Dissertation on

A MULTIVARIATE ANALYSIS OF INTRA VITREAL INJECTION OF ANTI VEGF BEVACIZUMAB IN THE TREATMENT OF RETINAL AND CHOROIDAL NEOVASCULARISATION

Submitted in partial fulfillment for

M.S. OPTHALMOLOGY
BRANCH - III

Regional Institute of Opthalmology
Madras Medical College & Research Institute,
Chennai – 600 003

THE TAMILNADU Dr.M.G.R. MEDICAL UNIVERSITY

CHENNAI – 600 003

TAMIL NADU

MARCH 2009

CERTIFICATE

Certified that this dissertation entitled "**A MULTIVARIATE ANALYSIS OF INTRA VITREAL INJECTION OF ANTI VEGF BEVACIZUMAB IN THE TREATMENT OF RETINAL AND CHOROIDAL NEOVASCULARISATION**" is the bonafide work by **Dr.L.ANITHA**, Post graduate student, done under my guidance and supervision during the period from June 2008 to November 2008 in partial fulfillment for the award of M.S. Degree (Ophthalmology) of the Tamil Nadu Dr. M.G.R. Medical University, Chennai.

Prof. Dr.B.Jayasuganthi, M.S., D.O.
Chief, Retina Clinic
RIO - GOH,
Chennai - 8.

Prof.Dr.M.Radhakrishnan, M.S., D.O.
Director & Superintendent,
RIO - GOH,
Chennai - 8.

Dr.T.P.Kalanati, M.D.,
Dean,
Madras Medical College,
Chennai

ACKNOWLEDGEMENT

My sincere thanks and gratitude to **Prof. T.P.KALANITI, M.D.,** Dean, Madras Medical College for permitting to utilize the clinical materials of this hospital.

I have immense pleasure in thanking **Prof. M. Radha krishnan M.S., D.O.,** Director and Superintendent, Regional Institute of Ophthalmology and Govt. Ophthalmic Hospital for his guidance and suggestions during this study.

I have great pleasure in thanking my unit chief **Prof. B.Jayasuganthi M.S., D.O** and my associate **Prof. R. Ravikumar M.S., D.O** for their continuous guidance, valuable advise and constant support at every stage of my dissertation.

I take immense pleasure in thanking my unit Assistant Professors, **Dr.Zaibunissa M.S., D.O., Dr. Padmapriya M.S., and Dr. A.Palaniraj M.S.,** for their valuable suggestion, guidance and help during the study.

I am grateful to **Prof.K.Maragatham M.S., D.O and Dr.N.Sharmila M.S** who have guided me to complete this study.

I am thankful to all the professors and assistant professors of this institute who have guided me in this study.

I am thankful to all my colleagues and friends for their valuable help.

I am grateful to all the patients without whose cooperation this study would not have been possible.

CONTENTS

Sl. No.	Title	Page No.
	PART – I	
1	FUNCTIONAL ANATOMY, FINE STRUCTURE AND BASIC PATHOLOGY OF RETINAL VASCULATURE	1
2.	RETINAL VASCULAR DEVELOPMENT	7
3.	RETINAL ANGIOGENESIS AND GROWTH FACTORS	10
4.	VASCULAR ENDOTHELIAL GROWTH FACTOR	12
5.	RATIONALE FOR ANGIOGENESIS INHIBITORS IN RETINAL DISEASES	15
6.	AN UPDATE OF BEVACIZUMAB	28
7.	INTRAVITREAL INJECTIONS – PROCEDURE GUIDELINES	36
	PART - II	
7	AIM OF THE STUDY	38
8	DESIGN	39
9	MATERIALS AND METHODS	40
10	OBSERVATIONS AND RESULTS	44
11	DISCUSSION	62
12	SUMMARY	70
13	CONCLUSION	71
	PART – III	
14	BIBLIOGRAPHY	
15	PROFORMA	
16	MASTER CHART	
17	KEY TO MASTER CHART	
18	LIST OF FEW SURGERIES PERFORMED	

FUNCTIONAL ANATOMY, FINE STRUCTURE AND BASIC PATHOLOGY OF RETINAL VASCULATURE

1. Anatomical organization of retinal vasculature

The retinal vasculature is arranged in 3 dimensional network. The central retinal artery is a direct branch of the ophthalmic artery arising from bifurcations adjacent to the optic disc to form a unique, intra retinal, end artery micro vascular system.

Oxygen tension in the inner retina has been identified as a key regulator of retinal cell differentiation and micro vascular permeability, growth and survival by altering expression of VEGF.

In the mature retinal micro vasculature this oxygen regulated control of capillary density is well illustrated by the appearance of a so called “capillary free zone”. Adjacent to arterial walls where oxygen tension is high and local expression of VEGF is low.

Cilio retinal arteries may also contribute to the retinal circulation and these arise from posterior ciliary arteries.

Branch retinal arteries lack an internal elastic lamina and anatomically speaking arterioles. These arterioles in the peripheral retina

bifurcate to third and fourth orders and finally to pre capillary arterioles. The peri papillary retina has four layers of capillaries while the macular and peripheral retinas have three and two respectively. There is a capillary free zone at the fovea where the inner retinal neurons and their processes show lateral displacement to allow unobstructed passage of light to the midget central cones for accurate resolution of visual images.

Each capillary unit is 10-15 micro meters in diameter and consists of continuous endothelium surrounded by pericytes. Retinal pericytes occur in a 1:1 ratio with endothelial cells which is the unique feature of this micro vasculature.

The capillary flow drains into the venular system which is localized in the deeper retina and eventually into the retinal veins. The central retinal vein lies with in the optic nerve head and is drained by the ophthalmic vein and cavernous sinus.

While the retinal vasculature is a classic end artery system, it lacks any obvious autonomic nerve supply and blood flow in to the capillary bed is auto regulated in response to the local metabolic needs of the retinal parenchyma.

An important normal physiological function of the retinal vasculature is maintenance of the inner blood retinal barrier, which prevents non specific permeation of the retinal neuropile by macromolecules yet facilitates exchange of respiratory gases, amino acids, salts, sugars and peptides. The endothelial cells of the retinal vessels form a continuous, non fenestrated, mono layer, with each cell being fused to juxta posed neighbours by zonulae occludens that maintain barrier function.

2. Responses of the retinal vasculature to stress and disease

A. Hemodynamic changes:

Increased arteriolar intra luminal pressure induces reactive vessel narrowing probably by stretch activated calcium channels which may lead to occlusion of pre arteriolar branches, subsequent to endothelial damage and insudation of plasma in to the vessel wall. Occlusion of down stream retinal vessels may cause impaired axoplasmic transport clinically manifested as cotton wool spots and electron microscopy reveals swollen axons containing cytoid bodies in the nerve fiber layer. Normalization of intra vascular pressure results in recovery of competence and sometimes local reorganization of the effected micro vasculature, but the legacy of focal capillary drop out often persists in the

form of micro aneurysms, persistent inner retinal exudates and focal reactive micro gliosis. Sudden increase in venous intra luminal pressure results in CRVO/ BRVO, in such case blood is shunted into the non obstructed circulation via competent capillary/ venular collaterals. Retinal arteriole macro aneurysms may reflect long standing arteriolar stress in patients with hyper tension. The area of abnormally perfused retina is sufficiently large, ischemic/ hypoxic/ metabolically compromised retina can produce a range of angiogenic growth factors and leads to pre retinal /optic disc / iris / anterior chamber angle neo vascularisation.

B. Oxygen saturation changes

Reduced oxygen saturation rapidly affects the metabolically demanding retinal neuropile, which can release metabolites such as adenosine and lactate, and this triggers local vaso dilatation and increased blood flow as a direct consequence of vasogenic agents. Sustained hyperoxia has an exaggerated effect on immature retinal vessels with vascular closure and death of growth factor sensitive retinal vascular cells. Similarly chronic hypoxia induces vascular endothelial cell proliferation to revascularise metabolically deprived retina causes pre retinal neovascularization.

C. Occlusion- ischemia

Collapse of circulation is characterized by dilated capillaries, veno-venous shunts, micro aneurysms, advential sclerosis and areas of capillary closure. These disorders can lead to focal retinal ischemia and significant damage in the form of macular edema, cystiod degeneration, focal atrophy of macular photo receptors, glial cell abnormalities and patho physiological changes in the RPE.

D. Repair and remodeling

Micro vascular repair and remodeling are a feature of acute and chronic vaso occlusion where there is continuing stasis, hypoxia and variations in tissue perfusion pressure. Capillaries dilate or attenuate and micro aneurysms form and subsequently show a pattern of sclerosis or recanalisation. A limited degree of intra retinal neo vascularisation occurs where redundant and acellular basement membrane tubes are recanalised and connect with residual radicals of the existing circulation. The form and orientation of these new vessels is determined by concentration gradients of growth factors, e.g., VEGF, TGF- beta and availability of angiogenic stem cells.

E. Metabolic stresses

The retinal micro vasculature can be influenced by a range of systemic disorders the most common being diabetes. Retinal vascular dysfunction commences soon after the onset of diabetes and is characterized by impaired auto regulation in the micro vasculature. The changes that manifest include basement membrane thickening, pericyte loss with formation of acellular capillaries corresponding to non perfused micro vasculature. Increasing closure of capillaries may be linked with cotton wool spots in the neural retina and also the occurrence of intra retinal micro vascular abnormalities. They could reflect increasing retinal ischemia and an attempt to revascularise hypoxic neuropile, possibly to form shunt like channels. Hypoxia increase expression of VEGF and other peptide growth factors that have an important modulatory role in the development of macular edema and pre retinal neo vascularisation.

F. Primary neuropile atrophy and degeneration

Normal function of the retinal circulation is completely dependent on intimate cell-cell communication with neural and glial elements of the retina. In retinitis pigmentosa, trauma, toxic retinopathy and loss of retinal parenchyma are associated with retinal capillary cell attrition, closure of capillary beds, narrowing of supply vessels and involutional sclerosis of larger radicals.

RETINAL VASCULAR DEVELOPMENT

1. Introduction

Blood vessel formation occurs by three processes, the initial formation of vessels from yolk sacs during early embryogenesis, and by the distinct process of vasculogenesis and angiogenesis during subsequent development.

YOLK SACS

Angiogenic clusters containing hematopoietic cells at the centre and angioblasts lining the periphery.

VASCULOGENESIS

The assembly of vessels from separate endothelial precursor cells as they differentiate into mature endothelial cells.

ANGIOGENESIS

The formation of new blood vessels from preexisting capillaries. Differentiated endothelial cells are induced to proliferate, thus facilitating the sprouting of new vessels from existing vessels.

2. ENDOTHELIAL CELLS

Form the vessel wall creating the lumen through which blood flows. The types are Continuous, Fenestrated, and Discontinuous. The retinal vasculature is continuous type which helps to regulate the neural microenvironment by protecting the retina from fluctuations in plasma composition, whereas choroidal vasculature is fenestrated.

3. MURAL CELLS

Perivascular cells that associate with the vessels and lie just external to the endothelial cells. Appropriate recruitment of the various mural cells is important for stabilization and maturation of new vessels during developmental neovascularisation. Vessels lacking mural cells have been found to be most susceptible to apoptosis and degeneration during vascular remodeling. Mural cells are also important for maintaining vascular quiescence after vascular development is complete.

4. ROLE OF ASTROCYTES

Astrocytes are only observed in regions where vascularisation occurs. For example, astrocytes do not develop in the macula, which also remains avascular. Astrocytes secrete VEGF, which the endothelial cells respond to through VEGF receptors on the endothelial cell surface. Astrocytes also play a critical role during guidance and maintenance of the neovascular plexus. As the vasculature matures, astrocytes begin to

wrap around the newly formed vessels and this vessel-astrocyte association remains as an important aspect of the blood-retinal barrier throughout the adult life.

5. DEVELOPMENT OF THE DEEP RETINAL VASCULAR PLEXUSES

As the retina continues to expand, the vascular branches sprout perpendicular to the superficial plexus and dive towards the outer edge of the inner nuclear layer where they anastomose laterally and form a planar micro vascular plexus. General consensus is that the deep and intermediate plexuses form solely by the process of angiogenesis. Mechanisms involving specific expression of growth factors and cell-cell adhesion molecules are also important for initiation and guidance of the deep retinal vascular plexuses.

6. VASCULAR MATURATION

This involves appropriate mural cell recruitment and remodeling of the vascular plexus. Mural cell recruitment occurs almost concomitantly with neovascular formation. As the new vessels grow, endothelial cells secrete platelet derived growth factor (PDGF). Mural cells respond to this signal through receptors on their cell surface and are thereby recruited to the neo vessel surface.

RETINAL ANGIOGENESIS AND GROWTH FACTORS

1. VASCULOGENESIS

Vasculogenesis in the embryo is different from that after birth. In the embryo, mesoderm-derived endothelial precursor cells give rise to the first embryonic blood vessels. The endothelial progenitors give rise to a primitive vascular labyrinth of arteries and veins. During subsequent angiogenesis the network expands, pericytes and smooth muscle cells cover nascent endothelial channels and a stereotypically organized vascular network emerges.

Whereas in adults the bone marrow progenitor cells are recruited and incorporated in to nascent vessels or stimulate new vessel growth by releasing pro angiogenic factors an inducing the proliferation of resident endothelial cells.

2. ANGIOGENESIS

After vasculogenesis the nascent primitive vascular labyrinth expands and become remodeled in to a more complex network of larger vessels ramifying in to smaller vessels.

This process includes, release of angiogenic cues that diffuse into the near by tissues and activate endothelial cells to induce endothelial cell matrix degradation. Endothelial cells then proliferate to navigate toward these cues and form a sprout, endothelial progenitor cells are also recruited from blood circulation to participate in the formation of new blood vessels

3. ARTERIOGENESIS

The establishment of functional vascular network requires the nascent vessels- formed by vasculogenesis and angiogenesis- mature in to durable, stable, non leaky and functional vessels. This stabilization requires recruitment of mural peri endothelial and smooth muscle cells, generation of an extra cellular matrix and specialization of vessel wall for structural support and regulation of vessel function- a process termed arteriogenesis.

VASCULAR ENDOTHELIAL GROWTH FACTORS

1. VEGF regulation and receptors

Vascular endothelial growth factor (VEGF), or vascular permeability factor (VPF) is a 48 kDa homodynamic glycoprotein that functions as an endothelial cell- specific mitogen and vaso permeability factor. It is activated by hypoxia, high glucose, protein kinase C activation, advanced glycation end products, reactive oxygen species, activated oncogenes and a variety of cytokines.

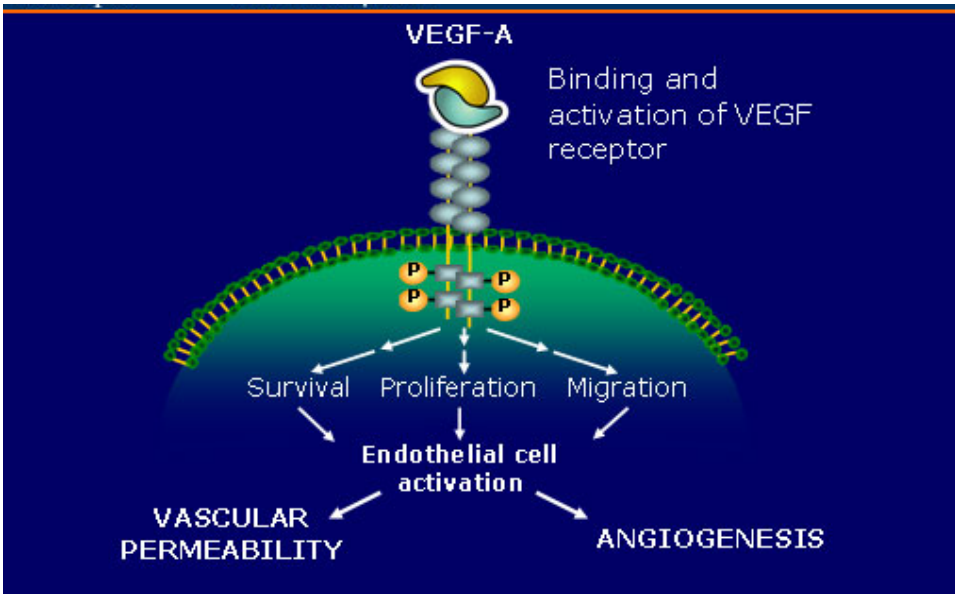
Activation of VEGF induces endothelial cell proliferation, induces vascular permeability, promotes cell migration and inhibits apoptosis

The VEGF molecular family consists of five members

1. Placental growth factor(PlGF)
2. VEGF A
3. VEGF B
4. VEGF C
5. VEGF D

There are at least 6 known major isoforms of VEGF that arise from alternate splicing of the mRNA of a single gene: $VEGF_{121}$, $VEGF_{145}$, $VEGF_{165}$, $VEGF_{183}$, $VEGF_{189}$, and $VEGF_{206}$. $VEGF_{165}$ is the predominant

pathologic isoform. VEGF can be inhibited by blocking its production or receptors or the molecule itself in the extra cellular space.



2. VEGF and systemic diseases

VEGF stimulated collateral blood vessel formation helps to preserve myocardial function during coronary arterial occlusion. Several observations including the fact that direct VEGF gene transfer therapies have proved to be effective in coronary heart disease as well as peripheral vascular disease suggest that VEGF plays a significant role in this adaptive process. Thus although anti VEGF therapies appear promising as a means of reducing neo vascular complications from ischemic ocular diseases , they also have the potential to decrease collateral vascular

formation and there by increase macro vascular complications associated with myocardial infarction and peripheral limb ischemia.

