

A Novel Avastin Injection Technique—“Sunalp Protocol”

Direct Visualization Delivery of Bevacizumab in Pseudophakic Eyes for the Treatment of Subretinal Neovascularization

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Abstract

Purpose: The introduction of vascular endothelial growth factor (VEGF) inhibitors began a new era in the treatment of exudative age-related macular degeneration (ARMD). These drugs are effective at suppressing choroidal neovascularization (CNV) resulting in improvement or stabilization of visual acuity; however, the chronic nature of the disease require these drugs be administered periodically (usually monthly) for the life of the patient. Since intravitreal injections are administered through the sclera, there is the possibility of adverse events, such as vitreous hemorrhage, endophthalmitis, retinal tears, or retinal detachment. To avoid some of the adverse events associated with intravitreal delivery via the scleral route we have developed a technique to deliver bevacizumab (Avastin®) into the vitreous cavity in pseudophakic eyes via a corneal route. **Methods:** A 27-gauge, 5 mm angled cannula attached to a 1.0 ml syringe is fitted into an 11 o'clock limbal incision and advanced through the anterior and posterior chamber. The cannula is maneuvered through the zonules into the vitreous and 0.1 ml of Avastin is delivered behind the lens into the vitreous cavity. The procedure was performed in 50 eyes (Addendum 1: 499 injections 2014–2015), of five exudative ARMD patients, 21 diabetic macular edema (DME) patients, two cystoid macular edema (CME) patients, and one central retinal vein occlusion (CRVO) patient. Visual acuity (VA), edema, optical coherence tomography (OCT), and endothelial cell counts were performed 1 day following Avastin administration. VA was also determined in 16 eyes at 1 month after Avastin administration. **Results:** At 1 day post-Avastin administration, vision acuity and edema index improved or remained stable in all eyes, with the exception of one eye from an exudative ARMD patient whose vision deteriorated. At 1 month the average visual acuity in 16 eyes was also significantly improved. The improvement in edema was evident through retinal OCTs. No change in endothelial cell counts was observed. **Conclusions:** Administration of Avastin via an anterior chamber route in pseudophakic (Addendum 2: Phakic eyes were also treated with no cataract formation) patients is effective for the treatment of exudative ARMD, DME, CME and CRVO, minimizing the possible adverse events related to the administration by the traditional scleral route. In addition, anterior segment administration allows the ophthalmologist to directly observe the delivery of the drug with microscope precision. Pars plana injections are usually performed without magnification and no direct visualization.

Keywords

Age-related macular degeneration, anterior segment, bevacizumab, choroidal neovascularization, diabetic macular edema, pseudophakic, Sunalp protocol

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Compliance with Ethics Guidelines: All procedures were followed in accordance with the responsible committee on human experimentation and with the Helsinki Declaration of 1975 and subsequent revisions, and informed consent was received from the patients involved in this study.

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Supplementary Information: An accompanying video to this article can be found at www.touchophthalmology.com/gallery/dr-murad-sunalp-demonstrates-sunalp-protocol-subretinal-neovascularization.

In 2006, the US Food and Drug Administration (FDA) approved Genentech's ranibizumab (Lucentis®), a Fab fragment of a humanized monoclonal anti-vascular endothelial growth factor (VEGF)-A designed for intraocular use for

the treatment of exudative age-related macular degeneration (ARMD). Since 2006, ranibizumab and its parent monoclonal antibody bevacizumab have been extensively used to treat exudative ARMD. Intravitreal injections of

