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Suprachoroidal Anti Vascular Endothelial Growth Factor –An Innovative, Potent and Safe Therapy for Wet Age Related Macular Degeneration

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ABSTRACT

Wet Age related macular degeneration (AMD) is a disease originating from the choroid. Abnormal neovascular tissue originating from the choroidal vessels breaches the Retinal Pigment Epithelium (RPE) and proliferates into the retina. Vascular Endothelial Growth Factor (VEGF) is the predominant cytokine responsible for neovascularization and increasing vascular permeability. Leaking, bleeding and ultimately hypertrophied scar forms, distorting the retinal layers. Thus by injecting anti VEGF agent (ranibizumab) through the suprachoroidal route a superior effect is expected as drug is deposited adjacent the target tissue i.e. choroid.
Hence, the study was aimed to evaluate the effectiveness of suprachoroidally administered anti VEGF agent in newly diagnosed cases of wet AMD.

Patients and methods:

This was a randomized prospective interventional study. After obtaining ethical committee's clearance and informed consent, 32 patients of wet AMD were enrolled and administered suprachoroidal anti VEGF and follow up was obtained.
The data was analyzed using paired t- test. The results obtained were compared to previous studies. GraphPad in stat 3 software program was used for statistical analysis.

Results

Significant improvement in LogMAR visual acuity from pretreatment value occurred in AMD patients who received suprachoroidal anti VEGF agent. Furthermore, improvement in visual acuity was fast (within 3 days) and sustained for long duration (12 weeks).

Conclusion

Suprachoroidal anti VEGF is a highly efficacious and safe treatment in wet AMD patients. In future it may emerge as a better and safer alternative to the conventional intravitreal route.

Keywords: Anti VEGF, choroidal neovascularization, suprachoroidal, OCT.

INTRODUCTION

AMD is a leading cause of central (macular) blindness in the developed world in people over 50 years of age; with dry AMD accounting for 85 to 90% and wet AMD around 10 to 15%. Risk factors includes increasing age, genetic predisposition, female sex, hypertension, smoking.[1] As the average