3. VEGF and retinal vascular disease

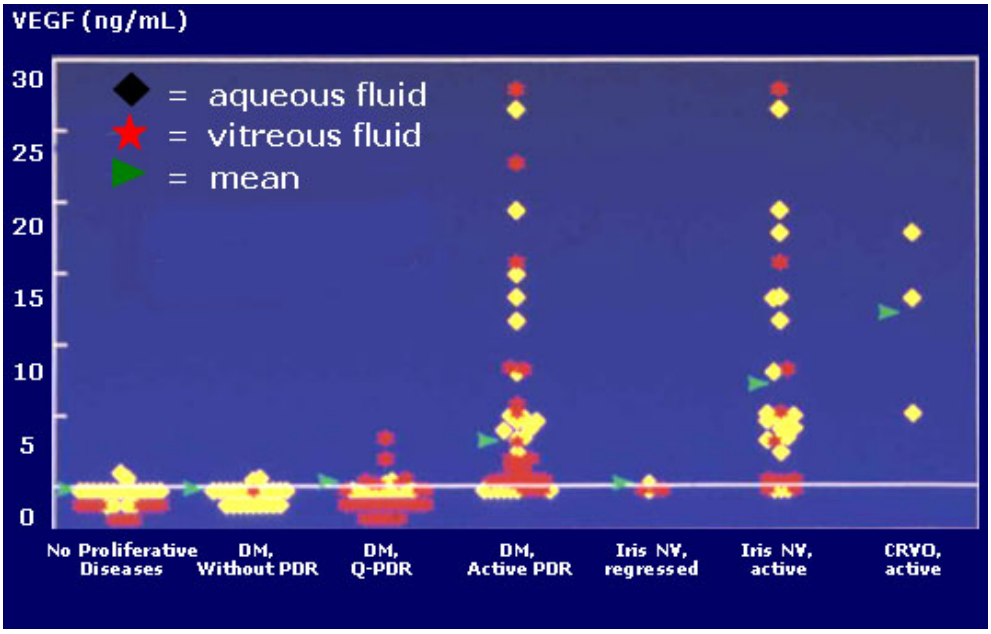
Levels of ocular VEGF are tightly correlated with both growth and permeability of new vessels. In patients with proliferative diabetic retinopathy in which tissue hypoxia promotes neovascularization, levels of VEGF are elevated in ocular tissues. These elevated levels of VEGF decline when treatment with pan retinal laser photocoagulation induces regression of neovascularization.

Severe hypertension itself can induce a retinopathy characterized by increased retinal vascular leakage. The mechanism is increasing cyclic stretch in vascular walls, an action that may also involve the enhancement of angiotensin actions.

Patients with both branch and central retinal vascular occlusions are at risk for development of retinal neovascularization. Increased VEGF levels are also correlated with the onset and persistence of neovascularization of the iris in cases of ischemic CRVO, and with increasing vascular permeability and severity of macular edema in cases of BRVO.

RATIONALE FOR ANGIOGENESIS INHIBITORS IN RETINAL DISEASES

The introduction of VEGF as a potential target in AMD came from examination of excised CNV membranes and autopsy specimens. These studies showed that retinal pigment epithelial cells removed with the CNV membranes over expressed VEGF. Similarly, Frank and colleagues found high levels of VEGF in excised AMD-related CNV membranes. The presence of VEGF has been reported in CNV regardless of the fluorescein angiographic lesion subtype. Animal studies have also supported the role of VEGF in the pathogenesis of AMD. Indeed, the injection of a sub retinal recombinant adenovirus vector expressing VEGF in rats led to new blood vessel growth from the choriocapillaris, formation of breaks in Bruch's membrane, and CNV formation in the sub retinal space.



VEGF in human ocular fluids

The growth of neovascular vessels in response to retinal ischemia ("factor X") was initially proposed by Michaelson almost a half century ago. More recently, retinal hypoxia, which has been implicated in the pathogenesis of diabetic macular oedema, was shown to cause increased expression of VEGF. Indeed, evidence suggests that VEGF is a major mediator of diabetic retinopathy and diabetic macular oedema (DME). In 1994, Aiello and colleagues demonstrated high levels of VEGF in ocular fluid of patients with diabetic retinopathy and other vascular retinal disorders. Further work by Aiello found that suppression of retinal neovascularization was achievable in vivo by inhibition of VEGF using soluble VEGF-receptor chimeric proteins.

1. VEGF Inhibition in Age-Related Macular Degeneration

VEGF inhibitors injected into the vitreous cavity have revolutionized treatment of AMD. In December 2004, pegaptanib sodium became the first anti-VEGF agent approved by the United States Food and Drug Administration (FDA) for treatment of all neovascular AMD, regardless of lesion composition.

Pegaptanib is a pegylated aptamer that consists of an RNA oligonucleotide ligand that binds human $VEGF_{165}$ with high affinity and specificity. Pegaptanib does not block the other isoforms of VEGF.

Bevacizumab is a full-length, recombinant, humanized, monoclonal antibody directed against all VEGF isoforms. It was the first anti-VEGF agent approved by the FDA for systemic administration in treatment of colorectal cancer. Unfortunately, systemic effects, such as elevation of systolic blood pressure and the potential for systemic thromboembolic events, were concerns in the cancer studies, and although the first case using systemic bevacizumab for AMD held promise, the potential for adverse effects was deemed risky. In the summer of 2005, Rosenfeld pioneered the use of intravitreal fractionated dose of bevacizumab for retinopathy and AMD with impressive results. Since then, case series using intravitreal bevacizumab have shown good

short-term efficacy (improved visual acuity and decrease of retinal thickness on ocular computed tomography [OCT]) with no obvious safety issues.

Ranibizumab is a fragment of a humanized monoclonal antibody directed toward all isoforms of VEGF-A. It has a molecular weight of 48 kD and is produced by an *E. coli*-expression system. Its unique structure was specifically engineered for ocular disease: Ranibizumab is made up of just the Fab fragment that was the basis for the full-length antibody, bevacizumab, and has been affinity-matured to have a higher binding affinity for VEGF than bevacizumab has. Eliminating the Fc portion results in less antigenicity and greater retinal penetration because of the smaller molecule size. The binding of ranibizumab to all isoforms of VEGF-A prevents dimerization with the VEGF receptors on cell surfaces (VEGFR1 and VEGFR2), thus reducing vascular leakage, angiogenesis, and endothelial cell proliferation.

Both ranibizumab and bevacizumab block all forms of VEGF. Nevertheless, they have distinct differences that offer each advantages over the other. One advantage of ranibizumab is that it lacks the Fc region of the antibody, making it less likely to cause complement-mediated inflammation after injection. Ranibizumab has only 1 binding site for VEGF while bevacizumab has 2.

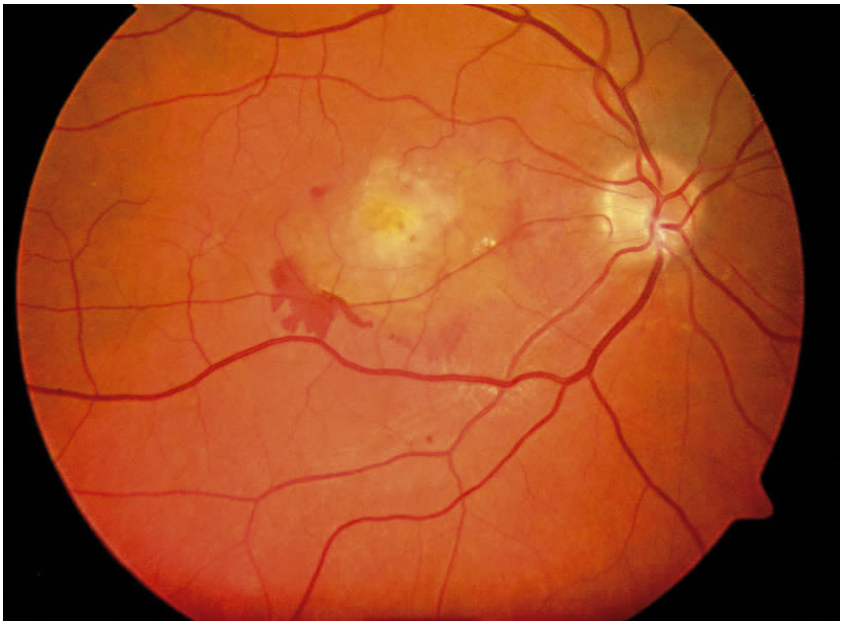
In terms of clinical evidence, ranibizumab has the advantage over bevacizumab because it has been studied in placebo-controlled, phase 3 trials, which led to its approval for the treatment of AMD by the US FDA in June 2006.

In both the MARINA and ANCHOR studies, patients received monthly ranibizumab injections for 24 months. However, a monthly schedule in the real world is not particularly feasible because of both cost and time concerns. As such, research is ongoing to determine the best treatment protocol for ranibizumab.

At this time, the primary issues surrounding the use of ranibizumab appear to be dosing, cost, and frequency of injection. Recently, however, the question of adverse effects was raised. Although ranibizumab has had a good safety profile in the phase 3 trials (the most common side effects are generally conjunctival haemorrhage, eye pain, and vitreous floaters), the manufacturer issued a warning of the possibility of increased risk for stroke. This warning was based on an interim analysis of the SAILOR trial, a phase 3b trial of 5000 patients that is studying 3 monthly injections followed by as-needed dosing. The final results from SAILOR will be awaited, both for the safety concerns as well as for the information it can provide about optimal dosing.

Preliminary research into other types of anti-VEGF therapy is also ongoing. The most promising may be the VEGF trap -- a soluble protein that acts as a decoy VEGF receptor. It appears to bind VEGF-A with higher affinity than the other anti-VEGFs and can penetrate all retinal layers because of its small size. RNA interference, which seeks to inhibit production of VEGF, is also under study, although the recent results of a phase 2 trial of bevasiranib, a small interfering (si)RNA, were disappointing. Still, other siRNA agents are being evaluated, as are tyrosine kinase inhibitors, which target the activation of VEGF receptors and downstream pathways. Whether these new approaches prove to be more efficacious than existing options awaits further research, as does the determination of optimal therapeutic approaches. It may well be that these types of drugs work best in synergy or that practitioners gain a new armamentarium of drug options. Certainly, randomized, placebo-controlled, phase 3 trials will be needed to fully explore both existing and future treatment possibilities.

Neovascular AMD



2. VEGF Inhibition for Diabetic Retinopathy and Diabetic Macular Oedema

The success of anti-VEGF therapy in AMD has led researchers naturally to diabetic retinopathy and its leading cause of visual loss, DME. Although laser photocoagulation is still considered the standard of care for DME, there are instances when it is inappropriate or when it does not work; as a result, practitioners need reliable alternatives.

Pegaptanib has been studied in DME with promising results. A placebo-controlled phase 2 trial randomized 172 patients with DME involving the center of the macula to intravitreal pegaptanib (0.3 mg, 1 mg, 3 mg) or sham injections at study entry, week 6, and week 12. Additional injections and/or focal photocoagulation as needed were given for another 18 weeks. Median visual acuity improved and mean central retinal thickness decreased in the pegaptanib group compared with the sham group. In addition, fewer pegaptanib patients needed photocoagulation.

A 12-month study of 15 patients with refractory DME showed improvements in visual acuity, foveal thickness, and macular volume. Finally, the pilot READ study was mounted to establish the safety of ranibizumab in DME. No systemic or ocular toxicities were noted in the phase 1 study. Moreover, visual acuity improved by 12 letters at 12 months, and a significant reduction in mean retinal thickness was noted at 7 months. The larger READ 2 study is currently enrolling patients and will examine the benefits of ranibizumab with laser photocoagulation vs ranibizumab vs laser photocoagulation alone.

As with ranibizumab, bevacizumab has provided researchers with potential new avenues of treatment. Recent large case series indicate that

it can be beneficial for DME, providing stability or improvement in visual acuity, OCT, and fluorescein angiography. The Pan American Ophthalmology Collaborative Groups reported 6-month results for patients with DME receiving at least 1 intravitreal injection of 1.25 mg or 2.5 mg bevacizumab. Final best corrected visual acuity (BCVA) analysis by subgroups demonstrated that 32 (41.1%) eyes remained stable, 43 (55.1%) improved 2 or more ETDRS lines of BCVA, and 3 (3.8%) decreased 2 or more ETDRS lines of BCVA. No ocular or systemic adverse events were observed. More substantial results should be forthcoming now that the DRCR.net has completed recruitment for a large study to assess the safety and efficacy of intravitreal bevacizumab for DME.

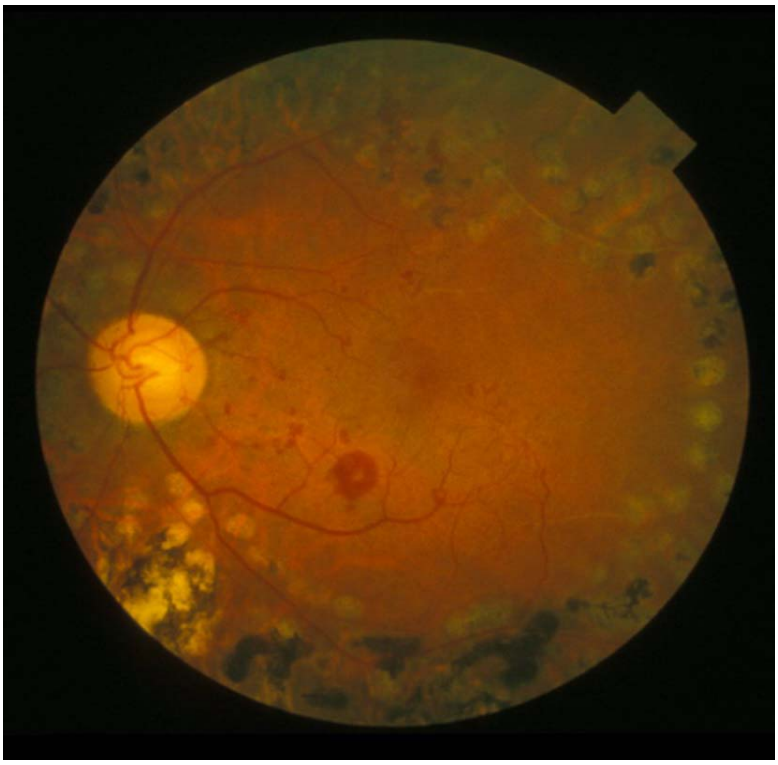
Bevacizumab is also being tried for neovascular complications of proliferative diabetic retinopathy. Avery and colleagues conducted a retrospective, interventional, consecutive case series of 45 eyes in 32 patients with retinal and/or iris neovascularization secondary to diabetes mellitus treated with intravitreal bevacizumab (6.2 micrograms-1.25 mg). No significant ocular or systemic adverse events were observed. Complete resolution of angiographic leakage of neovascularization of the disc was noted in 19 of 26 (73%) eyes, and leakage of iris neovascularization completely resolved in 9 of 11 (82%) eyes. Leakage

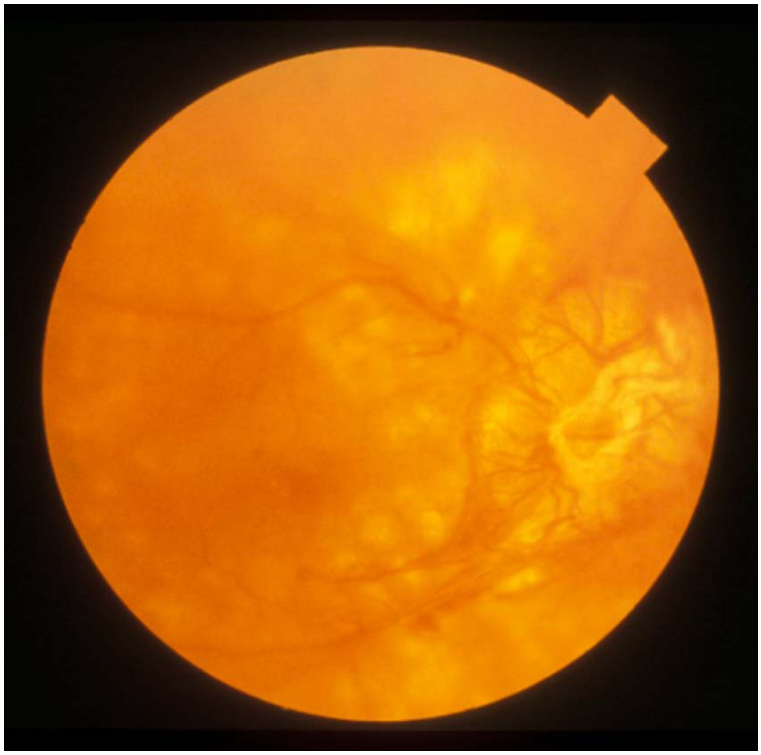
was noted to diminish as early as 24 hours after injection. Short-term results suggested that intravitreal bevacizumab was well tolerated and associated with rapid regression of retinal and iris neovascularization secondary to proliferative diabetic retinopathy even with the lowest dose (6.2 micrograms) tested. However, observation of a possible therapeutic effect in the fellow eye raises concern that systemic side effects are possible in patients being treated with intravitreal bevacizumab (1.25 mg). Lower doses may achieve a therapeutic result with less risk for systemic side effects.

In general, these studies of pegaptanib, ranibizumab, and bevacizumab suggest that anti-VEGF therapy may have a role in DME and diabetic retinopathy.

At ARVO 2007, results from the first study investigating the efficacy of VEGF trap for DME were reported. The pilot study demonstrated significant reductions in central retinal thickness and improved acuity with treatment. In this study of 5 patients, 4 patients had visual improvement between 6 and 10 letters. Future trials were planned based on these impressive results.

PDR with NVE (Post laser status)





3. VEGF Inhibition for CNV in Causes Other than AMD

Because the most common cause of CNV is AMD, most FDA-approved treatments for CNV are for CNV secondary to AMD. There is therefore an unmet clinical need for treatment of patients with CNV secondary to other causes -- which include myopic macular degeneration, presumed ocular histoplasmosis syndrome, angioid streaks, inflammatory retinal diseases, and idiopathic membranes. The only FDA-approved treatment for some of these diseases is PDT/verteporfin. However, as in CNV secondary to AMD, PDT/verteporfin can help stabilize but not restore vision. It is assumed that anti-VEGF therapy will have a role in CNV secondary to other causes as in AMD, although the published literature thus far consists only of case reports and nonrandomized case series.

The first published treatment with anti-VEGF agents for non-AMD CNV was reported by Bennett and colleagues. In this case report, a single patient was treated with intravitreal pegaptanib for myopic degeneration and CNV with impressive results. Since this initial report, many newer agents have been investigated, such as ranibizumab and bevacizumab, and numerous reports were presented at the 2007 ARVO meeting.