bevacizumab and ranibizumab have become the most common treatment for exudative ARMD resulting in visual stabilization in 90 % of patients and a gain of 3 or more lines of visual acuity (VA) in 30–40 % of the patients.^{1–3} Even though the development of inhibitors of VEGF has transformed the treatment of exudative ARMD and other ocular neovascular diseases, the repeated intravitreal injections necessary to prevent the reoccurrence of neovascularization are not without side effects. These include endophthalmitis,⁴ ocular hypertension, submacular hemorrhage, and the possibility of systemic diffusion resulting in long-term thromboembolic events.^{5–8} Since the introduction of the anti-VEGF antibodies bevacizumab (Avastin®) and ranibizumab (Lucentis) for the treatment of ARMD, ophthalmologists have used these anti-VEGF for the treatment of other neovascular ocular diseases, such as proliferative diabetic retinopathy, diabetic macular edema (DME), and cystoid macular edema (CME).^{8–11} Even though the rates of serious ocular adverse events are low, in the range of 1–2 %, ^{8,9} the increased use of these drugs has meant an number of cases with significant serious side effects. Intravitreal injection with an anti-angiogenic drug is accomplished by anesthetizing the patient locally with an injection of lidocaine or a topical anesthetic, followed by the injection of the anti-VEGF, usually infero-temporally, 3.5 to 4 mm posterior to the limbus through the pars plana. Even though the procedure is simple, it is not possible to observe the precise site where the injected agent is delivered, thus risking possible injury to the retina and choroid and lens. In addition, the injection is painful and frightening for the patient (see *Figure 1A*). To decrease the difficulties associated with intravitreal injections we have explored the delivery of bevacizumab via a corneal route in pseudophakic eyes. Here we report that the delivery of bevacizumab via a corneal route is effective in decreasing edema in patients with diabetes and in stabilizing and/or increasing vision in exudative ARMD patients, while minimizing potential retinal damage and adverse affects on corneal endothelial cells (see *Figure 1B*).

Material and Methods

Administration Procedure

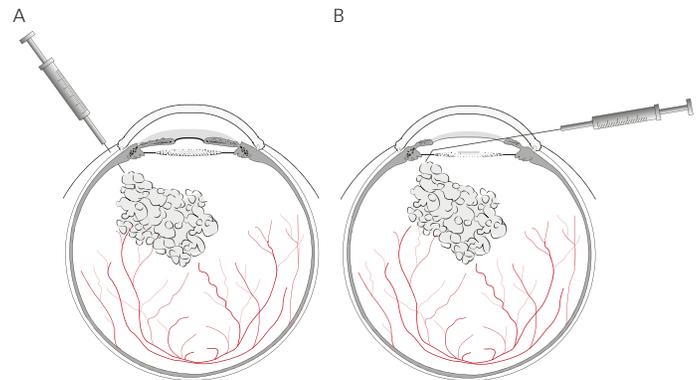
Informed consent was obtained from all patients.

The eye is dilated using one drop of tropicamide ophthalmic solution (1 %) and one drop of phenylephrine hydrochloride ophthalmic solution (2.5 %). The patient is placed supine under the operating microscope with the microscope light off. After scrubbing the eyelids with 1 % povidone iodine, a drop of povidone iodine is instilled in the eye, followed by a drop of the local anesthetic, 0.5 % tetracaine hydrochloride (Alcon Laboratories, Dallas, TX, US). The eye is draped with Tegaderm dressing (3M, St Paul, MN, US). A lid speculum is placed.

A Mastel ring light and fixation light are used to fixate the eye. Using an Alcon (Fort Worth, TX, US) single-use ophthalmic 15° angled knife, a 0.4 mm paracentesis is made at the limbus at 11 o'clock.

A 27-gauge irrigating, 5 mm angled cannula, attached to a 1.0 ml syringe is fitted into the paracentesis incision and advanced through the limbus and through the anterior and posterior chamber. The cannula is maneuvered through the zonules into the vitreous, the tip of the cannula and bevacizumab release can be visualized within the vitreous. Bevacizumab (0.1 ml) is injected into the vitreous cavity (see *Figure 1B*), and the cannula is removed immediately so as not to chafe the iris. Betadine and antibiotic drops are placed.

Figure 1: The Standard (A) Transcleral and Our Perilimbal Sunalp Procedure (B) Approaches to Intravitreal Anti-vascular Endothelial Growth Factor Agent Administration



After delivery of the bevacizumab, the paracentesis site is hydrated and the fundus examined by indirect ophthalmoscopy to insure normal central artery perfusion.

Note: We have started using the Malosa Medical “Sunalp Protocol” Single-Use Avastin trays in 2015 (see *Attachment 4*).

Patients

Avastin was administered via the corneal route in (a) nine eyes with neovascular ARMD from five patients ranging from 74 years to 92 years of age; (b) in 38 eyes from 21 diabetic retinopathy patients ranging in age from 47 to 80 years of age; (c) two eyes from two CME, aged 68 and 80, respectively; and (d) one eye from a central retinal vein occlusion (CRVO) patient 65 years of age.