life expectancy steadily increases in the developing countries AMD will soon be a frequent occurrence in this part of the world too. "Wet" AMD, is actually a choroidal pathology characterized by choroidal neovascularization originating from the choriocapillaries, breaching the degenerated Bruch's membrane into retina. This proliferation of pathogenic blood vessels in the retina and choroid is stimulated by various angiogenic factors, vascular endothelial growth factor (VEGF) being the most important. VEGF is a multifunctional cytokine with predominant effect on vascular endothelium. Tissue hypoxia provokes a number of cell types to produce VEGF. VEGF produces a complex cascade of changes in endothelial cells causing gene expression, increased vascular permeability (chiefly postcapillary venules and small veins) and angiogenesis by endothelial cell division, migration and by production of matrix degrading proteases enzymes. VEGF has two Class Ill tyrosine kinases receptors, fit-1 and KDR, that are expressed predominantly on vascular endothelium. VEGF increases microvasculture permeability by up regulating function of an organelle called vesicular vacuolar organelle (VVO). VVO increases vascular permeability of plasma and plasma proteins like fibrin, fribronectin causing them to leak into the surrounding tissue. Extravasated fibrin immediately forms a crosslinking structure. This provides a favorable surface for cell adhesion, migration promoting angiogenesis.[2] These new vessels are fragile, leaky and may bleed predominantly below the macula. Bleeding, leaking, and hypertrophic scarring from these blood vessels eventually cause irreversible damage to the RPE-photoreceptor complex with permanent vision loss. Ellipsoid zone disruption, Drusenoid PED, RPE thickening, and subretinal hyperreflective material were associated with higher risk of progression to neovascular AMD.[3] Now the suprachoroidal space (SCS) is a potential space between the choroid and the sclera. While the inner border of the choroid, which is the Bruch's membrane, is compact, the outer border is a zone of transition, consisting of several fibrous lamellae with variable thickness.[4] Until recently, the SCS could only be visualized on histology,[5] and could only be demonstrated in vivo by ultrasonography in pathologic conditions such as idiopathic uveal effusion syndrome or posterior scleritis where excess fluid accumulation around the optic nerve causes a "T sign".[6] The advent of Optical coherence tomography (OCT) has heralded a new era for retinal conditions enabling detailed in vivo imaging of retinal structures with an axial resolution as high as 3 µm.[7] Further advances in OCT like enhanced depth imaging (EDI)-OCT[8] or swept-source OCT, has deeper penetration allowing better visualization of the suprachoroidal space.[9] Importantly, the Suprachoroidal space may also provide a new route for both medical and surgical treatments. Intravitreal injections are currently the mainstay of treatment for a wide variety of retinal diseases, and constitute an effective method to achieve high intraocular levels of antibiotic, antiviral, antifungal, steroidal, and anti-VEGF drugs.[10,11] But it should be remembered that intravitreal injections can cause complications including cataract formation, glaucoma, choroidal hemorrhage, endophthalmitis, vitreous hemorrhage, and retinal detachment.[12] The suprachoroidal route bypasses the sclera without the risk of intraocular penetration. Animal studies have shown that the Suprachoroidal space can accommodate up to 1 mL of fluid.[13] This volume is much higher than what is required for achieving therapeutic levels for clinically relevant drugs.[14,15] Drug injected via the Suprachoroidal space mainly concentrates around the choroid and the retina. In contrast, when the same drug is injected into the vitreous, the drug spreads diffusely across all parts of the eye and significant amount is lost which crossing the internal limiting membrane and inner blood retinal barrier. Thus suprachoroidal route allows for lower or less frequent dosing because of high effective drug levels being achieved.[16] Several techniques for injections into the SCS have been described. Most commonly SCS drug delivery is performed using microneedles – small-gauge needles (26-30 G) 0.5–1.0 mm in length that are only long enough to penetrate the sclera and reach the SCS.[17] Therefore, this study was conducted to evaluate this novel route for administration of anti-VEGF in wet AMD. Moreover as already stated wet AMD is a disease of the choroid so by depositing the drug just next to the choroidal tissue a beneficial effect is expected.

MATERIALS AND METHODS:

The study was a hospital based randomized, prospective interventional study which included newly diagnosed patients of Wet AMD presenting to

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Department of Ophthalmology, at a tertiary care centre in India. The study and data accumulation were carried out with the approval from the Ethical committee, of the institution and reference no.is E.C./BMHR/2020/41.A total of 32 patients of newly diagnosed AMD were enrolled, given a single injection of suprachoroidal anti VEGF and followed regularly on 3rd day, 1st week and then for every 2 weeks for a total duration of 12 weeks. Two OCTs were performed one pre injection, another after 15 days of suprachoroidal anti VEGF injection to assess the status of choroidal neovascular tissue. 2 patients were lost to follow up. All participants provided informed consent to participate in this study, and this study was conducted in accordance with the Declaration of Helsinki.

INCLUSION CRITERIA:

- Patients newly diagnosed of Wet AMD.

EXCLUSION CRITERIA:

- Patients not willing to participate or ready for follow up.
- Patients with raised RBS levels (>200mg %).
- Patients with any ocular infection, raised Intraocular pressure (IOP), any corneal pathology, scleritis, staphyloma or any other anterior segment pathology.
- Patients diagnosed of any other retinal or vitreous pathologies except wet AMD.

PROCEDURE:

- One eye per patient was included.
- BCVA was calculated using LogMAR visual chart.
- Fundus examination by indirect ophthalmoloscope.
- B-scan to rule out any other posterior segment pathology.
- Spectral domain optical coherence tomography.
- Finally Suprachoroidal injection of anti-VEGF (Ranibizumab) was administered by an indigenously designed needle. A 26 G hypodermic needle when inserted with a 20 G steel sleeve leaving behind 500-1000 microns (0.5-1mm) of sharp bevel to deliver anti VEGF.
- The needle can be adjusted to pierce a depth ranging from 500-1000 microns deep depending on scleral thickness to inject the drug in Suprachoroidal space. 0.1 ml of anti VEGF was injected.