Blinder and colleagues reported on the use of intravitreal 1.25-mg bevacizumab in 28 eyes of 28 individuals with CNV due to ocular histoplasmosis syndrome. In this retrospective chart review, the average pre-treatment visual acuity improved from 20 of 88 to 20 of 54 after almost 22 weeks of follow-up and an average of 1.8 injections per patient. A total of 71% of the patients studied had increased visual acuity.

These preliminary results suggest that the anti-VEGF agents may, as with CNV secondary to AMD, improve vision in CNV secondary to other causes. Again, however, such issues as dose, cost, frequency, and safety will need to be addressed.

4. VEGF Inhibition for Branch Retinal Vein Occlusion and Central Retinal Vein Occlusion

Existing treatment options for BRVO and CRVO are unsatisfactory, and the potential for VEGF inhibition to combat macular oedema is increasing the amount of research into anti-VEGFs for BRVO and CRVO. Bevacizumab is receiving most of the attention.

Avery and colleagues published their experience on treatment of macular oedema secondary to BRVO in 2007. In their retrospective review of patients treated with intravitreal bevacizumab (1.25 mg), 27

consecutive patients were evaluated. Mean visual acuity improved from 20 of 200 at baseline to 20 of 100 at 3 months ($P < .001$). Similarly, the mean central subfield thickness decreased from 478 microns at baseline to 332 microns at last follow-up ($P < .001$). No adverse events -- including endophthalmitis, clinically evident inflammation, increased intraocular pressure, retinal tears, retinal detachment, or thromboembolic events -- were observed in any patient.

Although several reports have noted visual improvement with use of bevacizumab, others have noted anatomic responses but not visual ones. For example, Fine and colleagues conducted a retrospective study of 16 eyes of 15 patients with macular oedema due to CRVO who received a mean 2.8 injections of bevacizumab. Although the mean central macular thickness improved, mean baseline acuity was unchanged. Similarly, several case series that were presented at ARVO on treatment of both BRVO and CRVO with bevacizumab showed anatomic responses but variable visual outcomes. In addition, results of some of the cases warn of the possibility of recurrent macular oedema (so-called rebound oedema) following bevacizumab treatment. In these instances, the recurrent macular oedema may be more severe than the original macular oedema.

Research into the use of anti-VEGF agents in the treatment of CRVO and BRVO is in the preliminary stages. So far, it has focused on bevacizumab with mixed results. Clearly, larger, prospective studies will be needed to better determine the effects on visual outcome, as well as to establish treatment issues, such as safety and dose.

AN UPDATE ON BEVACIZUMAB

Bevacizumab (Avastin, Genentech) is a full-length, humanized, murine monclonal antibody directed against all the biologically active forms of vascular endothelial growth factor-A (VEGF). Bevacizumab, the first anti-VEGF drug to be approved by the Food and Drug Administration, was developed as an intravenous therapy for cancer patients because VEGF is one of the major angiogenic stimuli responsible for neovascularization in tumors. Anti-VEGF therapy has shown promising results in several forms of cancer, but the drug is currently approved only for the treatment of metastatic colorectal cancer. When used in cancer therapy, bevacizumab is infused at a dose of 5 mg/kg every two weeks until the patient dies or significant disease progression is observed. In clinical trials, the most common adverse event caused by bevacizumab was hypertension.

Systemic Bevacizumab

The role of VEGF in neovascular AMD has now been confirmed as the result of the Phase III clinical trial of the anti-VEGF drug pegaptanib sodium (Macugen, Eyetech). Pegaptanib sodium is now approved for the treatment of all neovascular AMD; however, the average pegaptanib-treated patient still continues to lose vision while receiving therapy.

Another anti-VEGF drug known as ranibizumab (Lucentis, Genentech) was shown to improve visual acuity, angiographic and optical coherence tomography outcomes in open-label, uncontrolled Phase I/II studies. Genentech's one-year, Phase III results confirm earlier studies in AMD patients. Patients with predominantly occult macular neovascularization treated with ranibizumab had an overall vision improvement and statistically significant better outcomes than the sham-injected controls. The disadvantages of systemic therapy, however, include systemic exposure to an antiangiogenic drug at therapeutic levels, resulting in a higher risk of systemic adverse events compared to intravenous injection.

SANA

In the spring of 2004, Systemic Avastin for Neovascular AMD (SANA) study at the Bascom Palmer Eye Institute. In this study systemic bevacizumab was offered as salvage therapy for patients who were not candidates for verteporfin photodynamic therapy or who refused PDT. Pegaptanib sodium was not yet commercially available. Unlike the regimens used in cancer therapy, treating patients only two or three times followed by a period of close observation was proposed, with retreatment possible if the leakage from the neovascularization recurred. Since this article was published, a total of 18 patients have been followed for at least 24 weeks, and the 24-week results confirm and improve upon the pre-

liminary results observed at 12 weeks (submitted for publication). Of the 18 patients, nine initially received three treatments, and 11 received only two treatments. The majority of patients did not require another treatment through 24 weeks.

With improvement in visual acuity, OCT and angiographic outcomes, the systemic use of bevacizumab appeared to be both effective and durable. Moreover, the cost of intravenous bevacizumab therapy is comparable to the cost of pegaptanib therapy. The average drug cost for bevacizumab is $2,200 per infusion, and the cost for the 24 weeks of therapy is $4,400 for most patients, roughly equivalent to four intravitreal injections of pegaptanib over 24 weeks.

Intravitreal Bevacizumab

Bevacizumab was used as an intravitreal injection in humans in any of the early clinical studies. The preclinical data in primates suggested that intravitreal bevacizumab would be too large to penetrate the retina and result in any therapeutic effect, but bevacizumab was never tested in an animal model of macular neovascularization to see if this assumption was correct. Once we observed the dramatic results of systemic intravenous bevacizumab in patients with neovascular AMD, a much lower dose of bevacizumab injected into the eye could result in a similar benefit while reducing the risk of systemic adverse events. It has been

calculated that a dose of about 1 to 1.5 mg of bevacizumab would be approximately 400-fold less than the systemic dose of bevacizumab used in the SANA study.

Another appealing feature of intravitreal bevacizumab is its low cost. Compared with the cost of pegaptanib sodium, an intravitreal dose of bevacizumab would be a bargain. While a dose of pegaptanib (0.3 mg) is approximately $1,000 or $3,300 per mg, the proposed 1-mg dose of bevacizumab would cost $5.50. Moreover, a dose of 1 to 1.25 mg could be conveniently injected using 0.04 ml to 0.05 ml of the commercially supplied bevacizumab, which is not known to contain preservatives or additives that may be toxic to the retina. At the Bascom Palmer Eye Institute, off-label intravitreal bevacizumab was offered to patients as a salvage treatment for those who continue to lose vision associated with neovascular lesions and worsening OCT profiles despite treatment with approved therapies. In the first report of a patient receiving intravitreal bevacizumab, improvement in angiographic and OCT outcomes after one injection were observed, nearly identical to the outcomes that observed following systemic bevacizumab and intravitreal ranibizumab. The patient’s vision remained stable over four weeks, and this patient has remained stable through six months and has not required another injection.

Since this first patient was injected, anecdotal experience with intravitreal bevacizumab has grown, and the positive outcomes were observed in this first patient have been reliably reproduced in other patients. It is now obvious that a large, prospective clinical study must be initiated to determine the safety and efficacy of intravitreal bevacizumab. With an intravitreal half-life that may be twice as long as ranibizumab, we may be able to dose less frequently than ranibizumab, perhaps every eight weeks or 12 weeks. If intravitreal bevacizumab proves to be safe and effective for the treatment of neovascularization and macular edema from a wide range of ocular diseases, then intravitreal bevacizumab would have immediate global impact because of its low cost and worldwide availability.

REVIEW OF LITERATURE

- **MARINA** (Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular AMD). This Phase III multicenter, randomized, double-masked, sham injection-controlled trial included 716 patients with minimally classic/occult CNV secondary to AMD. Eligible patients had not previously received subfoveal laser treatment, verteporfin (Visudyne) photodynamic therapy, or experimental treatments for their AMD in the study eye. Patients were

randomized 1:1:1 to sham injection or to ranibizumab (0.3 mg or 0.5 mg) injected intravitreally monthly for 24 months. The primary efficacy endpoint is the proportion of subjects losing less than 15 ETDRS letters at one year. Approximately one-third of the patients had minimally classic CNV and two-thirds had occult CNV. Preliminary analysis of one-year MARINA data revealed that approximately 95 percent of patients treated with ranibizumab lost fewer than 15 letters at one year, compared to approximately 62 percent in the control group ($p<.0001$). On average, the patients treated with ranibizumab had a significant visual acuity improvement compared to baseline, while the control group experienced a substantial decrease from baseline in mean VA. Ocular adverse events were similar to those of earlier trials, and no increase in the serious non-ocular adverse events relative to the control group was noted. The incidences of uveitis and endophthalmitis were each less than 1 percent.

- **FOCUS** (RhuFab V2 Ocular Treatment Combining the Use of Visudyne to Evaluate Safety) is a randomized, single-masked, Phase I/II trial investigating safety, tolerability and efficacy of ranibizumab 0.5 mg in combination with verteporfin PDT versus verteporfin PDT alone in patients with subfoveal predominantly classic CNV due to AMD. One week before the first administration of either intravitreal ranibizumab or sham injection to the study eye, patients are treated with verteporfin PDT,

with as many as 23 additional monthly injections with ranibizumab or sham injection. Patients may continue to receive verteporfin PDT at the investigators' discretion and in accord with product labeling. The primary efficacy endpoint is the proportion of subjects losing fewer than 15 letters of VA at one year. The study enrolled 162 patients. The study has met its primary endpoint based on one-year data: Approximately 90 percent of patients treated with the combination therapy had stable or improved visual acuity, compared with approximately 68 percent of patients in the control arm of PDT alone (p=.0003). Patients treated with combination therapy had significantly improved average VA compared to baseline; mean VA in the PDT-alone control group decreased from baseline. There was an increased risk of uveitis in combination therapy patients compared with those treated with PDT alone. The study protocol was amended after data safety monitoring identified this imbalance. Endophthalmitis was the next most common ocular serious adverse event occurring in ranibizumab-treated patients. The frequency of cerebral vascular events was slightly higher in patients treated with ranibizumab, whereas myocardial infarctions were slightly more frequent in the PDT-alone arm; the differences between these groups was not statistically significant.

- **ANCHOR** (Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in AMD) is a

multicenter, randomized, double-masked, active-treatment controlled Phase III trial evaluating the safety and efficacy of ranibizumab in 423 subjects with predominantly classic subfoveal CNV, with sites in the United States, Europe and Australia. Inclusion criteria were the same as those of the MARINA study. Patients in this trial are being randomized 1:1:1 to either verteporfin PDT plus sham injection or to placebo PDT plus ranibizumab (0.3 mg or 0.5 mg) monthly for 24 months. Patients in the ANCHOR trial are being evaluated by fluorescein angiography every three months to determine the need for additional PDT or placebo PDT. The study is ongoing.

INTRAVITREAL INJECTIONS–PROCEDURE GUIDELINES

Injection procedure guidelines include consideration of pre existing conditions such as active external infection, eyelid abnormalities, povidone iodine, lid scrubs, pre injection topical antibiotics, lid speculum, drape, gloves, and anaesthesia and post injection topical antibiotics.

In general the risk of endophthalmitis following intra vitreal injection is estimated to be approximately < 0.1%.

Guidelines for intra vitreal injection:

1. Povidone iodine for ocular surface, eyelid and eye lashes
2. Use of speculum and avoid contamination of the needle with eye lid margin
3. Avoid extensive massage of the eye lids either pre or post injection
4. Dilate pupil
5. Adequate use of anaesthetic (topical drops/ sub conjunctival injection)
6. Avoid prophylactic or post injection paracentesis

7. IOP to be checked following injection

8. Dilated fundoscopic examination should be performed following injection to confirm central retinal artery perfusion and intra ocular location of the drug.

Guidelines for follow up

Patients should be followed up on the immediate day following intra vitreal injection. How ever patients should be instructed to contact ophthalmologist if there if increased ocular redness or discomfort or decreased vision compared to that present right after the injection procedure.

AIM OF THE STUDY

1. To evaluate the visual acuity responses following intravitreal injection of bevacizumab in case of

    a. Neo-vascular AMD

    b. Progressing neovascularization inspite of complete PRP in cases of PDR

    c. NVD / NVE not responding to PRP in cases of Retinal vein occlusion.

2. To evaluate the change in macular thickness by OCT following injection in above said conditions.

3. To evaluate the angiographic changes following treatment.

4. To evaluate the safety and efficacy of intravitreal injection of Bevacizumab.

DESIGN

Interventional, Prospective, Non-randomized clinical study.

MATERIALS AND METHODS

This study was done in Retina clinic- Regional Institute of Ophthalmology and Government Ophthalmic Hospital, Chennai during the period of June – 2008 to November 2008.

INCLUSION CRITERIA:

1. CNV attributable to AMD diagnosed by FFA and OCT with BCVA of less than 6/24.
2. PDR patients with disease progression despite complete PRP.
3. CRVO patients with neovascularization not responding to laser photocoagulation.
4. Ability to understand and sign consent form.

EXCLUSION CRITERIA:

1. Prior treatment for CNV.
2. Patients with tractional retinal detachment in a case of high risk PDR.
3. History of uveitis.
4. History of vitrectomy.
5. Patients with uncontrolled hypertension.

6. Patients with recent myocardial infarction.
7. Patients with recent cerebral vascular accident.

PROCEDURE

Patients who were referred to Retina clinic with provisional diagnosis of AMD, PDR, and CRVO were screened and selected for the study.

All the patients were taken a brief history, and subjected to detailed systemic and ophthalmic evaluation.

Anterior segment examination with Slit lamp biomicroscope and posterior segment examination using 90D, binocular indirect ophthalmoscope and a detailed fundus drawings were done and Fundus photograph was also taken for documentation. B-scan USG, Fundus fluorescein angiography and Optical coherence tomography were done for all the patients.

Twenty eight eyes of 28 patients with neovascular AMD, four eyes of 4 patients with proliferative diabetic retinopathy with post laser status and two eyes of 2 patients with retinal vein occlusion were included.

The off-label use of the drug and its potential risks and benefits were discussed extensively with all patients. All patients signed a

comprehensive consent form before administration of the intravitreal bevacizumab.

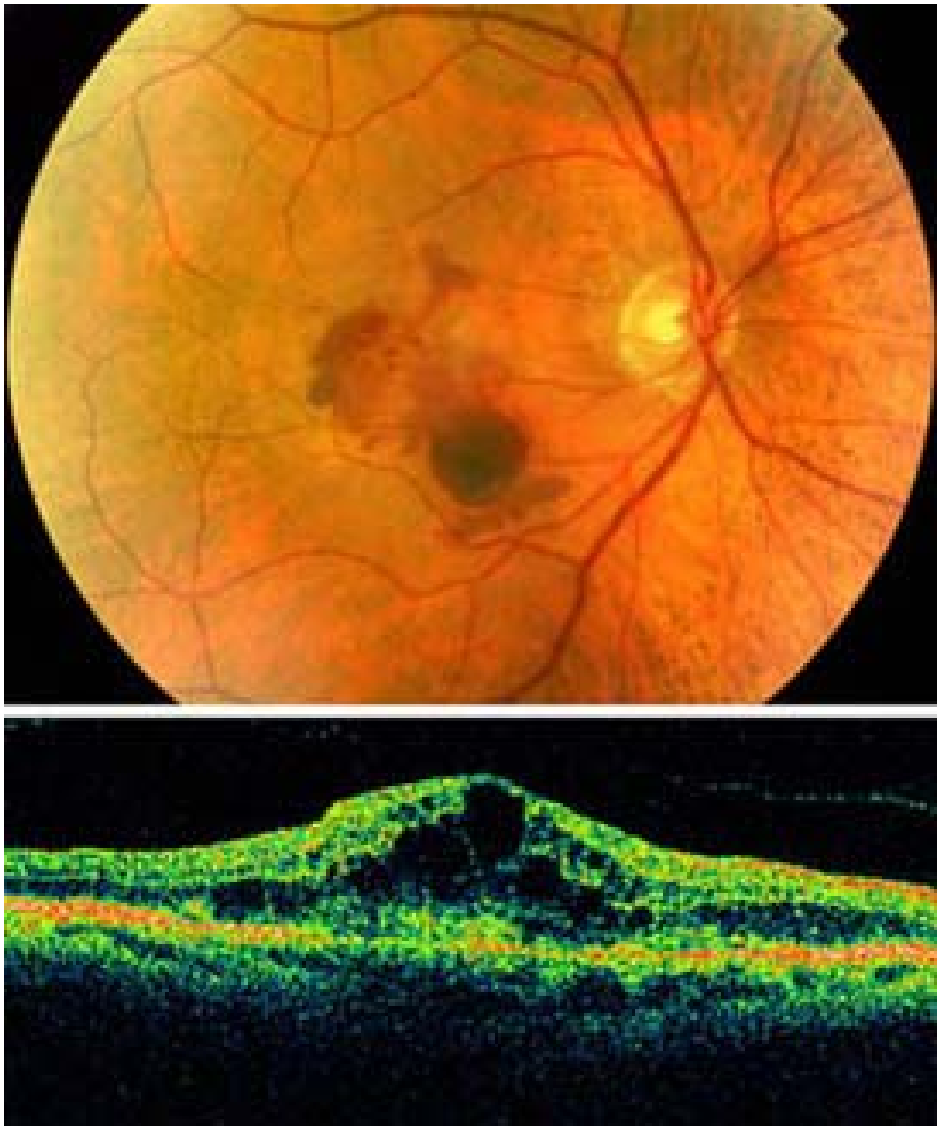
A commercially available bevacizumab (1.25mg/0.05ml) was prepared for each patient and placed in a tuberculin syringe using aseptic techniques. After the eye had been prepared in a standard fashion using 5% povidone iodine and topical antibiotics, 1.25 mg (0.05 ml) of bevacizumab was injected intravitreally via the pars plana. After the injection, intraocular pressure and retinal artery perfusion were checked, and patients were instructed to administer topical antibiotics for 3 days. Patients were called 2 to 3 days after injection and were re examined within 1 week.

Patients received reinjections on a monthly basis until macular edema, /or pigment epithelial detachment (PED) / or neovascularization resolved.