Visual Acuity

VA was measured pre-injection and at 1 day post-Avastin administration in all eyes and at 1 month post-Avastin administration in 16 eyes.

The average pre-injection VA in the eyes of ARMD patients was 20/250 and after 1 day the average was 20/150; three out of nine eyes gained 3 or more lines, five remained stable and one deteriorated. In 16 eyes from 12 patients who returned for an examination at 1 month pre-injection VA was 20/70 and post-injection VA was 20/50. The average pre-injection VA in patients with diabetic retinopathy was 20/150; 11 eyes gained 2 or more lines, seven eyes gained 3 or more lines; in 36 eyes vision remained stable and in only one eye vision deteriorated. No significant change was observed in the two eyes from the CME patients. Some patients were lost to follow up.

Macular Edema

Macular edema was determined using the Heidelberg and NIDEK units (see section on Optical Coherence Tomography Equipment), 50 eyes of 29 patients, which included 21 DME patients, five ARMD patients, two CME patients, and one CRVO patient. Macular edema was significantly lower 1 day and 1 month after Avastin administrations as shown by the Wilcoxon rank-sum test ($p=0.00358$) and confirmed with the optical coherence tomography (OCT) pictures.

Representative OCTs from DME (see *Attachment 1*), ARMD (see *Attachment 2*), and CME (see *Attachment 3*) patients all show that after one injection the edema has decreased.

Optical Coherence Tomography Equipment

- 1) Heidelberg OCT (Heidelberg Engineering GmbH, Heidelberg, Germany).
- 2) Nidek OCT RS-3000 Advance (NIDEK Co., Ltd, Hiroishi, Japan).

Corneal Endothelial Cell Counts

Using a Konan specular microscope corneal endothelial cell counts and morphology were performed on 43 eyes from 24 patients. Statistical analysis of endothelial cell counts was carried out using a paired t-test.

No significant changes in corneal endothelial cell morphology and counts were observed one day after Avastin administration. The pre-Avastin endothelial average cell counts for the 43 eyes were $2,580.47 \pm 192.88$ and the post-Avastin counts were $2,490.05 \pm 232.94$; $p=0.0442$. The difference between pre- and post-Avastin administration is not significantly different.

Discussion

With the approval of ranibizumab (Lucentis) in 2006 and the off-label use of bevacizumab (Avastin) ophthalmologists are treating neovascular macular degeneration and other retinal neovascular diseases, intravitreal injections have become routine in practices specializing in retinal diseases and in many general ophthalmology practices. Even though the rate of adverse side effects is low^{8,9} the number of intravitreal injection is so large that even these low rates result in significant numbers of patients suffering adverse events. In 2008, the number of intravitreal injections billed to Medicare was over one million in the US¹² and it may now have reached three million; with three million intravitreal injections at the rate of 2 % adverse events would affect 60,000 patients in the US alone.

Some complications associated with intravitreal injections, such as conjunctival hemorrhage, retinal tears, and retinal detachment are caused by the injection through the sclera without the ability to visualize the delivery point. We have shown that it is feasible to administer Avastin via a corneal route in the vitreous cavity in pseudophakic patients without

any complications and with similar effectiveness as administration via the intravitreal route, and with minimal discomfort and no pain.

Is the administration of Avastin via the corneal route safe and is there is loss of drug via aqueous outflow? A number of studies in animal models and in humans¹³⁻¹⁵ have shown that intracameral bevacizumab for the treatment of neovascular glaucoma in humans is safe and effective and does not have any harmful effects on the cornea and on endothelial cells in particular. Our data support other findings that injections of bevacizumab via the corneal route does not affect endothelial cell numbers or morphology.