STATISTICS:

For assessing improvement in visual acuity in the study group from pretreatment value to the final value at 12 weeks paired t –test was applied.

Significant level at 95% confidence limit was kept at 0.05.

GraphPad in stat 3 software program was used for statistical analysis.

Value of α error for the study was 5%.Power of the study was 80%.

For sample size calculation for the study, following formula was used-

$$\text{Number of patients } \{n\} = \frac{2x\left(Z\left(1-\frac{\alpha}{2}\right)\leftarrow Z\beta\right)^2 x\sigma^2}{\Delta^2}$$

Where α=significance level;β= power, probability of detecting a significant result;σ=SD of data;Δ= size of difference. p-value of <0.05 was considered significant at 95% confidence interval.

RESULTS:

LogMAR mean visual acuity of the group improved from pretreatment value of 1.21±0.26 to 0.41±0.19 over the total duration of 12 weeks.

Table 1*:* logMAR visual acuity in AMD patients receiving suprachoroidal anti VEGF injection over 12 weeks.

Figure 1: Graphical representation of the above data showing gradual improvement in visual acuity.

Paired t-test applied showed highly significant correlation between suprachoroidal anti-VEGF and improved LogMAR visual acuity in wet AMD ($p<0.001$) from the pretreatment value to final acuity at 12 weeks.

The visual acuity promptly started to improve as early as 3rd day post injection and the improved vision was sustained for a long duration of 12 weeks.

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Comparison of pre injection OCT and 15 days post injection OCT in three patients included as shown in

Figure 2: Comparison of OCT 1: pre suprachoroidal injection and 15 day post injection in AMD patient show significant reduction in neovascular tissue and restored retinal anatomy

Figure 3: Comparison of OCT 2: pre suprachoroidal injection and 15 day post injection in AMD patient show significant reduction in neovascular tissue and restored retinal anatomy.

Figure 4: Comparison of OCT 3: pre suprachoroidal injection and 15 day post injection in AMD patient show significant reduction in neovascular tissue and restored retinal anatomy.

Complications encountered were transient ocular pain, redness and discomfort, in few patients.

DISCUSSION:

The study conducted clearly shows that suprachoroidally administered Anti-VEGF is a highly efficacious treatment option for wet-AMD as evidenced subjectively (improved visual acuity) and objectively from OCT (reduction in fibrovascular tissue and restored outer retinal anatomy).

Drug is deposited in close proximity to the target tissue i.e. choroid, ensuring higher concentration in the target tissue.

Faster and longer duration of action for each dose of injection as evidenced by improvement in visual acuity as early as 3rd day which was also sustained till 12 weeks of follow up.

In the intravitreal route a significant amount of drug is lost as it has to diffuse through vitreous, all the retinal layers and RPE before it reaches the choroid. Hence only a small fraction of the drug reaches the target tissue. This drug loss is avoided via suprachoroidal route as drug is delivered at doorstep of target tissue.

Higher concentration of drug in choroid leads to complete ablation of the small and fresh CNV tissue. As all of our cases were newly diagnosed so the lesions were fresh, small, without scar; so a single injection with a high dose of drug ablates the tissue completely as evidenced in OCT Scan; causing a single injection to have a sustained effect for longer duration, so number of injections required is less as compared to intravitreal route.

Dreaded complications like raised IOP, endophthalmitis, cataract are unlikely to occur as ocular cavity is not penetrated in this route.

Thus, suprachoroidal Anti-VEGF may be given as a routine OPD procedure, just like an insulin shot; no need of costly OT setup with no added worry for sterility breach.

CONCLUSION:

Suprachoroidal anti VEGF in AMD has a faster, significantly better, and sustained improvement in visual acuity.

Learning curve is also easier for suprachoroidal injection because the outer 20 G cannula acts as a guard preventing deeper penetration into the vitreous.