MAIN OUTCOME MEASURES:

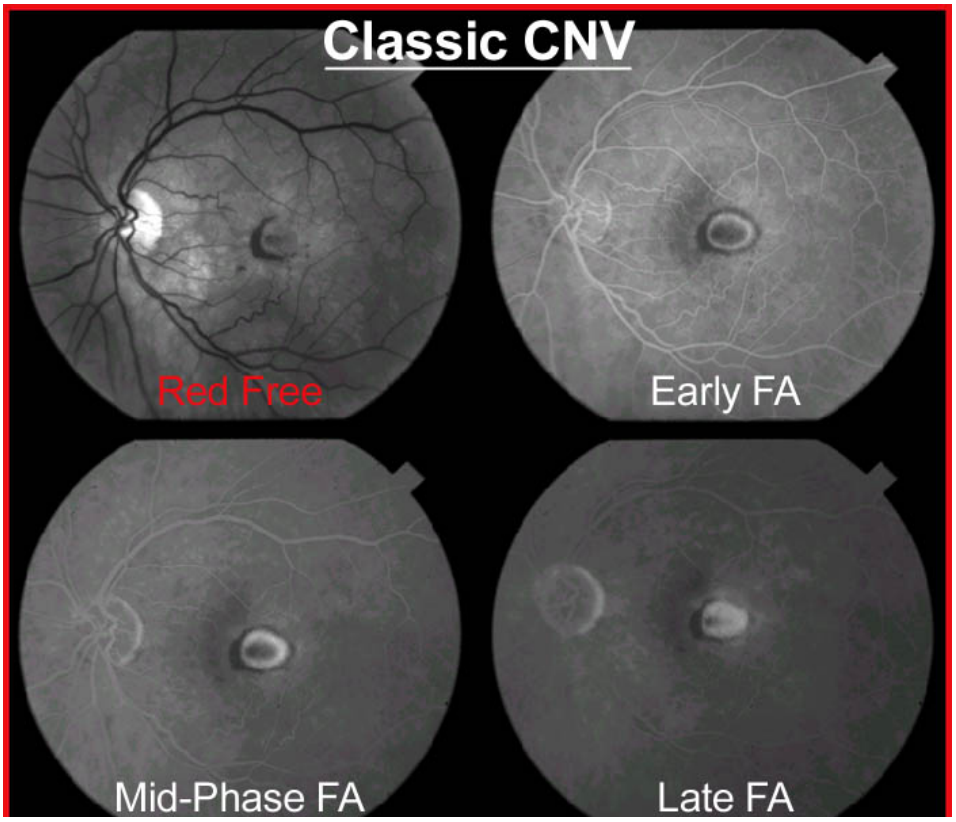
- Best corrected visual acuity (Snellen's chart)
- Macular thickness by OCT (SPECTRAL)
- Changes in Fluorescein angiogram patterns in the form of reduction in size of the lesion and decrease in leakage.

WET AMD with Macular thickness of 432µ

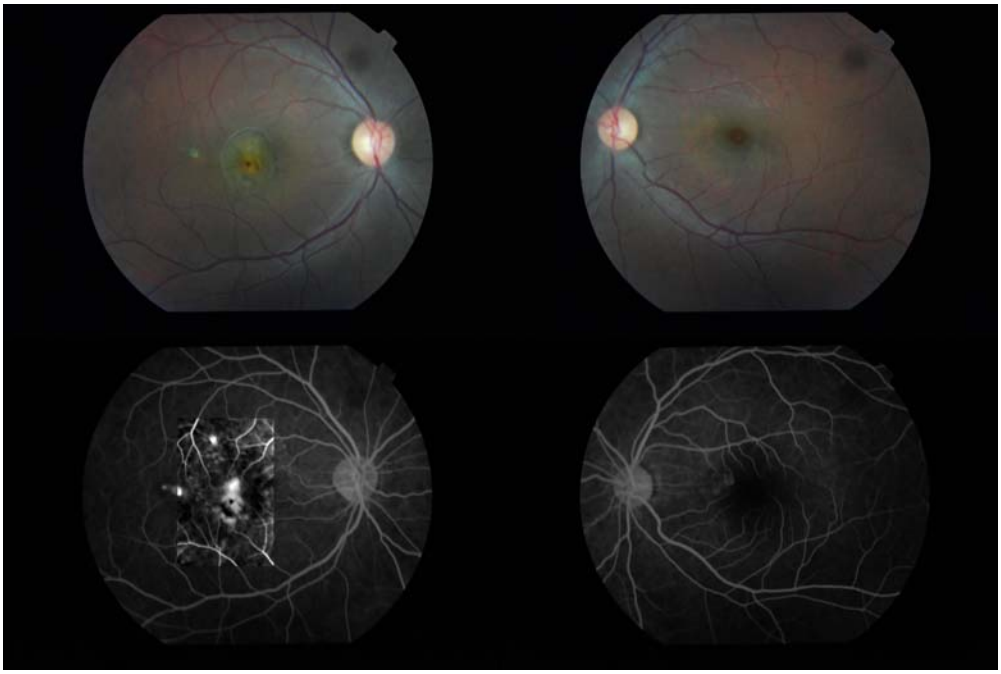


REVIEW

All the patients were asked for regular follow-up at 2weeks, 4 weeks, 8weeks, 12weeks and 16weeks. At each visit patients were checked for intra-ocular pressure, BCVA, were checked and Fundus photograph, FFA, and OCT were recorded.



Occult CNV

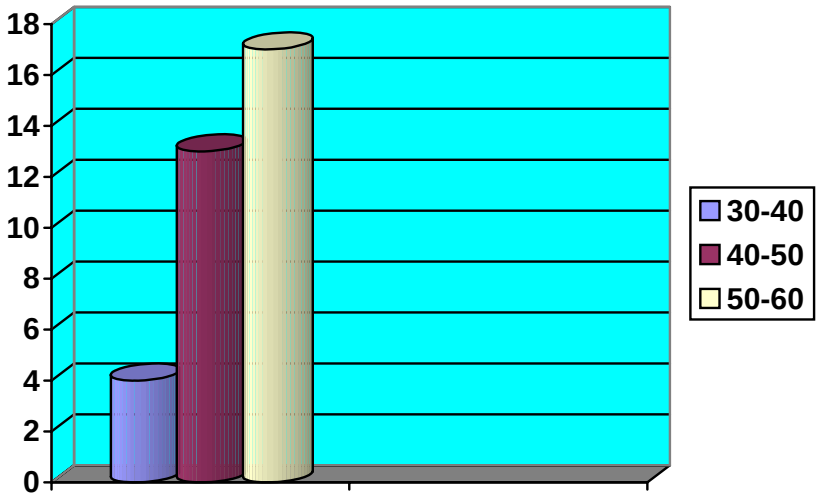


OBSERVATIONS AND RESULTS

TABLE 1: AGE DISTRIBUTION

Total no of patients—34

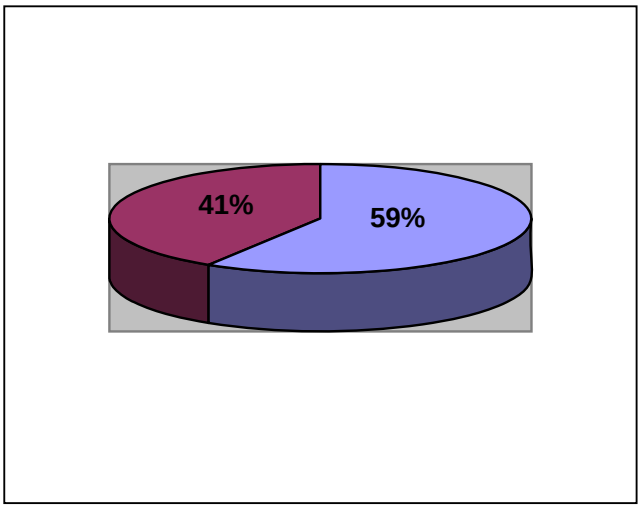
Age distribution	No of patients	Percentage
30-40 yrs	4	12
40-50 yrs	13	38
50-60 yrs	17	50



In our study, most of the patients were in the age group of 50-60 yrs which is about 50%. The upper age limit being 60yrs and lower age limit being 34.

TABLE 2: SEX DISTRIBUTION

Sex	No of patients	Percentage
Male	20	59
Female	14	41

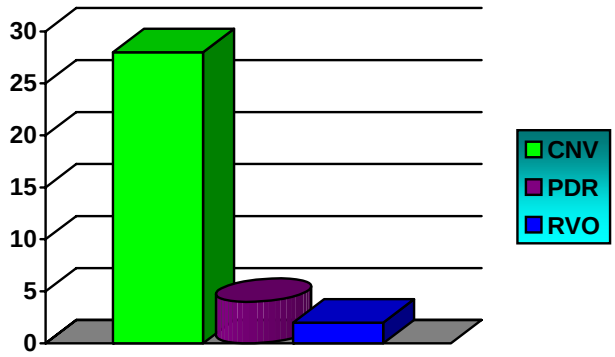


Male: Female ratio ~~1.5: 1

TABLE 3: INDICATIONS

Total no. of patients – 34

Indications	No of patients	Percentage(%)
Choroidal neovascularisation	28	82
Proliferative diabetic retinopathy	4	12
Retinal vein occlusion	2	6



Though there are a lot of indications for intravitreal anti VEGF, we have considered only 3 conditions–Choroidal neovascularization, and as adjunct to photocoagulation in cases with proliferative diabetic retinopathy and retinal vein occlusion not responding to PRP.

Of these, we have taken about 82% cases with CNV. Both classic and occult CNV irrespective of the location were equally considered.

TABLE – 4: VISUAL ACUITY – Pre treatment

TABLE – 4 A -in cases with CNV

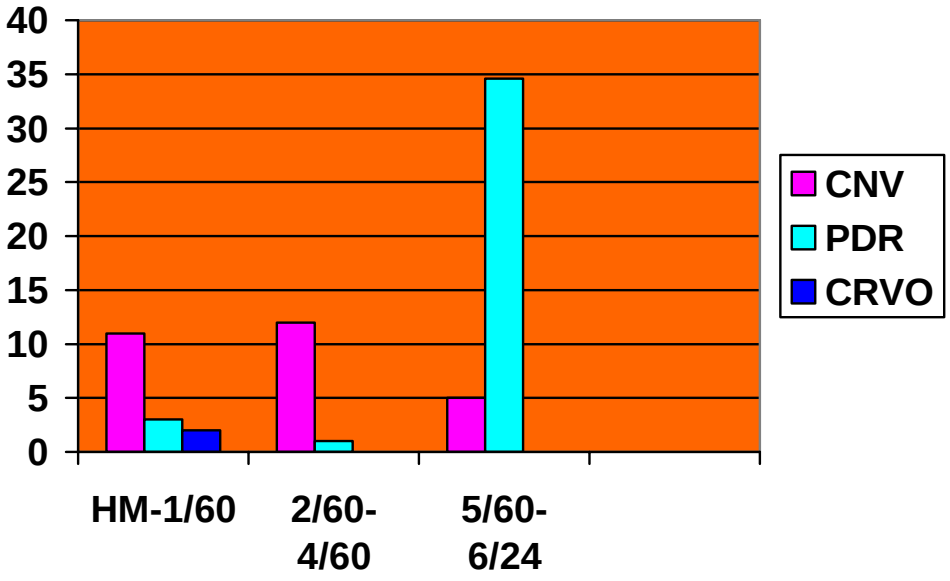
Visual acuity	No.of patients	Percentage
HM – 1/60	11	40
2/60 – 4/60	12	43
5/60 – 6/24	5	17

TABLE – 4 B – cases with PDR

Visual acuity	No.of patients	Percentage
HM – 1/60	3	75
2/60 – 4/60	1	25
5/60 – 6/24	-	--

TABLE – 4 C – cases with CRVO

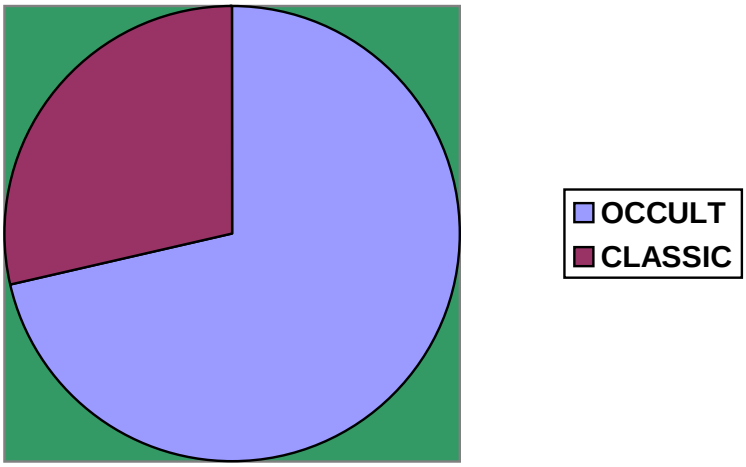
Visual acuity	No.of patients	Percentage
HM – 1/60	2	100
2/60 – 4/60	-	-
5/60 – 6/24	-	-



Most of the patients in our study, were having V/A of less than 1/60. 43% of CNV patients were having V/A of between 2/60 – 4/60. The least V/A of these is a patient of CNV with 6/24.

TABLE –5: Angiographic classification in CNV

Angiographic types	No.of patients	Percentage
Classic CNV	20	71
Occult CNV	8	29



In our study 71% of patients were with classical angiographic type with CNV.

TABLE – 6

TABLE – 6 A: Macular thickness in CNV – Pre- injection

Macular thickness	No.of cases		Percentage
	Classic	Occult	
100-150µ	--	--	--
150-200µ	1	2	11
200-250µ	3	3	21
250-350µ	10	2	43
More than 350µ	6	1	25

About 43% of patients were with macular thickness between 250 - 350µ and there were no patients with macular thickness less than 150µ.

TABLE – 6 B: Macular thickness in PDR

Macular thickness	No.of cases	Percentage
100-150µ	1	25
150-200µ	1	25
200-250µ	1	25
250-350µ	--	-
More than 350µ	1	25

Macular thickness in CNV—Pre injection

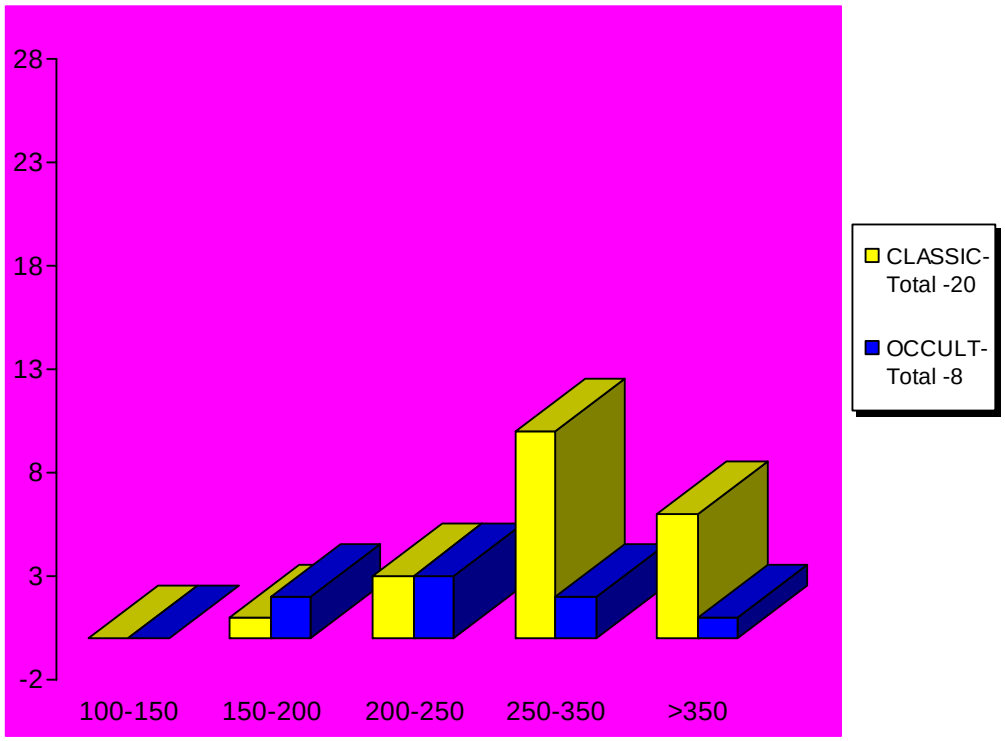


TABLE – 6 C: Macular thickness in RVO

Macular thickness	RVO	Percentage
100-150µ	--	--
150-200µ	--	--
200-250µ	2	100
250-350µ	--	--
More than 350µ	--	--

Both the patients of CRVO were with macular thickness ranging between 200 - 250µ.

