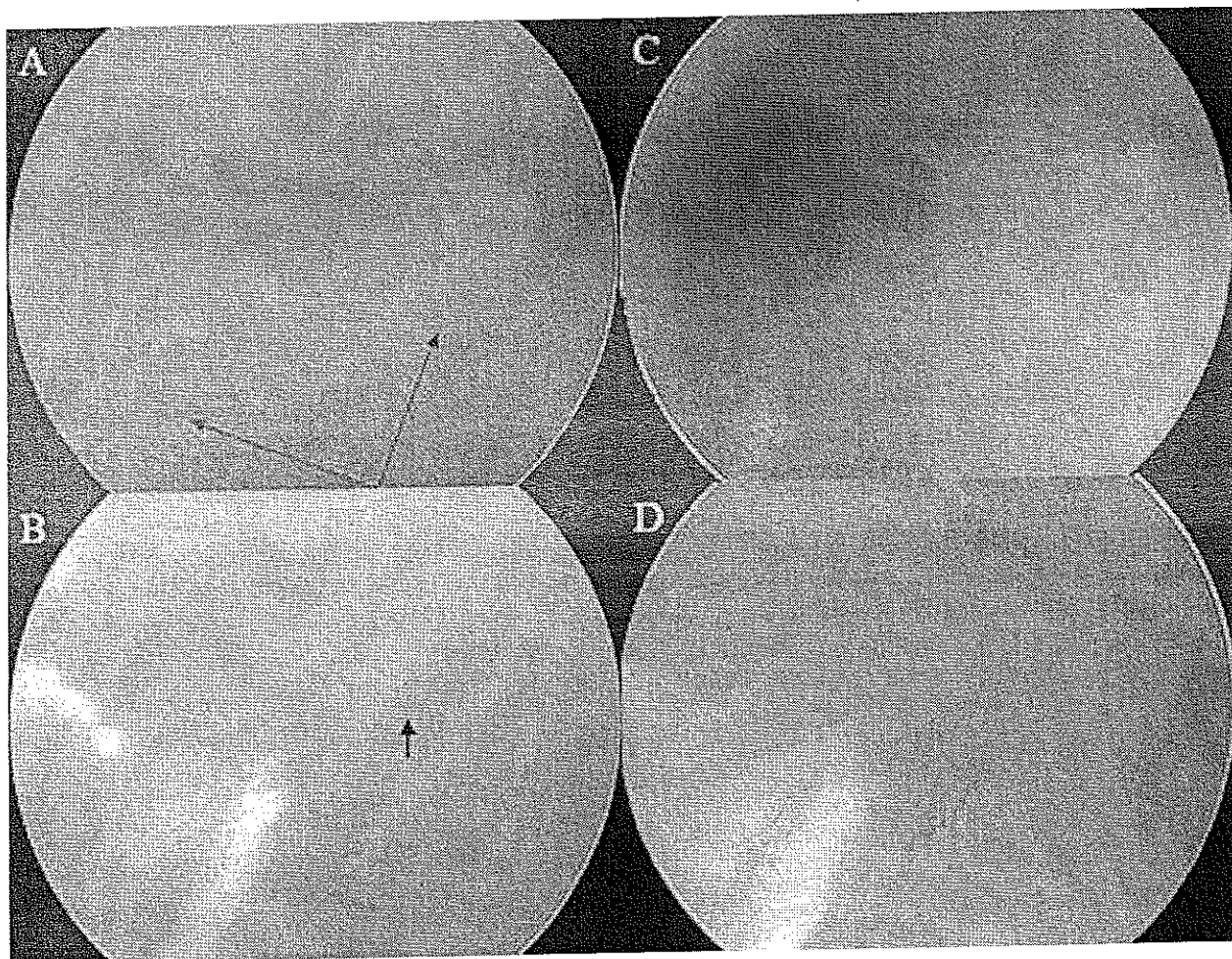


Figure 2

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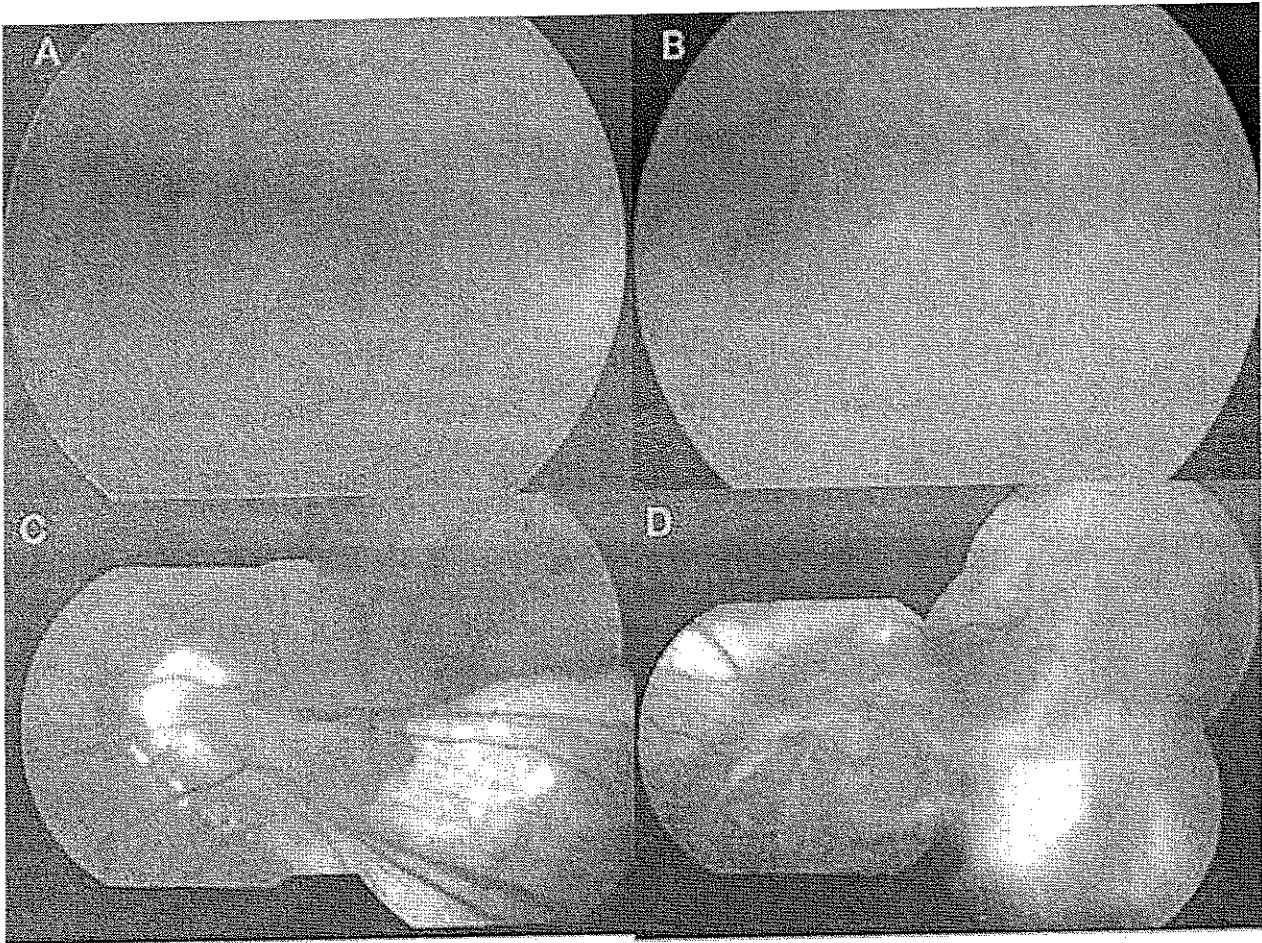


Figure 3  
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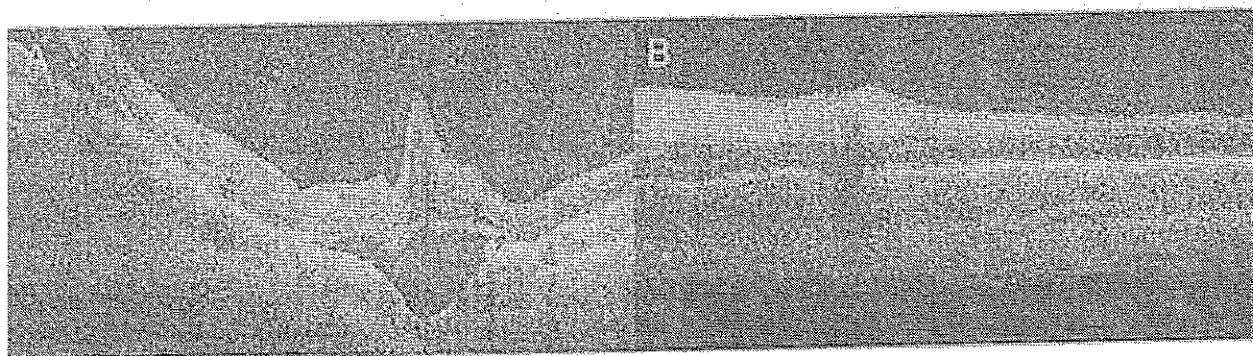


Figure Legends

Figure 1A-D. Patient 1. Color fundus photos pre and post- Macugen injection OD. A. Macula- Pre Macugen therapy. Temporal dragging of macula with significant elevation and exudation demonstrated between area marked by arrows. B. Periphery. Pre Macugen therapy. Significant vascular activity demonstrated by exudate and hemorrhage (arrow) temporal to the macula. C. Macula. Post Macugen therapy. Resolution of submacular exudation with an increase in retinal detail following intravitreal Macugen injection. D. Periphery. Post Macugen. Resolution of retinal hemorrhages and decrease in exudation demonstrated by an increase in retinal detail.

Figure 2 A-D. Patient 2. Color fundus photos pre and post- Macugen injection OS. A. Macula- Pre Macugen therapy. Temporal dragging of macula with significant elevation and exudation temporally. B. Periphery. Pre Macugen therapy. Significant vascular activity demonstrated by exudate temporal to the macula with fibrosis. C. Macula. Post Macugen therapy and vitrectomy. Organization of submacular exudation with an increase in retinal detail following intravitreal Macugen injection. D. Periphery. Post Macugen. Organization of subretinal exudate and fibrosis following Macugen injection and vitrectomy.

Figure 3A. Patient 2. Optical Coherence Tomography (OCT) imaging pre and post Macugen OS. A. OCT imaging before Macugen injection with areas of traction OS through the central macula. B. OCT following Macugen injection and vitrectomy