Furthermore bevacizumab (a much cheaper alternative to ranibizumab) which has a high propensity for cluster endophthalmitis following intravitreal injection[18] can be easily given by this route as ocular cavity is not entered. Hence risk of endophthalmitis is minimized.

Thus suprachoroidally administered anti VEGF reduces the economic burden of the disease by:

- Reduced number of injection, as each dose has longer action.
- No OT set up required.
- Bevacizumab can be given safely by this route.

This is highly beneficial for developing countries like India with a GDP per capita of only 2104 USD in 2019. Also the entire cost for anti VEGF injection is borne by the patient's pocket, as government does not have any policy to cover the treatment cost.

Thus by reducing the economic burden of the disease, we ensure better compliance from economically weaker section.

In near future suprachoroidal anti-VEGF may emerge as a better route to treat wet AMD.

LIMITATION:

- Small study group.
- Short duration of follow up.

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REFERENCES

1. McCannel C,Berrocal A, Holder G, Kim S, Leonard B, Rosen R, Spaide R, Sun J. Age related macular degeneration and other causes of choroidal neovascularisation. Basic and clinical science course 2019-2020,92 -121 Retina and vitreous part 12 of American academy of Ophthalmology.
2. Dvorak H, Brown L, Detmar M, Dvorak A. Vascular Permeability Factor/Vascular Endothelial Growth Factor, Microvascular Hyperpermeability, and Angiogenesis. American Journal of Pathology, Vol. 146, No. 5, May 1995; 1029-39.
3. 3.Amdbook.org/content/optical-coherence-tomography-age-related-macular-degeneration A.https://www. ncbi. nlm. nih.gov/pubmed/28715590
4. Buggage RR, Grossniklaus HE. Choroid and suprachoroid. In: Tasman W, Jaeger AE, editors. Duane's Foundations of Clinical Ophthalmology. Vol. 1. Northwestern University: J.B. Lippincott; Philadelphia, PA, USA: 1991.
5. Krohn J, Bertelsen T. Corrosion casts of the suprachoroidal space and uveoscleral drainage routes in the human eye. Acta Ophthalmol Scand. 1997;75(1):32–35. [PubMed]
6. Benson WE. Posterior scleritis. Surv Ophthalmol. 1988;32(5):297–316. [PubMed]
7. Ko TH, Fujimoto JG, Schuman JS, et al. Comparison of ultrahigh- and standard-resolution optical coherence tomography for imaging macular pathology. Ophthalmology. 2005;112(11):1922.e1–e15. [PMC free article] [PubMed]
8. Spaide RF, Koizumi H, Pozzoni MC. Enhanced depth imaging spectral-domain optical coherence tomography. Am J Ophthalmol. 2008;146(4):496–500. [PubMed]
9. Michalewska Z, Michalewski J, Nawrocki J. Going deeper and going wider. Retinal Physician. 2013;3:42–48.
10. Peyman GA, Lad EM, Moshfeghi DM. Intravitreal injection of therapeutic agents. Retina. 2009;29(7):875–912. [PubMed]
11. Heimann H. Chapter 5. Intravitreal injections: Techniques and sequelae. In: Holz FG, Spaide RF, editors. Medical Retina (Essentials in Ophthalmology) 1st ed. Berlin: Springer-Verlag Berlin Heidelberg; 2007. pp. 67–87.
12. Prasad AG, Schadlu R, Apte RS. Intravitreal pharmacotherapy: applications in retinal disease. Compr Seiler GS, Salmon JH, Mantuo R, Feingold S, Dayton PA, Gilger BC. Effect and distribution of contrast medium after injection into the anterior suprachoroidal space in ex vivo eyes. Invest Ophthalmol Vis Sci. 2011;52(8):5730–5736. [PubMed]
13. Seiler GS, Salmon JH, Mantuo R, Feingold S, Dayton PA, Gilger BC. Effect and distribution of contrast medium after injection into the anterior suprachoroidal space in ex vivo eyes. Invest Ophthalmol Vis Sci. 2011;52(8):5730–5736. [PubMed]
14. Gu B, Liu J, Li X, Ma Q, Shen M, Cheng L. Real-Time Monitoring of Suprachoroidal Space (SCS) Following SCS Injection Using Ultra-High Resolution Optical Coherence Tomography in Guinea Pig Eyes. Invest Ophthalmol Vis Sci. 2015;56(6):3623–3634. [PubMed]
15. Chen M, Li X, Liu J, Han Y, Cheng L. Safety and pharmacodynamics of suprachoroidal injection of triamcinolone acetonide as a controlled ocular drug release model. J Control Release. 2015;203:109–117. [PubMed]
16. Tetz M, Rizzo S, Augustin AJ. Safety of submacular suprachoroidal drug administration via a microcatheter: retrospective analysis of European treatment results. Ophthalmologica. 2012;227:183-189
17. Patel SR, Lin AS, Edelhauser HF, Prausnitz MR. Suprachoroidal drug delivery to the back of the eye using hollow microneedles. Pharm Res. 2011;28(1):166–176. [PMC free article] [PubMed] 42.