Macular thickness in PDR and CRVO- Pre injection

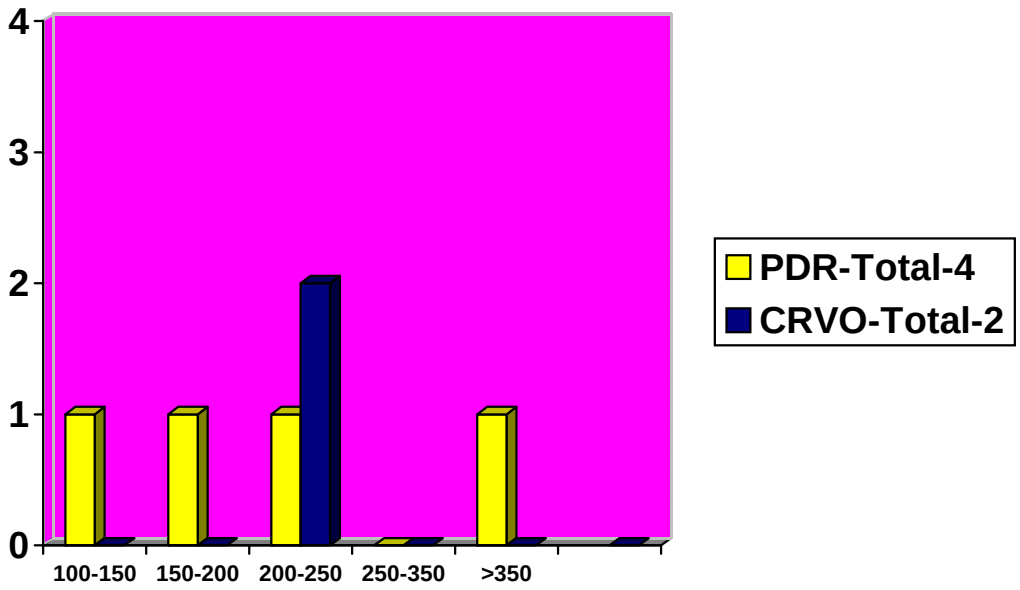


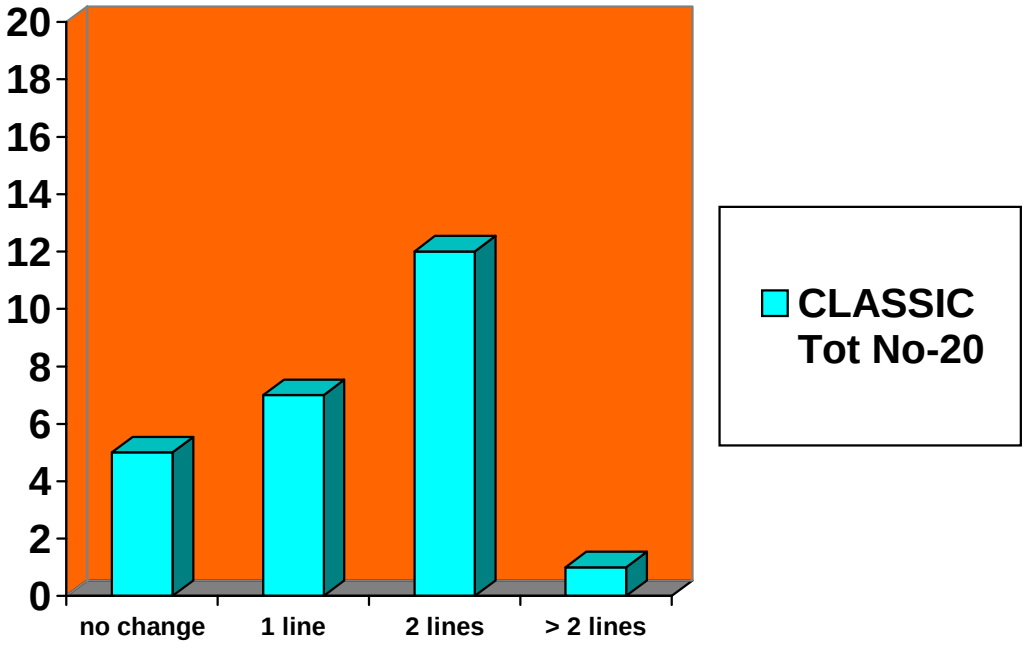
TABLE – 7

TABLE 7 A: Improvement in V/A–post injection in cases of classic CNV

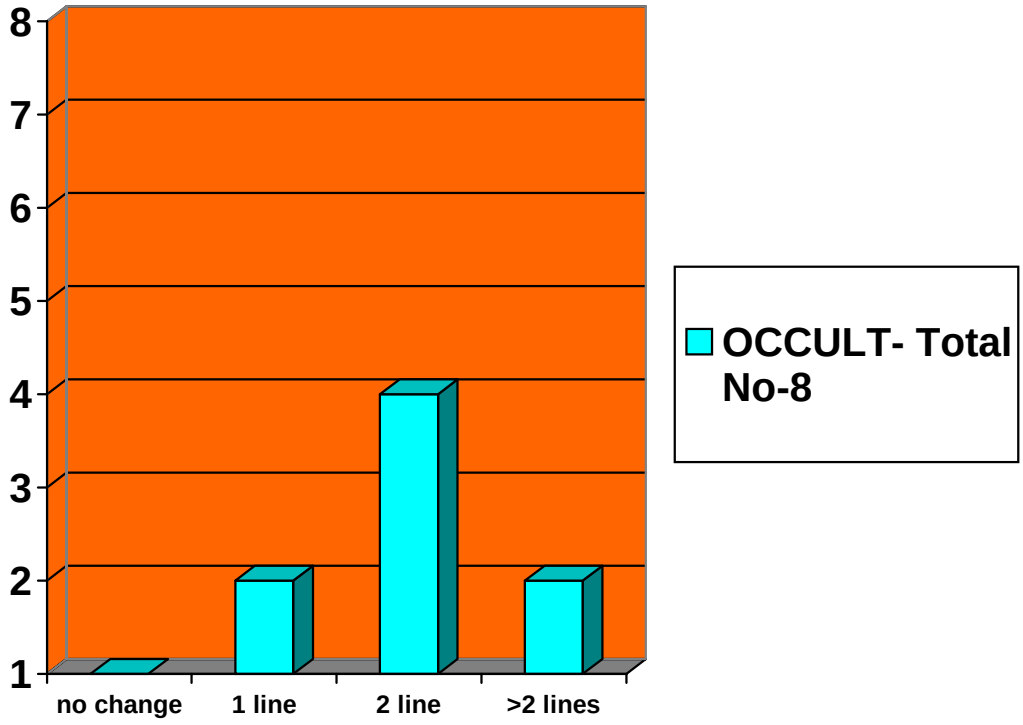
Lines of improvement in visual acuity	CLASSIC CNV				
	At 2wks	At 4wks	At 2months	At 3months	At 4months
No change	19	6	2	1	1
1 line	1	9	13	9	7
2 lines	--	5	6	9	12
More than 2 lines	--	--	1	1	1

Most of the cases showed no change in visual acuity in 2 weeks, but about 35% cases with classic CNV showed 1 line improvement, and 60% of cases showing 2lines improvement at the end of 4 months which correlates with Rich RM, Rosenfeld – et-all Retina ; 26:495-511. 1 patient showed no improvement because of macular scarring.

Improvement in V/A- post injection in classic CNV (at 4 months).



Improvement in V/A- post injection in occult CNV (at 4 months)



TABLE–7 B Improvement in V/A–post injection in cases of occult CNV

Lines of improvement in V/A	OCCULT CNV				
	At 2wks	At 4wks	At 2months	At 3months	At 4months
No change	7	3	2	1	--
1 line	1	4	2	3	2
2 lines	--	1	2	2	4
More than 2 lines	--	--	2	2	2

About 25% of occult CNV cases showing 2 line improvement at 4 weeks and 50% showed more than 2 line improvement at 4 months which is in par with Geitzenauer W – et-all, Klin Monatsbl Augenheilkd 2006; 223:822-7.

TABLE – 7 C: Improvement in V/A – Post injection in cases with PDR

Lines of improvement in v/a	PDR				
	At 2wks	At 4wks	At 2months	At 3months	At 4months
No change	4	2	1	1	2
1 line	--	2	2	3	2
2 lines	--	--	1	--	--
More than 2 lines	--	--	--	--	--

In cases with PDR, out of 4 patients, 3 showed 1 line improvement at the end of 3 months, but 1 dropped V/A because of macular oedema caused by new vessels elsewhere and he underwent repeat injection which goes with the study of Quiroz – Mercado H et - all Semin Ophthalmol ; 22:109-25.

Improvement in V/A – Post injection in cases with PDR

(at 4 months)

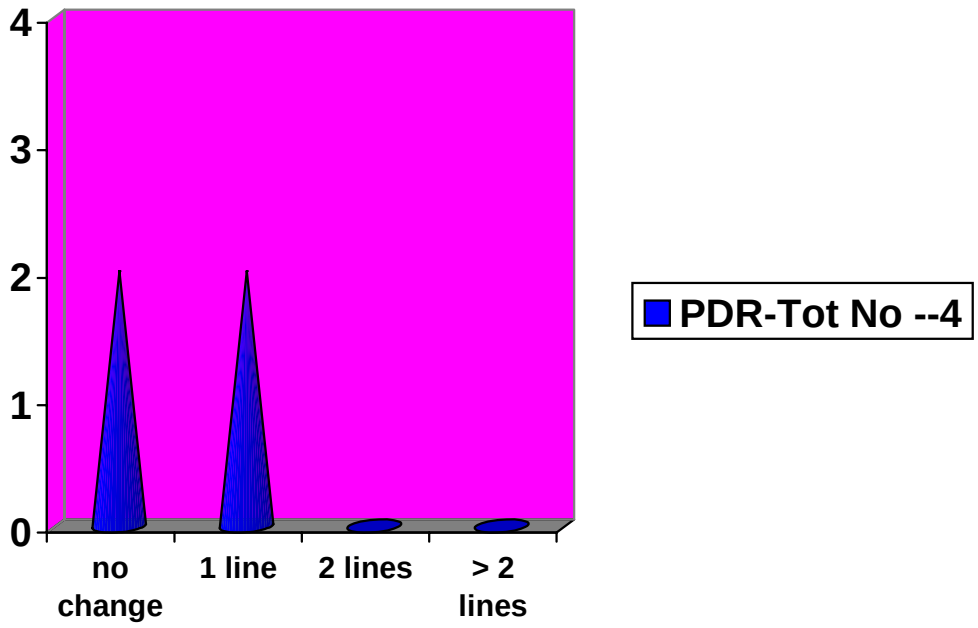


TABLE – 7 – D: Improvement of V/A – Post injection in cases with RVO

Lines of improvement in V/A	retinal vein occlusion				
	At 2wks	At 4wks	At 2months	At 3months	At 4months
No change	2	1	1	1	1
1 line	--	1	1	1	1
2 lines	--	--	--	--	--
More than 2 lines	--	--	--	--	--

Only 2 patients of CRVO were selected, who were not responding to pan retinal photocoagulation of 3 sittings. Of these 1 showed 1 line improvement at the end of 4 months which supports the study of Lynch SS, Cheng CM Ann Pharmacother 2007; 41:614-25 and 1 showed nil improvement because of glaucomatous optic atrophy.

Improvement in V/A – Post injection in cases with CRVO (at 4 months)

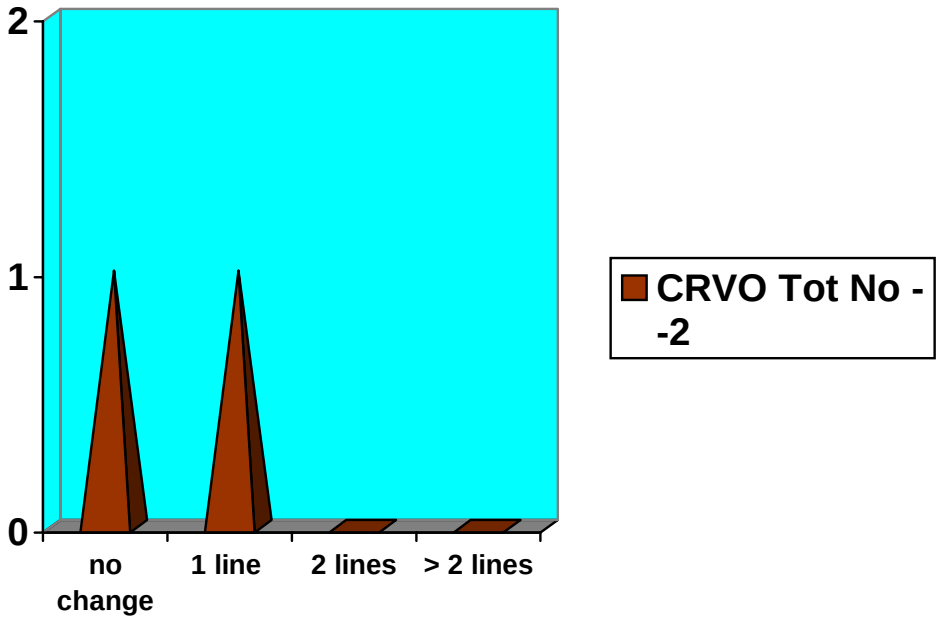


TABLE – 8

TABLE – 8 A: REDUCTION IN MACULAR THICKNESS in CNV –Classic type (Post-injection)

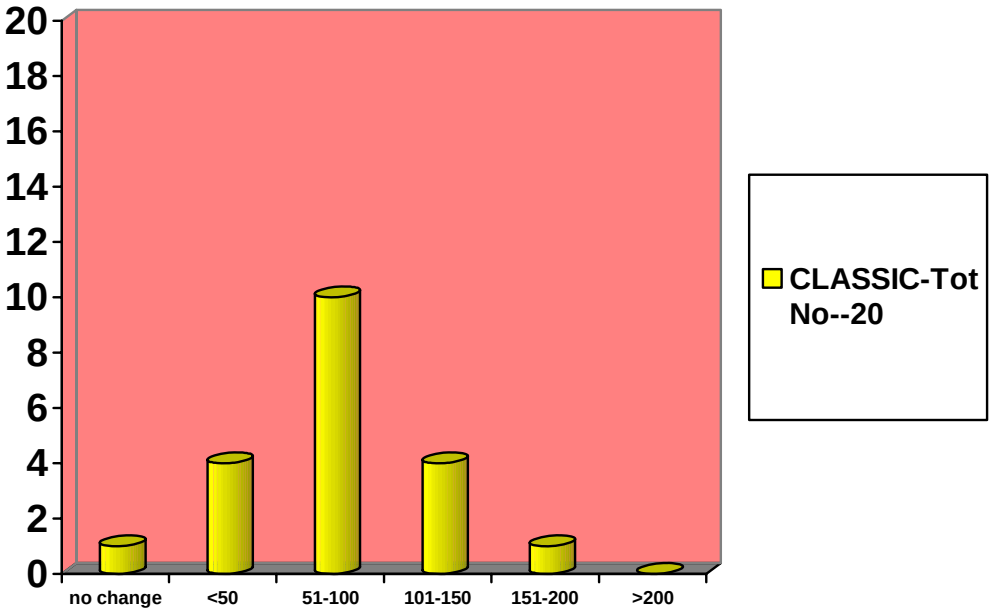
Reduction In Retinal Thickness	CLASSIC CNV				
	2 wks	4 wks	2m	3m	4m
UPTO 50µ	15	14	12	9	4
51-100µ	2	3	5	6	10
101-150µ	--	--	1	3	4
151-200µ	--	--	--	1	1
MORE THAN 200µ	--	--	--	--	--
NO CHANGE	3	3	2	1	1

TABLE – 8 B

Reduction in retinal thickness	OCCULT CNV				
	2 wks	4 wks	2m	3m	4m
UPTO 50µ	5	4	3	2	1
51-100µ	2	3	4	4	3
101-150µ	--	--	1	1	3
151-200µ	--	--	--	1	1
MORE THAN 200µ	--	--	--	--	--
NO CHANGE	1	1	--	--	--

About 73% of Classic CNV and 50% of Occult CNV showed reduction in macular thickness of 50µ at the end of 1month, and 50% of both CNV types showed reduction of 100µ at the end of 4months which correlates well with the study of Moschos MM – et-all Doc Ophthalmol 2007; 114:37-44. 1 patient showed no improvement and he was found to have CNVM with scar formation.

Reduction in macular thickness (µ) in classic CNV-Post injection at 4 months



Reduction in macular thickness (μ) in occult CNV-Post injection at 4 months

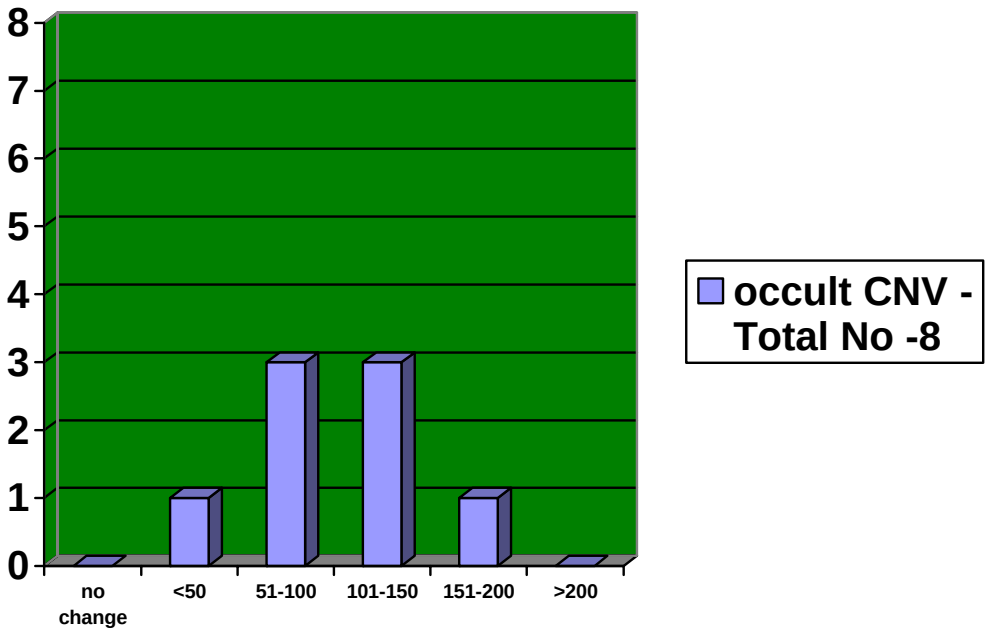


TABLE – 8 C: Reduction of macular thickness in PDR cases

Reduction In Macular Thickness	PDR				
	2 wks	4 wks	2m	3m	4m
UPTO 50µ	1	2	1	1	1
51-100µ	--	--	1	2	2
101-150µ	--	--	--	--	--
151-200µ	--	--	--	--	--
MORE THAN 200µ	--	--	--	--	--
NO CHANGE	3	2	2	1	1

In cases with PDR, 50% showed improvement of 50µ reduction at the end of 1month post injection, 50% showed reduction of upto 100µ at the end of 4 months and 1 patient showed no change because of non-resolving cystoid macular oedema associated with vitreo-macular traction.