To our knowledge, there are no studies on the effect of corneal route administration of anti-VEGFs on choroidal neovascularization (CNV). However, there are a number of studies in animals that show that intravitreal injection of bevacizumab diffuses freely into the aqueous and cornea. In a study on the effect of bevacizumab on corneal neovascularization in animal models both intracameral and intravitreal administration were effective and bevacizumab was detected in the anterior chamber by day 2 after administration.¹⁶ In a similar study, ranibizumab was detected in the aqueous 3 days after intravitreal injection¹⁷ indicating that these drugs persist in the vitreous and aqueous for some time. In fact, half-life of ranibizumab in the vitreous is 2.88 days and the half-life in the aqueous is 2.84 days¹⁷ indicating that these drugs do not exit with aqueous flow.

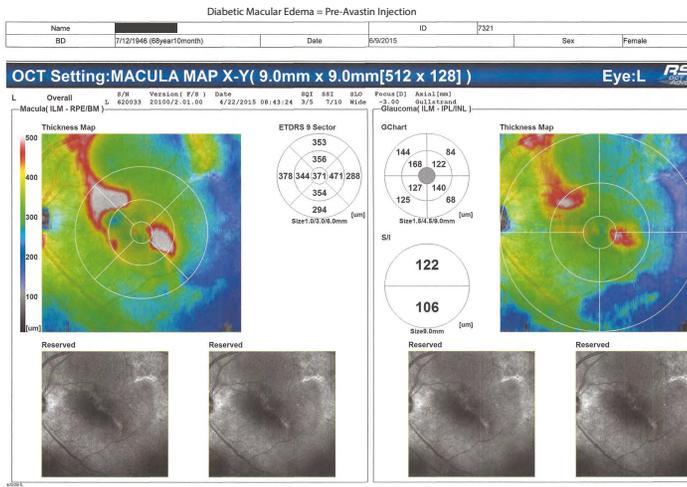
Since the route of penetration into the posterior retina of bevacizumab or ranibizumab is not known nor is known what the effective concentration of either of these drugs is necessary to inhibit CNV, the only reliable means to assess effectiveness is by experimentation. In the present study, VA improved in three of the nine eyes of neovascular ARMD patients, was stabilized in five eyes, and deteriorated in one; this result is similar to results obtained in a number of large studies using intravitreal administration. In addition, OCT images in our study clearly show that the edema accompanying diabetic retinopathy, exudative ARMD, and cystoid macular edema did recede following administration of bevacizumab via the corneal route indicating that an effective concentration of the drug reached the subretinal space. To our knowledge this is the first study demonstrating that corneal route administration of bevacizumab is effective for the treatment of subretinal neovascularization. ■

Summary Statement: Delivery of bevacizumab via anterior segment route in pseudophakic eyes is a safe and effective method for treatment of ARMD degeneration and DME that minimizes the possibility of injury to the retina or sclera.

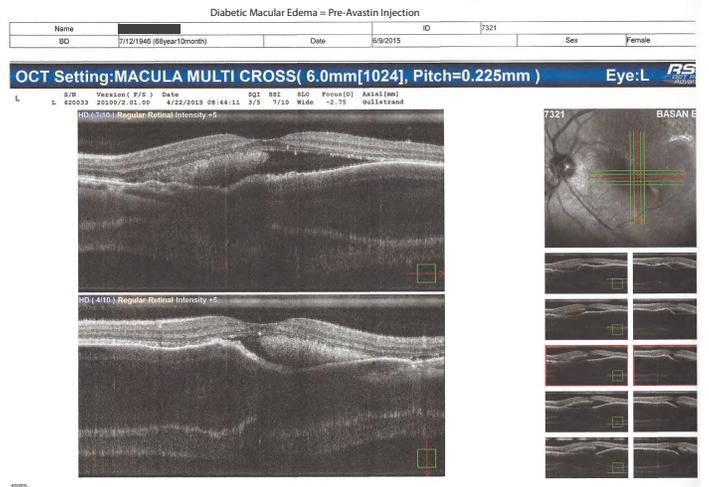
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Attachment 1: Optical Coherence Tomography of a Patient with Diabetic Macular Edema, Pre- and Post-Avastin