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18. Goldberg R, Flynn H, Miller D, Gonzalez S, Isom R. Streptococcus endophthalmitis outbreak after intravitreal injection of bevacizumab: one year outcomes and investigative results. Ophthalmology 120(7),2013, 1448-53.

Suprachoroidal anti VEGF	Pre-treatment logMAR VA*	3day post treatment logMAR VA	7day post treatment logMAR VA	2week post treatment logMAR VA	4week post treatment logMAR VA	6week post treatment logMAR VA	8week post treatment logMAR VA	10week post treatment logMAR VA	12week post treatment logMAR VA
Mean	1.21	1.13	0.93	0.75	0.57	0.46	0.43	0.42	0.41
Std deviation	0.26	0.25	0.22	0.24	0.24	0.18	0.18	0.18	0.19

***Visual Acuity**

Table 1: logMAR visual acuity in AMD patients receiving suprachoroidal anti VEGF injection over 12 weeks

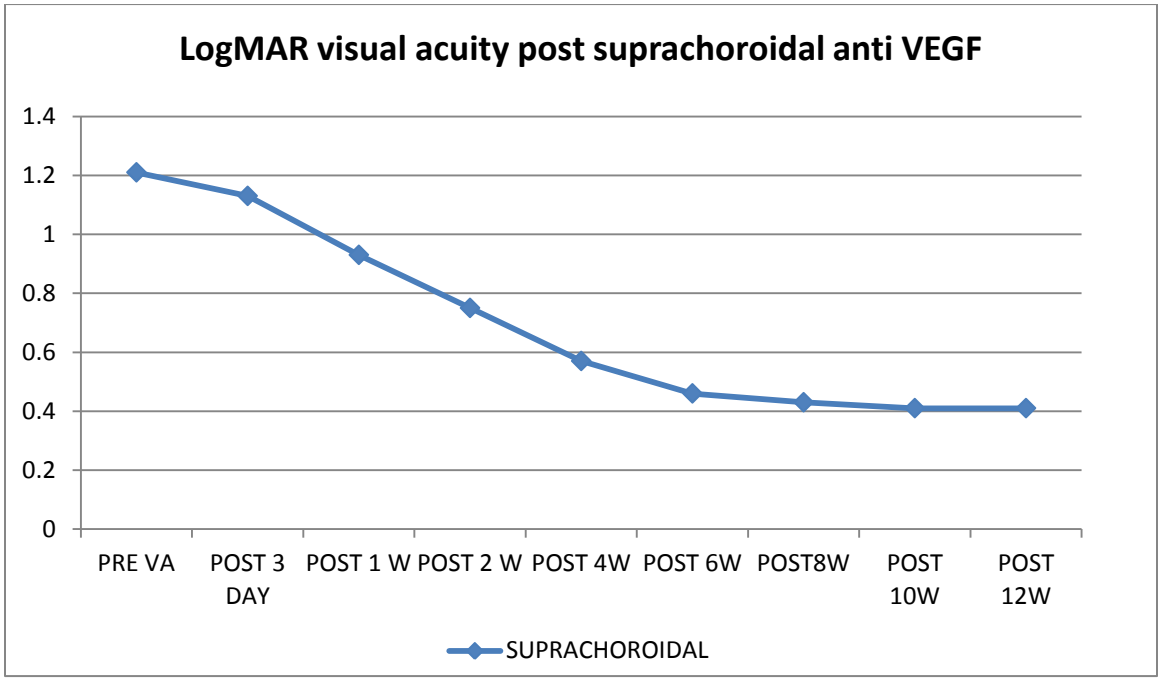

Figure 1: Graphical representation of the above data showing gradual improvement in visual acuity.

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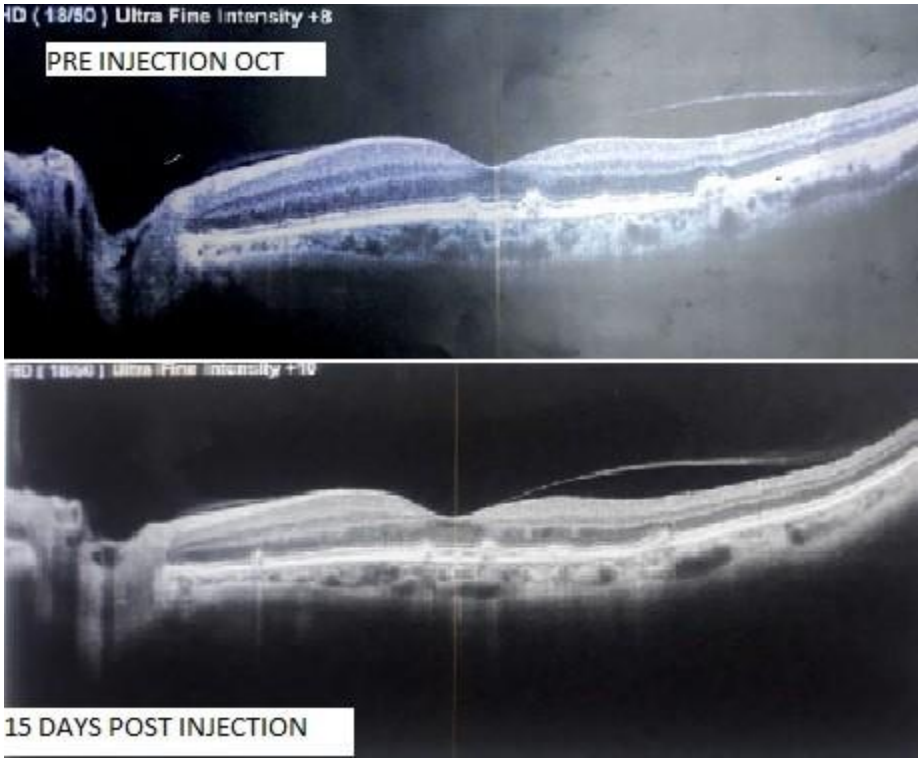

Figure 2: Comparison of OCT 1: pre suprachoroidal injection and 15 day post injection in AMD patient show significant reduction in neovascular tissue and restored retinal anatomy