Reduction in macular thickness (μ) in PDR-Post injection at 4 months

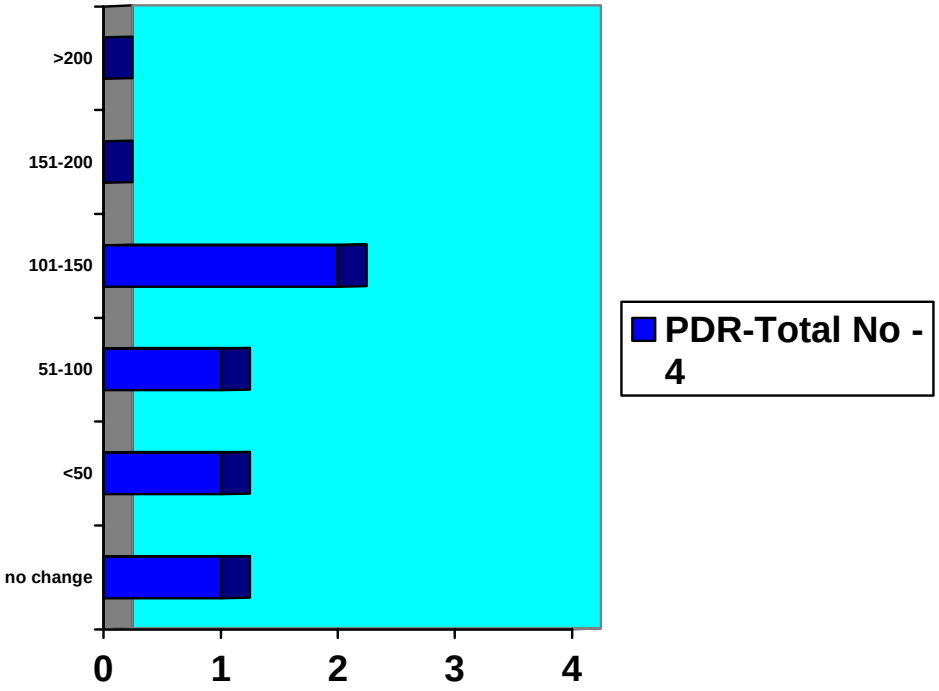


TABLE – 8 D: Reduction of macular thickness in CRVO cases

Reduction In Macular Thickness	CRVO				
	2 wks	4 wks	2m	3m	4m
Upto 50µ	--	--	1	2	2
51-100µ	--	--	--	--	--
101-150µ	--	--	--	--	--
151-200µ	--	--	--	--	--
More than 200µ	--	--	--	--	--
No change	2	2	1	--	--

In cases with CRVO, all the 2 showed improvement of 50µ reduction retinal thickness at the end of 4 months because of vascular perfusion factor associated with Anti VEGF which correlates with the study of Schaal KB et-all; ophthalmology 2007; 104; 285-9.

Reduction in macular thickness (μ) in CRVO cases-Post injection at 4 months

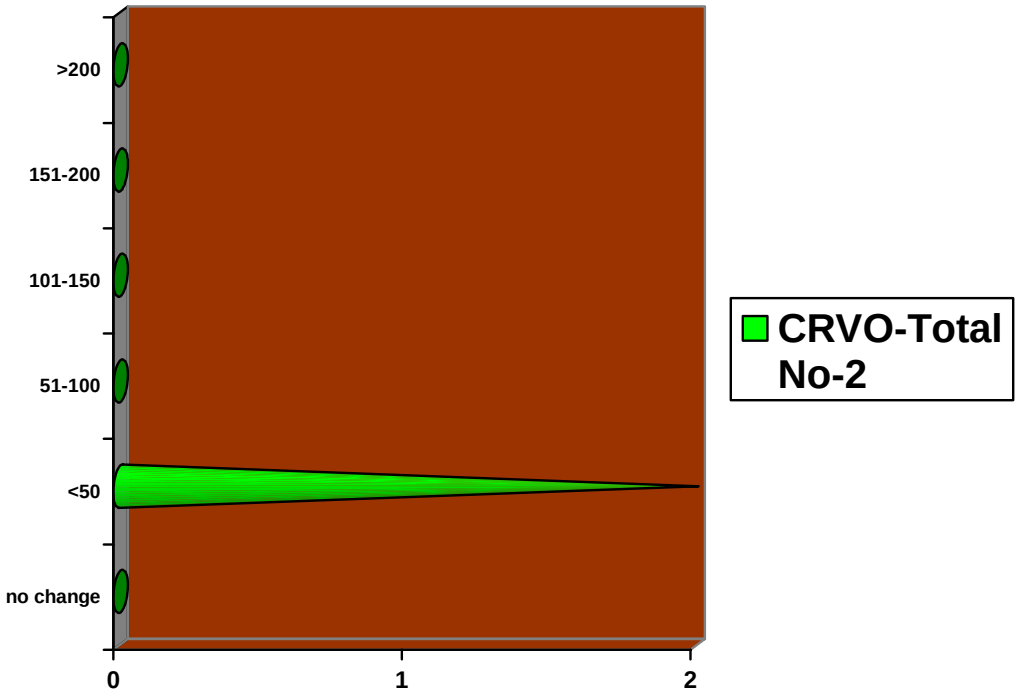


TABLE – 9: ANGIOGRAPHIC PATTERNS

TABLE – 9 A Post injection in cases with CNV:

Disease conditions	No of cases with leakage				
	At 2wks	At 4 wks	At 2 months	At 3months	at 4months
Classic CNV	14	9	7	3	1
Occult CNV	5	3	3	2	--

At the end of 4 weeks, 50% of both occult and classic types showed leakage and at the end of 4 months no cases of occult CNV showed leakage which supports the study of Aiesenbrey et-all Graefes Arch Clin Exp Ophthalmol 2007; 245:941-8. 1 patient of classic CNV showed leakage with staining at the end of 4 months because of macular scarring.

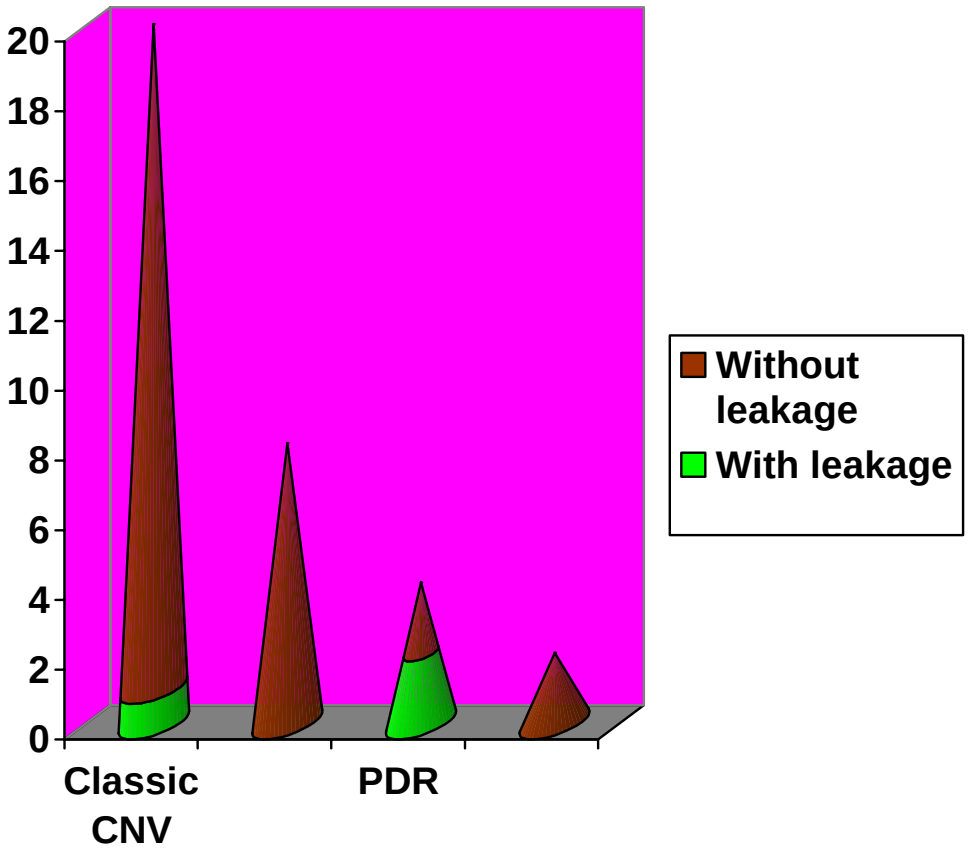
TABLE – 9 B

Disease	No of cases with leakage				
Conditions	**At 2 wks**	**At 4 wks**	**At 2months**	**At 3months**	**At 4months**
PDR	4	3	2	2	2
CRVO	1	1	--	--	--

All the cases of PDR showed leakage from NVE at the end of 1month, and 50% of them still showed leakage at the end of the study and 25% 0f them underwent repeat injection with fillin PRP. This leakage is attributable to uncontrolled diabetic status.

Out of 2 patients of CRVO, 1 showed leakage at the end of 2months and he stopped leakage at the end of 4 months.

ANGIOGRPAHIC PATTERNS AT 4 MONTHS



DISCUSSION

- This is a 6month prospective, non-randomized clinical study to investigate the safety and efficacy of intravitreal bevacizumab for the treatment of neovascular AMD, and as an adjunct to PDR and CRVO cases with progressing neovascularization inspite of complete PRP.

- The main aim was to evaluate the improvement in V/A, decrease in macular thickness and qualitative decrease in angiographic leakage in the above said conditions following intravitreal injection.

- Of the 34 patients who met the inclusion criteria for the study, 20 were male and 14 were female, the ratio being 1.5:1. The mean age was 55 years.

- Out of 34 eyes, 82% of cases were with CNV, of which 71% were with Classic type and 29% with Occult type of CNV. Out of 18% of the remaining, PDR cases constitutes about 12% and CRVO cases constitutes about 6%.

- The mean baseline pre-procedure V/A considered was 3/60, the least V/A being HM , and the highest V/A being 6/24. The baseline mean macular thickness was 356µ.

- All the patients were given 1.25mg of Bevacizumab intravitreally under aseptic precautions after explaining the procedure who then signed a consent form. Follow-up ranged from 2 to 16 weeks. All 34 patients completed a 16-week follow-up visit.

- During each follow-up, patients were checked for improvement in V/A, decrease in macular thickness and change in angiographic patterns. Fundus photographs were taken for documentation.

VISUAL ACUITY: **(Snellen's Chart)**

- The effect of intravitreal bevacizumab seems to be similar between both Classic and Occult CNV. Generally, there was a significant improvement in V/A by 4weeks of about 50% and by the end of 4 months, 60% of Classic CNV and 50% of Occult CNV showed 2 lines of improvement by Snellen's. 25% of both types showed more than 2 lines of improvement

by the end of the study. 1 case of Classic CNV showed no improvement because of macular scarring.

- The response of Bevacizumab to Proliferative diabetic retinopathy is less when compared to other conditions because of associated systemic factors. The mean V/A improves by 50% (1 line improvement) by the end of 4weeks which remained the same by the end of the study in 50% of cases. 1 case dropped V/A after 3rd month because of cystoid macular oedema with vitreo-macular traction and he underwent repeat injection.

- Out of 2 cases of CRVO, 1 case (50%) started showing 1 line improvement by 4th week and he maintained it till the end of the study, 1case showed no improvement because of optic atrophy.

- Unlike BCVA, the lesion size by fundus appearance did not show the same rapid improvement. This is because, VEGF is necessary for the growth of immature blood vessels but established blood vessels may not require VEGF and this may explain the less dramatic response of the clinical appearance of the lesion when compared with V/A.

- This study shows that the vast majority of patients demonstrated stability or improvement of the VA. Of those few patients with a visual decline, the change was felt to be due to disease progression rather than drug toxicity.

MACULAR THICKNESS: **(Stratus OCT)**

- The base line mean macular thickness in CNV cases was 345µ About 73% of Classic CNV and 50% of Occult CNV showed reduction in macular thickness of 50µ at the end of 1month, and 50% of both CNV types showed reduction of 100µ at the end of 4months. 1 case of Classic CNV showed no improvement till the end of the study because of macular scarring.

- In PDR cases, 50% (2cases) showed improvement of 50µ reduction at the end of 1month post injection, 50% showed reduction of upto 100µ at the end of 4 months and 25% (1case) showed no change because of non-resolving cystoid macular oedema associated with vitreo-macular traction.

- In CRVO, out of 2 cases, 1case showed reduction of macular thickness by the end of 2 months, both showed 50% reduction

by the end of the study and this is because of vascular perfusion factor associated with Anti VEGF Bevacizumab.

- Thus the qualitative assessment of the OCT showed marked reduction in subretinal fluid and cystic oedema 1month after injection. The earliest sign of reduction was the disappearance of SRF. Although PEDs were noted to decrease in elevation in most patients, quantitative evaluation of this change could not be obtained with the current OCT software, which measures the distance between the retinal pigment epithelial layer and the ILM and, thus, does not include the PED thickness in the calculations.

ANGIOGRAPHIC PATTERNS

- At the end of 4 weeks, 50% of both occult and classic types showed leakage and at the end of 4 months no cases of occult CNV showed leakage which supports the study of Aiesenbrey et-all Graefes Arch Clin Exp Ophthalmol 2007; 245:941-8. 1 patient of classic CNV showed leakage with staining at the end of 4 months because of macular scarring.

- All the cases of PDR showed leakage from NVE at the end of 1month, and 50% of them still showed leakage at the end of the study and 25% 0f them underwent repeat injection with fillin PRP.

- Out of 2 patients of CRVO, 1 showed leakage at the end of 2months and he stopped leakage at the end of 4 months.

- We identified no cases of uveitis, endophthalmitis, ocular toxicity, hypertension, or thromboembolic events after injection, a finding consistent with that of other investigators (Rosenfeld P. Changing strategies in the management of neovascular age-related macular degeneration. Presented at: Retina Society Meeting, September, 2005; San Diego, California).

The use of intravitreal bevacizumab is appealing for a number of reasons

First, the **MARINA** (Minimally Classic/ Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular AMD) results demonstrated, for the first time, an average improvement in VA with intravitreal ranibizumab treatment for neovascular AMD [Miller JW. Randomized, controlled phase III study of ranibizumab (Lucentis) for minimally classic or occult neovascular age-related macular degeneration.

Paper presented at: ASRS meeting, July 18, 2005; Montreal, Canada]. This has raised physician and patient expectations. Ranibizumab is not Food and Drug Administration approved and, to date, has been denied fast-track approval status. However, bevacizumab is Food and Drug Administration approved for colorectal cancer and, therefore, is available for use on an off-label basis. Given its molecular similarity to ranibizumab, one reasonably could expect similar results if it penetrates the retina.

Second, the half-life of intravitreal bevacizumab is expected to be about twice that of ranibizumab, and if, indeed, these preliminary data are confirmed by a prospective trial, and bevacizumab is found to be effective in sequestering VEGF and improving the outcome of patients with AMD, then less frequent administration than with ranibizumab may be required.

Third, the cost per dose of intravitreal bevacizumab is significantly less than that of pegaptanib or the anticipated cost of ranibizumab. Hence, the potential cost savings for the United States health care system could be substantial, and the treatment may be available worldwide to patients who may not be able to afford the more expensive alternatives.

The optimum dosing sequence for intravitreal bevacizumab is undetermined. We elected to defer reinjection into eyes when there was complete resolution of SRF, macular edema, and PEDs until there was a recurrence. Some patients have not recurred 15 weeks after a single injection. Those cases that did recur after initially resolving responded to repeat injections without loss of vision—a finding similar to what Michels et al reported in the systemic bevacizumab trial. It is possible that a different dosing schedule, such as a series of monthly injections for an extended period followed by retreatment for recurrences, may be superior to the method used in this study; however, we chose to err on the side of undertreatment until further toxicity data are obtained.

SUMMARY

A total of 34 Patients were included in this study.

Age group was between 30-60 years.

All the patients were examined for V/A, FFA for leakage, and OCT for macular thickness before and at 2wks, 4wks, 2, 3, and 4months after intravitreal injection.

1 out of 4 PDR patients was given repeat injection at the end of 3rd month as there was no response for single injection. Overall 70% of CNV cases (both classic & occult) responded with improvement and stabilization of V/A of upto 2 lines, where as only 50% of PDR and CRVO cases responded with 1line improvement by the end of the study.

78% of CNV cases irrespective of types and 50% of PDR cases responded with reduction of macular thickness of upto 100µ whereas both cases of CRVO cases responded with reduction of 50µ by the end of the study.

Almost all the cases of CNV and CRVO responded to treatment with no leakage in angiography whereas 50% of PDR cases showed leakage till the end of the study.

CONCLUSIONS

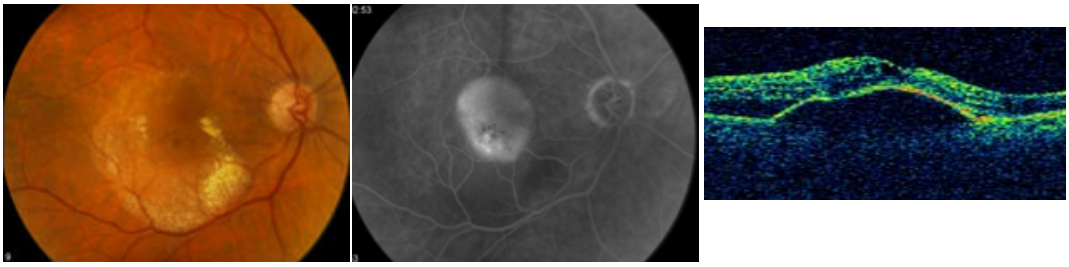
Intravitreal bevacizumab (1.25 mg) treatment is well tolerated over 6 months with significant safety and efficacy.

Nevertheless, this is a small interventional study, with no comparison arm to quantify the actual magnitude of benefit of this treatment modality compared with other therapies.

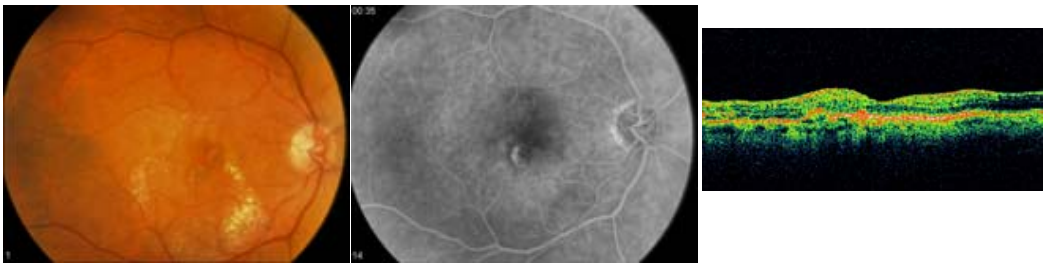
This would have to be studied subsequently in larger studies and also needs to be compared with other VEGF inhibitiors regarding safety and efficacy.