- DME = pre-Avastin injection

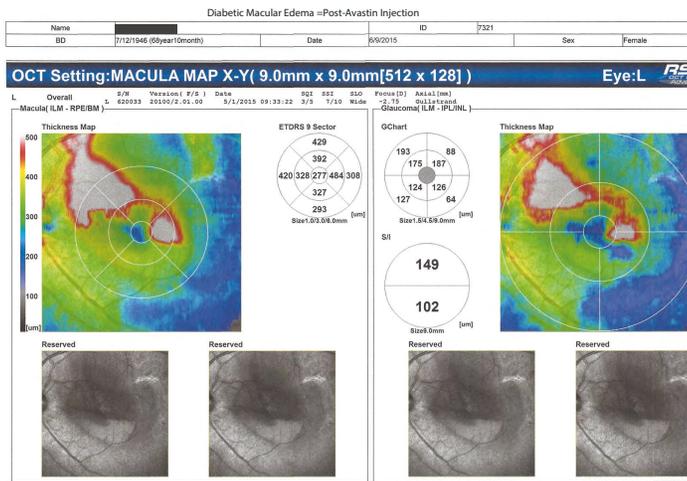


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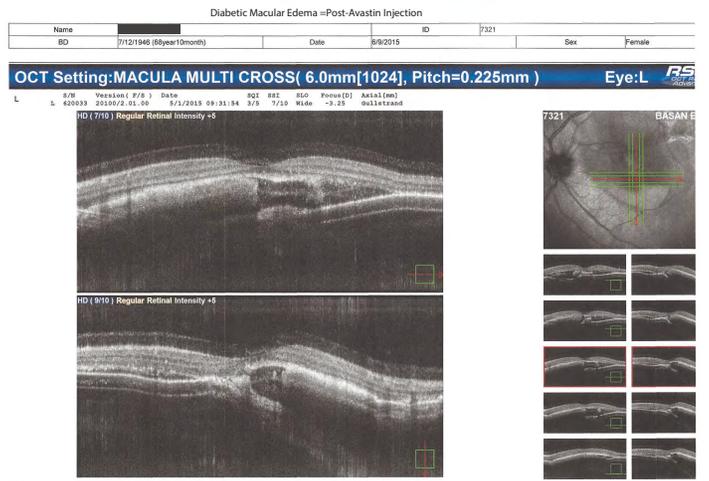


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- DME = post-Avastin injection



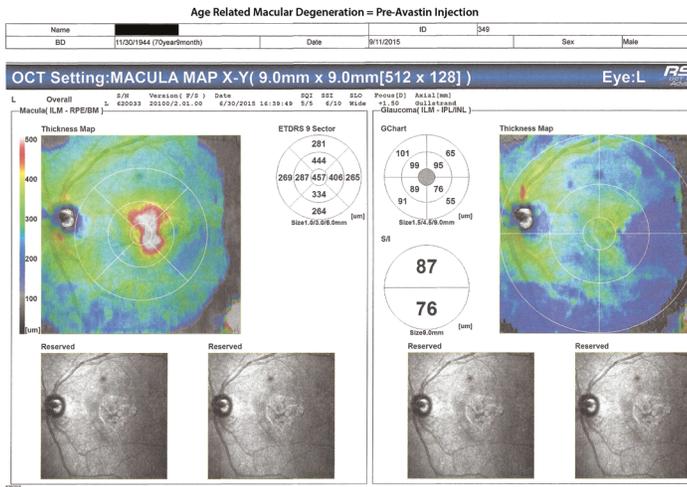
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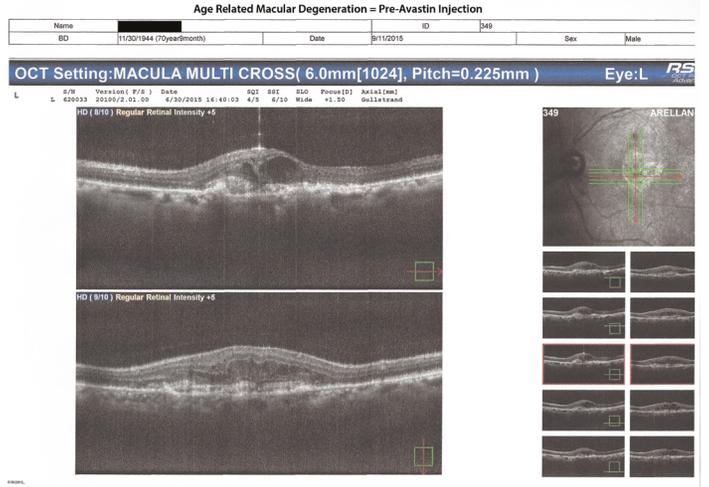
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Attachment 2: Optical Coherence Tomography of a Patient with Age-related Macular Degeneration, Pre- and Post-Avastin