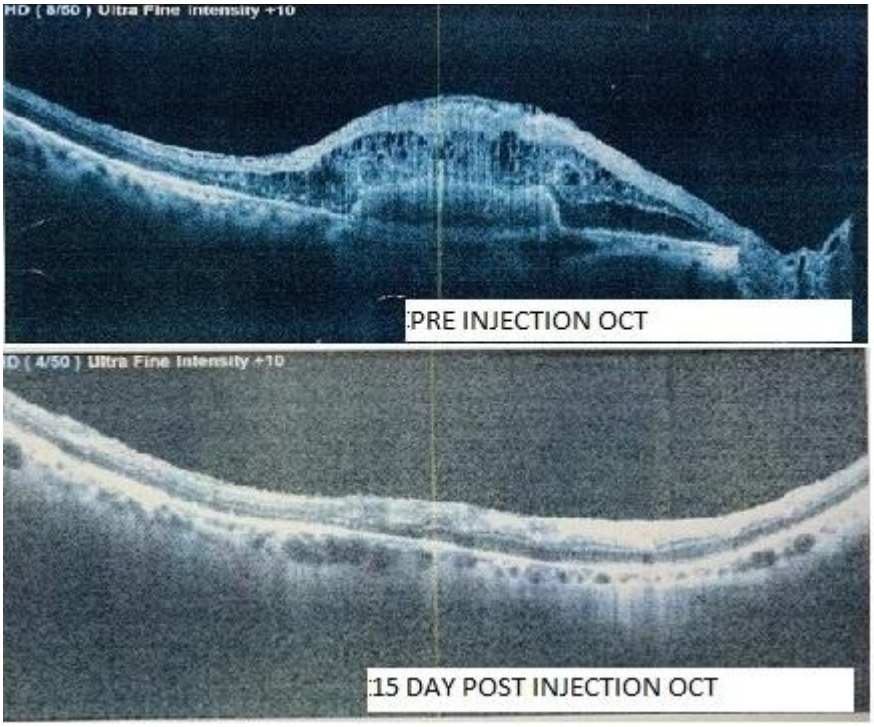

Figure 3: Comparison of OCT 2: pre suprachoroidal injection and 15 day post injection in AMD patient show significant reduction in neovascular tissue and restored retinal anatomy.

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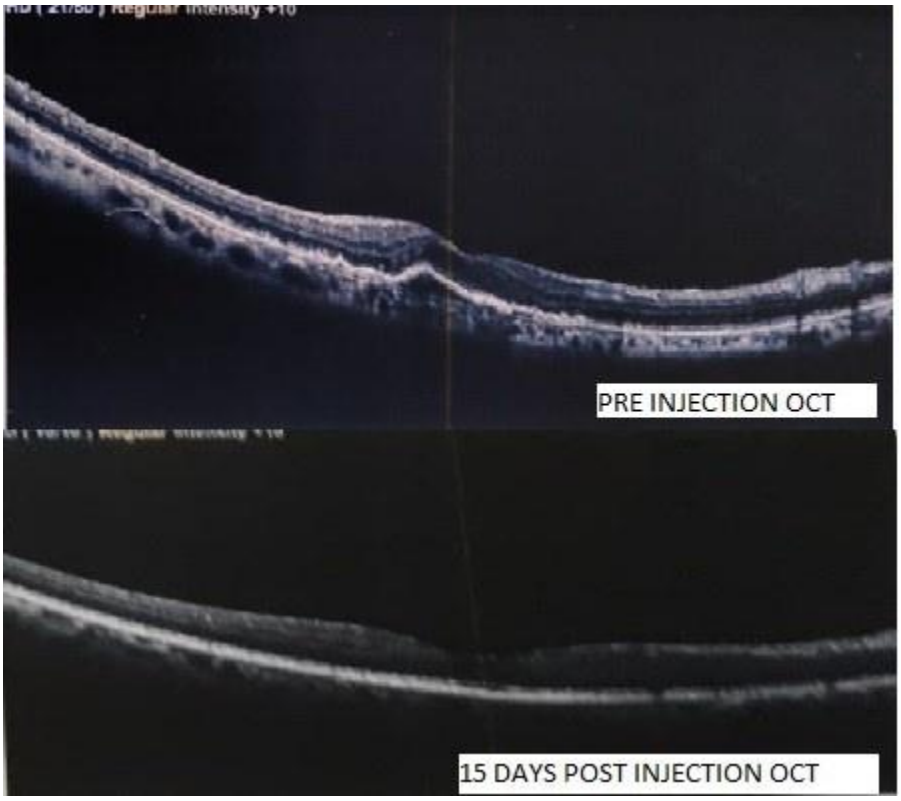

Figure 4: Comparison of OCT 3: pre suprachoroidal injection and 15 day post injection in AMD patient show significant reduction in neovascular tissue and restored retinal anatomy.

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