CASE NO - 1

Pre-injection

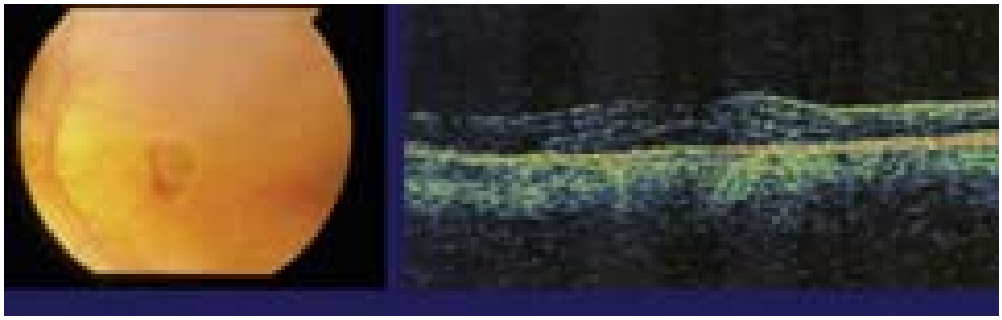


8wks post-injection



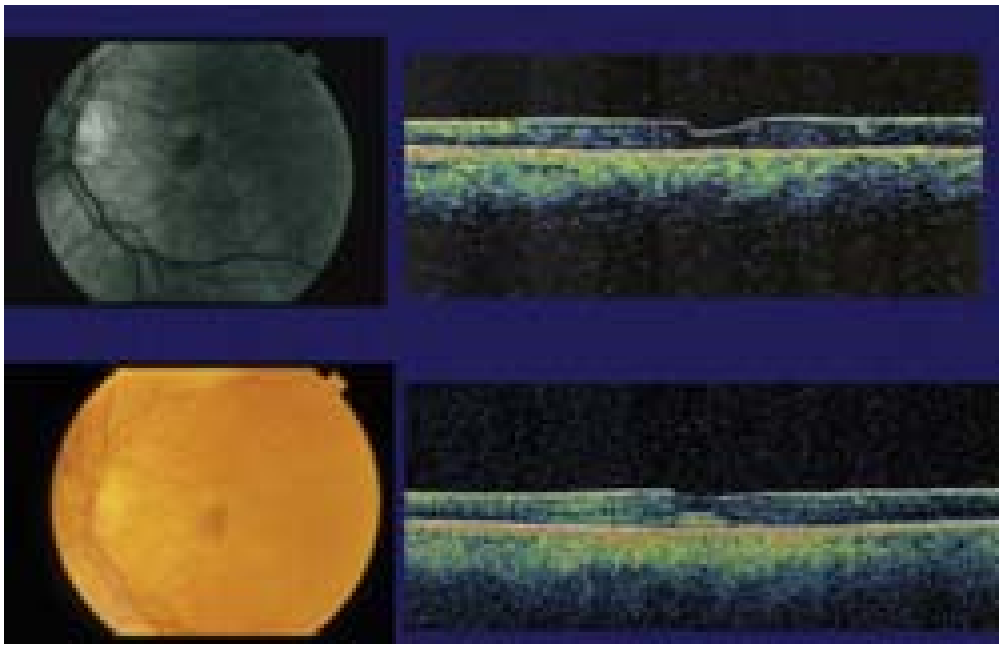
CASE – 2

Pre-injection

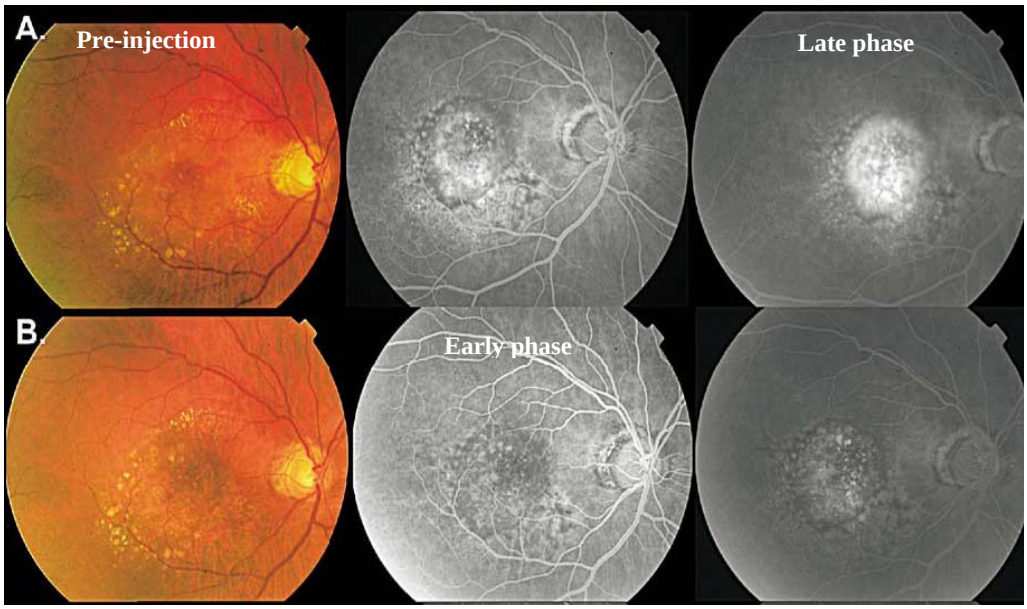


]