- ARMD = pre-Avastin injection

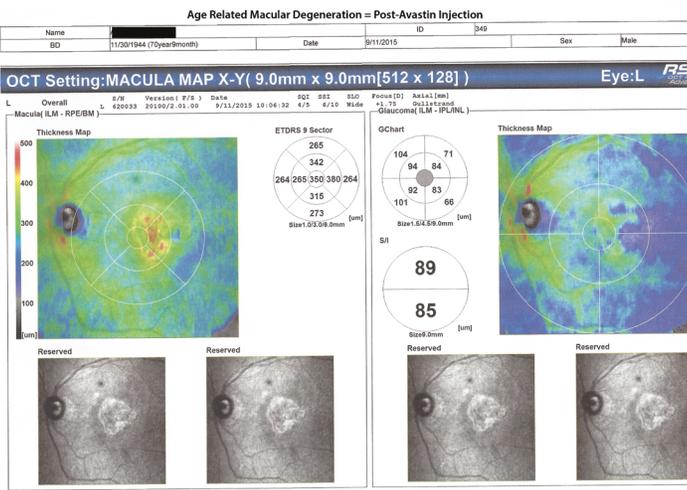


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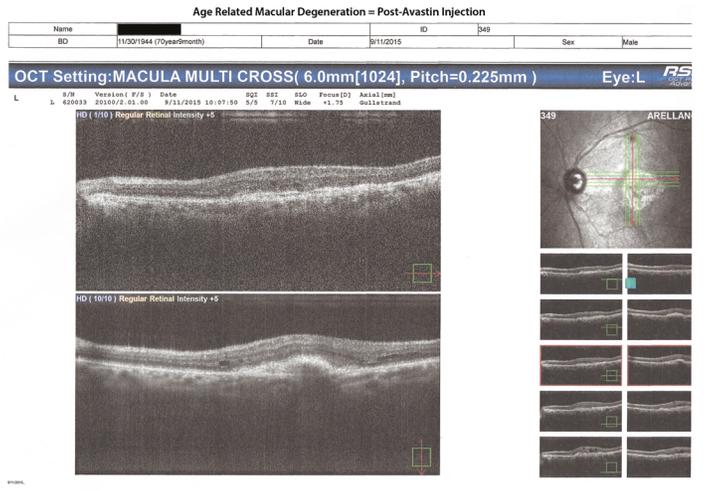


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- ARMD = post-Avastin injection



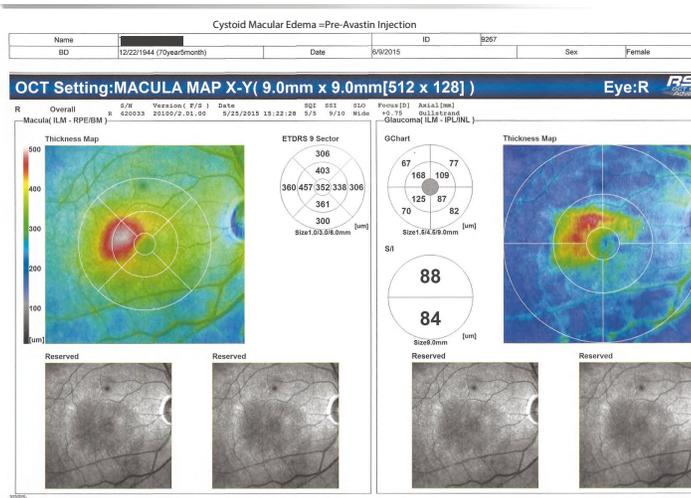
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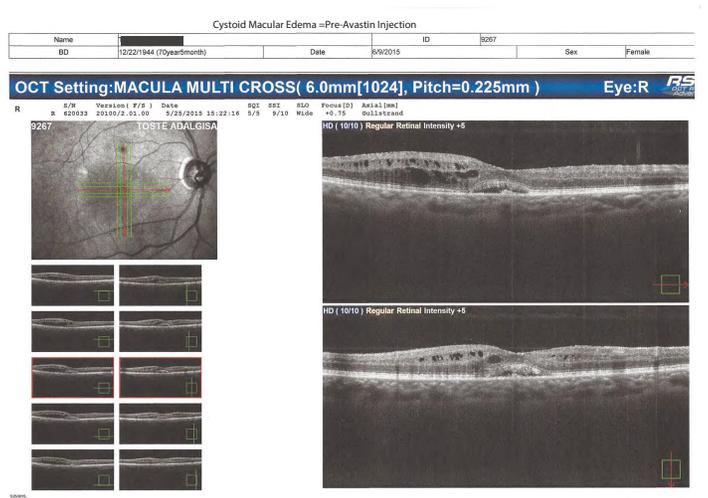
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Attachment 3: Optical Coherence Tomography of a Patient with Cystoid Macular Edema, Pre- and Post-Avastin

- CME = pre-Avastin injection

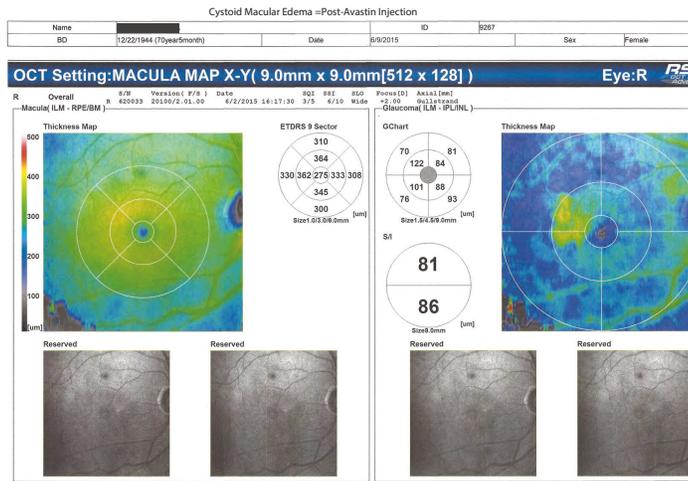


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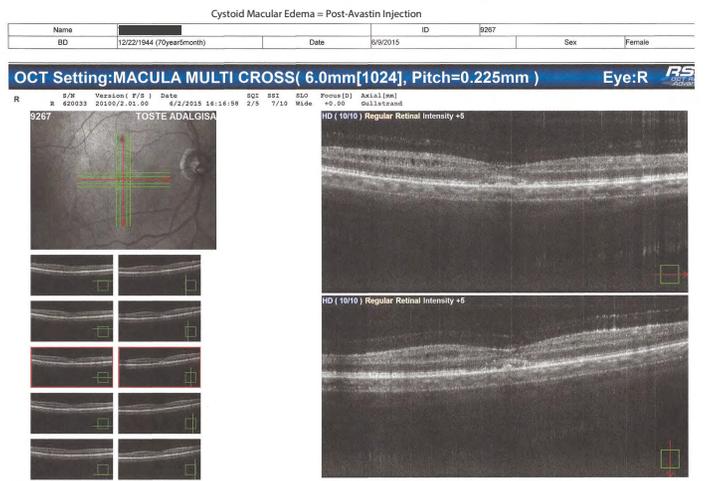


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- CME = post-Avastin injection



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Attachment 4: Malosa Medical "Sunalp Protocol" Single Avastin Tray



Malosa #	Qty	Description
MMSU0104	1	Paper Wrap, 90 × 90cm
MMSU0020	1	Latex Free Gloves, Large
MMSU0190	1	Duo-Tape Eyelash Strips, Pair
MMSU0195	1	Sealed Edge Eye Pad
MMSU0450	1	Stab Knife, 15°
MMSU1303	5	Cellulose Eye Spear
MMSU0021	2	Syringe - 1ml Luer Slip
MMSU0010	1	Filter Needle - 18G x 1 1/2", Pink
MMSU13**	1	Curved Hydrodissection Cannula, 27G
MMSU1474	1	Barraquer Speculum, Solid Curved (PP)
MMSU0170	1	Tray - 1 × Integrated Galipot