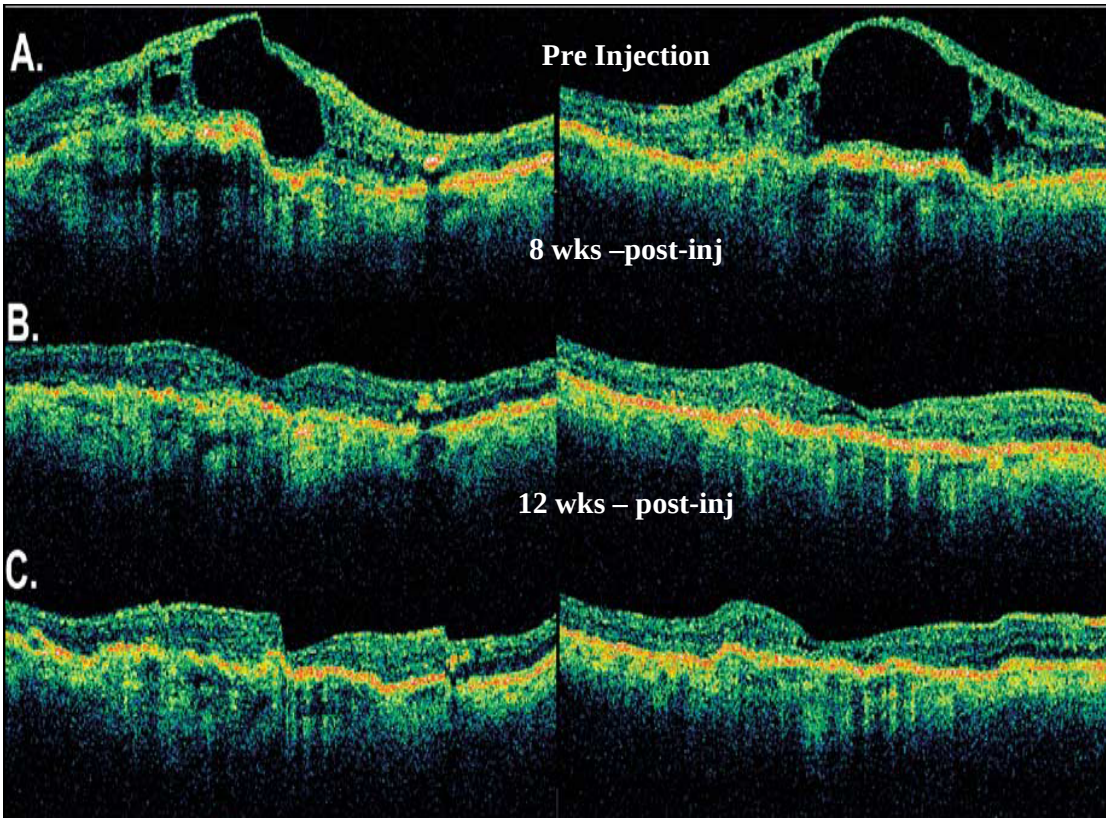
Post-injection



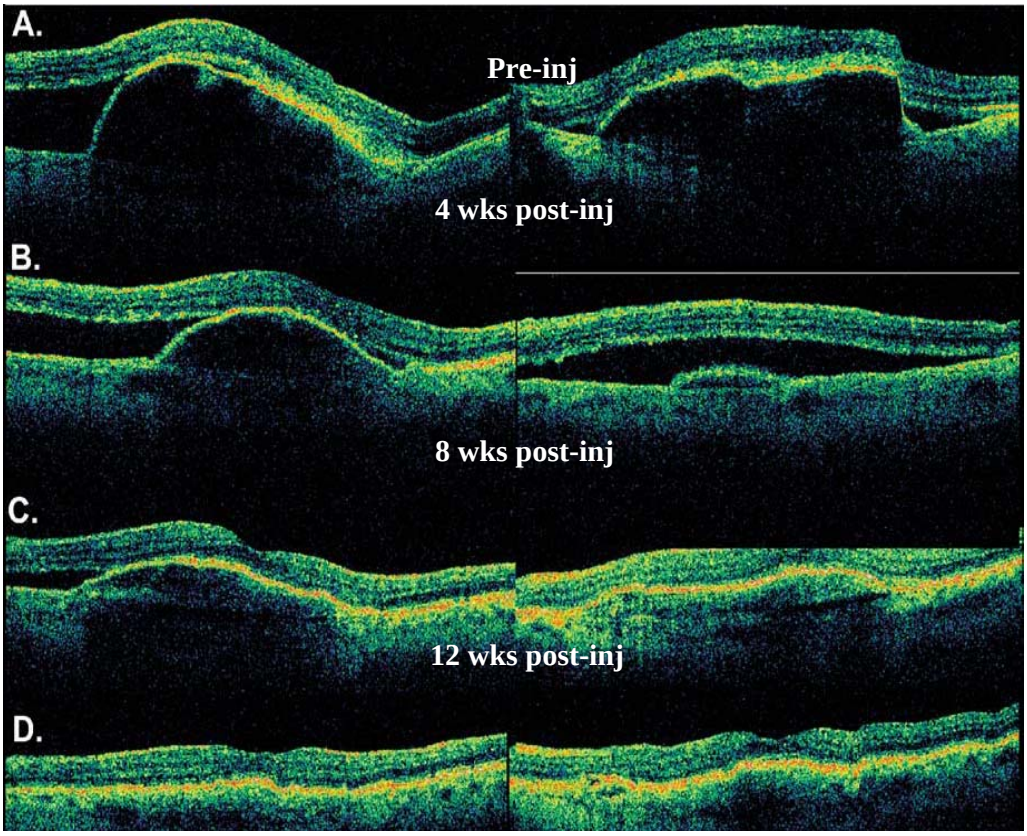
CASE – 3



CASE – 4

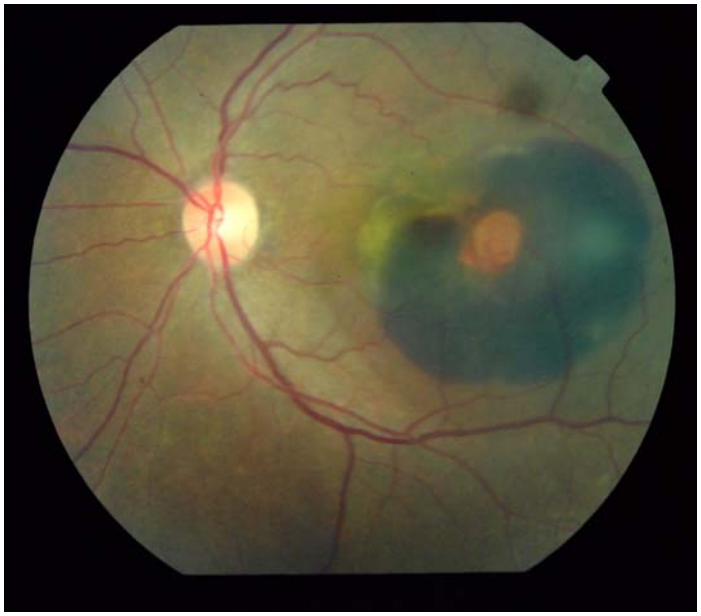


CASE – 5

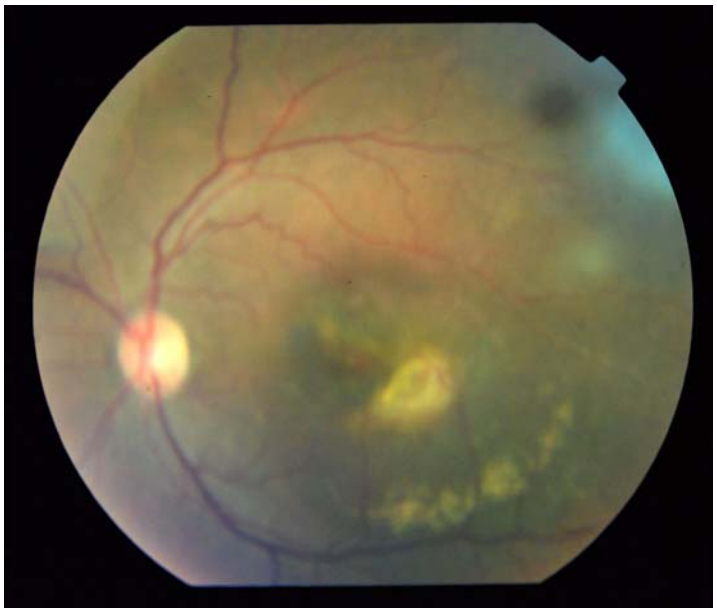


CASE – 6

Pre-Injection

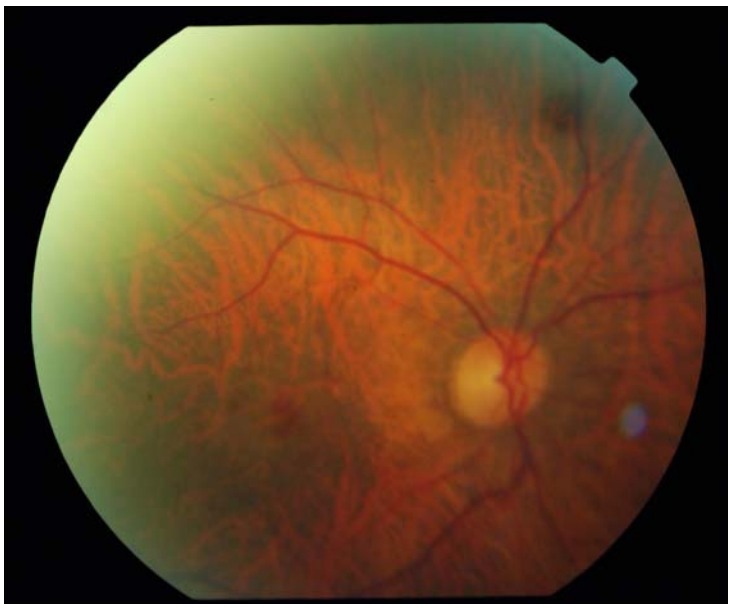


Post-Injection

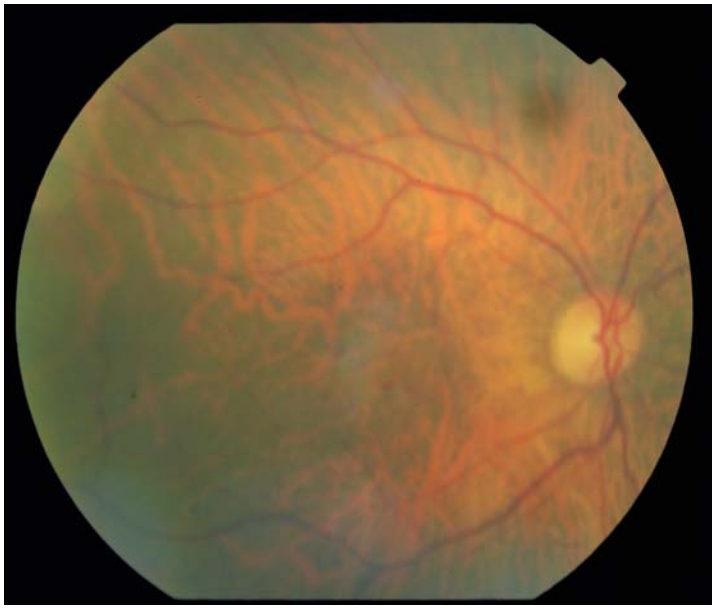


CASE – 7

Pre-Injection

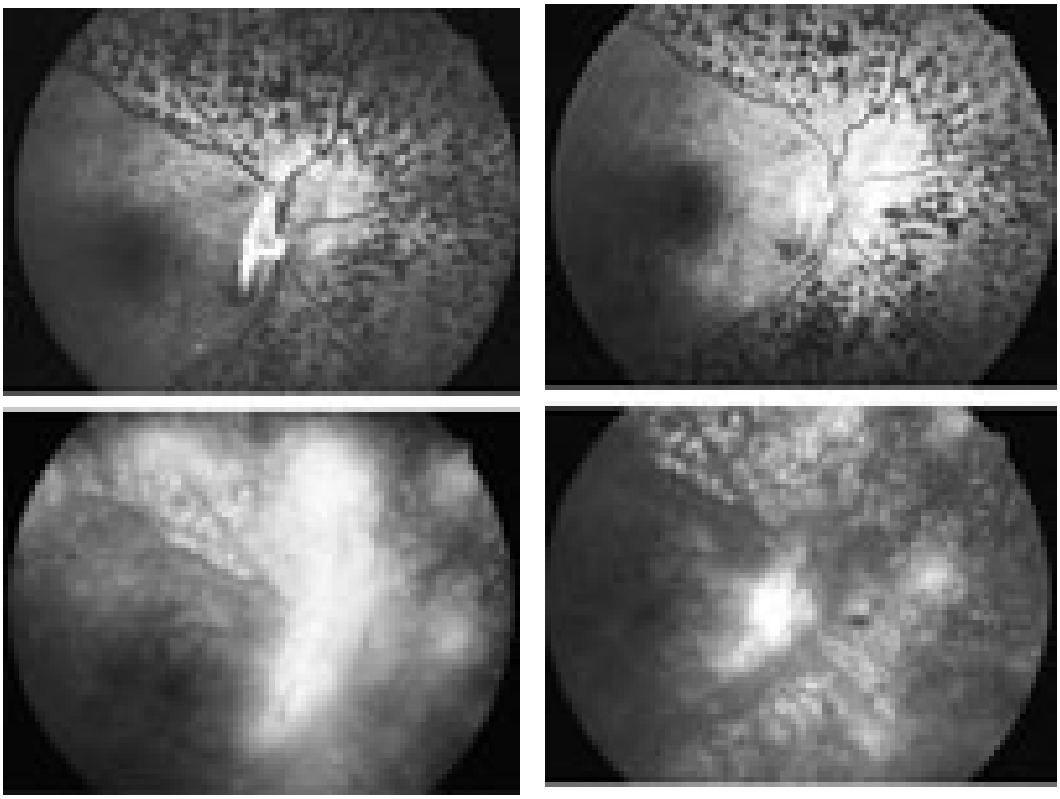


Post-Injection



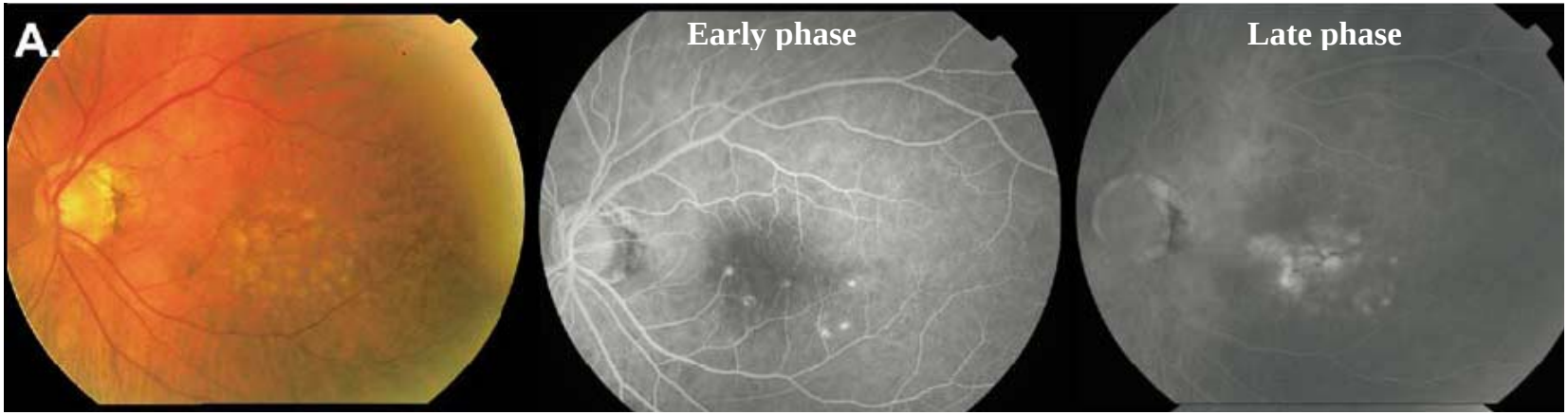
CASE – 8

Pre-Injection **Post-Injection**

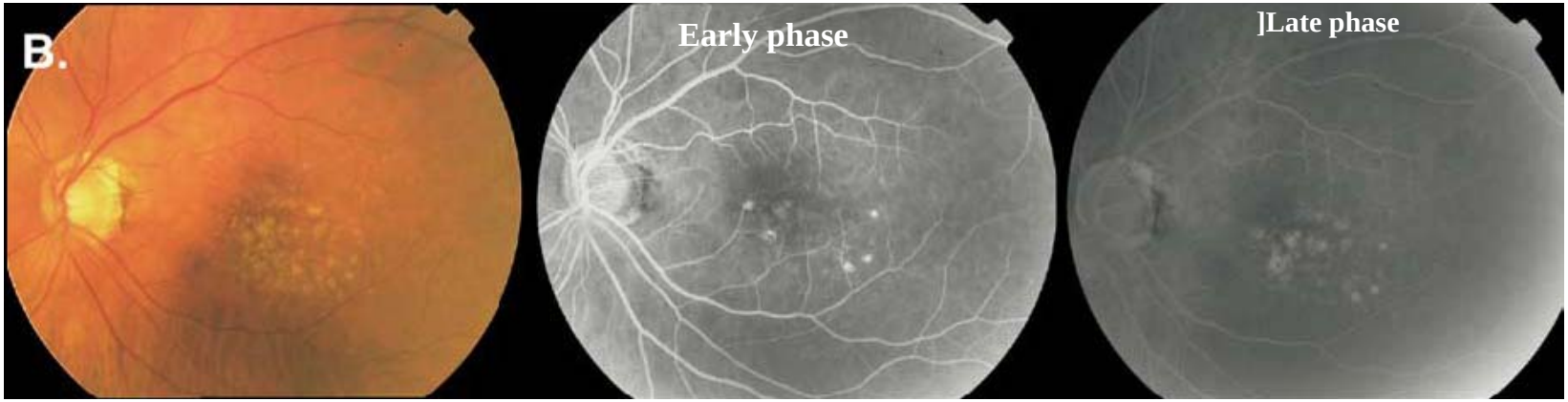


CASE-9

Pre-injection



Post-injection



BIBLIOGRAPHY

1. Ferrara N. Vascular endothelial growth factor: basic science and clinical progress. Endocr Rev 2004;25:581– 611.

2. Adamis AP, Shima DT. The role of vascular endothelial growth factor in ocular health and disease. Retina 2005;25:111–8.

3. Holz FG, Pauleikhoff D, Klein R, Bird AC. Pathogenesis of lesions in late age-related macular disease. Am J Ophthalmol 2004;137:504 –10.

4. Krzystolik MG, Afshari MA, Adamis AP, et al. Prevention of experimental choroidal neovascularization with intravitreal anti-vascular endothelial growth factor antibody fragment. Arch Ophthalmol 2002;120:338–46.

5. Gragoudas ES, Adamis AP, Cunningham ET Jr, et al, VEGF Inhibition Study in Ocular Neovascularization Clinical Trial Group. Pegaptanib for neovascular age-related macular degeneration. N Engl J Med 2004;351:2805–16.

6. VEGF Inhibition Study in Ocular Neovascularization (V.I.S.- I.O.N.) Clinical Trial Group. Enhanced efficacy associated with early treatment of neovascular age-related macular degeneration with pegaptanib sodium: an exploratory analysis. Retina 2005; 25:815-27.

7. van Wijngaarden P, Coster DJ, Williams KA. Inhibitors of ocular neovascularization: promises and potential problems. JAMA 2005;293:1509 –13.

8. Treatment of Age-Related Macular Degeneration with Photodynamic Therapy (TAP) Study Group. Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin: two-year results of 2 randomized clinical trials—TAP report 2. Arch Ophthalmol 2001;119:198 –207.

9. Treatment of Age-Related Macular Degeneration with Photodynamic Therapy Study Group, Verteporfin in Photodynamic Therapy Study Group. Photodynamic therapy of subfoveal\ choroidal neovascularization with verteporfin: fluorescein angiographic guidelines for evaluation and treatment—TAP and VIP report no. 2. Arch Ophthalmol 2003;121:1253– 68.

10. Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med 2004;350:2335– 42.

11. Rosenfeld PJ, Schwartz SD, Blumenkranz MS, et al. Maximum tolerated dose of a humanized anti-vascular endothelial growth factor antibody fragment for treating neovascular age-related macular degeneration. Ophthalmology 2005; 112:1048 –53.

12. Gaudreault J, Fei D, Rusit J, et al. Preclinical pharmacokinetics of Ranibizumab (rhuFabV2) after a single intravitreal administration. Invest Ophthalmol Vis Sci 2005;46:726 –33.

13. Mordenti J, Cuthbertson RA, Ferrara N, et al. Comparisons of the intraocular tissue distribution, pharmacokinetics, and safety of 125I-labeled full-length and Fab antibodies in rhesus monkeys following intravitreal administration. Toxicol Pathol 1999;27:536–44.

14. Michels S, Rosenfeld PJ, Puliafito CA, et al. Systemic bevacizumab (Avastin) therapy for neovascular age-related macular degeneration. Twelve-week results of an uncontrolled open-label clinical study. Ophthalmology 2005;112:1035–47.

15. Rosenfeld PJ, Moshfeghi AA, Puliafito CA. Optical coherencetomography findings after intravitreal injection of bevacizumab (Avastin) for neovascular age-related macular degeneration. Ophthalmic Surg Lasers Imaging 2005;36:331 5.

16. Nguyen QD, Shah S, Tatlipinar S, et al. Bevacizumab suppresses choroidal neovascularization caused by pathological myopia [letter]. Br J Ophthalmol 2005;89:1368 70.

17. FDA Medwatch. Barron H, Genentech. Important drug warning [letter]. Available at: http://www.fda.gov/medwatch/SAFETY/2005/ Avastin_dearhcp.pdf. Accessed October 10,2005.

18. Schachat AP, Chambers WA, Liesegang TJ, Albert DA. Safe and effective. Ophthalmology 2003;110:2073– 4.

19. Yourey PA, Gohari S, Su JL, Alderson RF. Vascular endothelial cell growth factors promote the in vitro development of rat photoreceptor cells. J Neurosci 2000;20:6781– 8.

20. Kim I, Ryan AM, Rohan R, et al. Constitutive expression of VEGF, VEGFR-1, and VEGFR-2 in normal eyes. Invest Ophthalmol Vis Sci 1999;40:2115–21.

21. Rosenfeld PJ, Fung AE, Puliafito CA. Optical coherence tomography findings after an intravitreal injection of bevacizumab (Avastin) for macular edema from central retinal vein occlusion. Ophthalmic Surg Lasers Imaging 2005;36:336–9.

22. Han DP. Intravitreal human immune globulin in a rabbit model of *Staphylococcus aureus* toxin-mediated endophthalmitis: a potential adjunct in the treatment of endophthalmitis. Trans Am Ophthalmol Soc 2004;102:305 20.

23. Green WR. Retina. In: Spencer WH, ed. Ophthalmic Pathology: An Atlas and Textbook. 4th ed. Vol. 2. Philadelphia: WB Saunders; 1996:673.

24. Green WR, Sebag J. Vitreoretinal interface. In: Ryan SJ, Ogden TE, Hinton DR, et al, eds. Retina. 3rd ed. Vol. 3. St. Louis: Mosby; 2001:1886 –91.

25. Hogan MJ, Alvarado JA, Weddell JE. Histology of the Human Eye: An Atlas and Textbook. Philadelphia: WB Saunders; 1971:497.

26. Matsumoto B, Blanks JC, Ryan SJ. Topographic variations in the rabbit and primate internal limiting membrane. Invest Ophthalmol Vis Sci 1984;25:71– 82.

27. Jackson TL, Antcliff RJ, Hillenkamp J, Marshall J. Human retinal molecular weight exclusion limit and estimate of species variation. Invest Ophthalmol Vis Sci 2003;44:2141– 6.

28. Hogan MJ, Alvarado JA, Weddell JE. Histology of the Human Eye: An Atlas and Textbook. Philadelphia: WB Saunders; 1971:491.

29. Kimura AE, Reddy CV, Folk JC, Farmer SG. Removal of subretinal hemorrhage facilitated by preoperative intravitreal tissue plasminogen activator [letter]. Retina 1994;14:83– 4.

30. Kamei M, Misono K, Lewis H. A study of the ability of tissue plasminogen activator to diffuse into the subretinal space after intravitreal injection in rabbits. Am J Ophthalmol 1999;128: 739–46.

31. Johnson MW. Pneumatic displacement of submacular hemorrhage. Curr Opin Ophthalmol 2000;11:201– 6.

32. Genentech. Genentech announces plans to file for FDA approval of Lucentis for the treatment of wet age-related macular degeneration in December [press release, September 7, 2005]. Available at: http://www.gene.com/gene/news/press-releases/display.M do?method_detail&id_8827&categoryid_3. Accessed November 12, 2005.

33. Reichel E. Intravitreal bevacizumab for choroidal neovascularization and cystoid macular edema: a cost-effective treatment? Ophthalmic Surg Lasers Imaging 2005;36:270 –1.

PROFORMA

Case-no:

Name Age Sex Occupation OP no.

Address Phone No.

Chief complaints

- Defective vision
- Distorted vision
- Pain in the eye

Past history:

*Diabetes - no o years

- type I / II
- On oral hypoglycemics / Insulin
- Whether blood sugar under control
- associated with NVG
- PRP given / not

If given – no of sittings

*Hypertension - No of years

- On what medication
- Associated with ischemic heart disease/hyper lipidemia / cerebrovascular insult

*H/O smoking

On systemic examination:

PR: BP:

RBS: Urine – alb & sugar:

HbA1c:

On ocular examination:

	RE	**LE**
Visual acuity	--	
Tension (By NCT)	--	
Conjunctiva	--	
Cornea	--	
Iris	--	
Ant.chamber	--	
Lens	--	
Slit lamp Ex	--	
Fields	--	
Colour vision	--	

Fundus by 90D

Fundus by IDO

FUNDUS FLUORESCEIN ANGIOGRAPHY:

Amsler's grid chart:

Optical coherence tomography:

Diagnosis:

Treatment history:

Under aseptic conditions, under topical anaesthesia, inj. Bevacizumab 1.25mg is injected intravitreally.

No.of sittings - Date

Outcome of treatment:

MASTER CHART

NAME	SEX	IP. NO	Diagnosis	PRE-PROCEDURE			POST - PROCEDURE											
							4 weeks			8 weeks			12 weeks			16 weeks		
				Vision	OCT	FFA	V/A	OCT	FFA	V/A	OCT	FFA	V/A	OCT	FFA	V/A	OCT	FFA
Nagammal	f	67894	RE-CNV	4/60ph5/60	160	+	5/60 PH 6/60	155	+	6/60 PH 6/36	145	_	6/36 NIP	134	_	6/36 NIP	122	_
Ganesan	m	45632	RE-CNV	3/60PH4/60	174	+	4/60 NIP	170	+	3/60 NIP	165	_	3/60 PH 4/60	144	_	3/60 PH 4/60	111	_
Anushya	f	67865	LE-PDR	HM	387	+	HM	387	+	CFCF	322	+	1/60 NIP	287	_	2/60 NIPS	245	+
sarathy	f	56784	RE-CNV	2/60PH 6/60	189	_	2/60 PH 3/60	176	+	4/60 PH 6/36	166	_	5/60 NIP	144	_	5/60 PH 6/60	122	_
Sivagami	f	76584	LE-CNV	1/60 PH 4/60	278	+	3/60 PH 5/60	255	+	4/60 PH 6/36	234	+	4/60 PH 6/36	213	_	4/60 PH 6/36	197	_
Janaki	f	87695	LE-CNV	HM	345	+	HM	330	_	CFCF	300	+	1/60 NIP	267	+	1/60 NIP	222	_
Devid	m	78659	RE-CNV	HM	335	+	1/60NIP	300	+	2/60 NIP	280	+	2/60 NIP	245	_	2/60 PH 3/60	210	_
Umapathy	m	78654	RE-CNV	5/60 PH 6/60	298	+	6/60 PH 6/36	278	+	5/60 PH 6/36	245	_	5/60 PH 6/36	234	_	5/60 PH 6/60	197	_
Thilagar	m	76589	LE-CNV	2/60 PH 3/60	300	+	3/60 PH 5/60	245	+	4/60 PH 6/36	233	_	5/60 PH 6/60	213	_	5/60 PH 6/60	200	_
Kasthuri	f	73099	RE-CNV	1/60 NIP	269	+	2/60 NIP	255	+	4/60 PH 6/60	222	+	4/60 PH 6/60	198	_	4/60 PH 6/36	278	+
Shanthi	f	87695	LE-CNV	HM	397	+	1/60 PH 2/60	345	+	2/60 PH 6/60	298	+	3/60 NIP	165	_	3/60 PH 6/60	255	_
Hussain	m	67895	RE-CNV	HM	456	+	HM	432	+	1/60 PH 6/60	389	+	1/60 PH 3/60	355	+	1/60 PH 3/60	322	+
Lakshman	m	78594	RE-CNV	1/60NIP	487	+	2/60 PH 3/60	487	+	3/6O NIP	400	+	3/60 NIP	366	+	3/6O NIP	314	_
Nagarajan	m	78659	RE-CRVO	1/6O	246	+	1/60 PH 2/60	246	_	2/60 PH 6/60	222	_	2/60 PH 5/60	203	_	3/60 NIP	192	_
Samasath	m	89765	LE-CNV	2/60 NIP	376	+	2/60NIP	376	+	3/60 PH 6/60	344	+	3/60 PH 6/60	312	+	4/60 PH 6/60	278	+
Rahmadulla	m	87965	RE-PDR	1/60 NIP	220	+	1/60 NIP	220	_	2/60 PH 6/60	198	_	2/60 PH 6/60	220	_	2/60 PH 6/60	220	_

Meera moid	m	87650	LE-CNV	4/60 PH 6/60	378	+	5/60 PH 6/60	365	+	6/60 NIP	320	+	5/60 NIP	287	_	5/60 NIP	256	_
Abdulkader	m	78596	RE-CNV	6/60 PH 6/24	269	+	6/36 PH 6/18	260	+	6/24 PH 6/18	220	_	6/24 PH 6/18	198	_	6/24 PH 6/18	177	_
Janardanan	m	83459	RE-CNV	5/60 PH 6/36	255	+	6/60 PH 6/36	250	+	6/36 PH 6/18	211	_	6/36 PH 6/12	187	_	6/36 PH 6/24	168	_
Srinivasalu	m	76859	LE-CNV	1/60 PH 4/60	289	+	2/60 PH 3/60	280	+	6/36 PH 6/24	234	_	6/36 PH 6/24	213	-	6/36 PH 6/24	191	_
Indirani	f	85420	LE-PDR	3/60 PH 6/60	146	+	6/60 PH 6/36	122	_	6/36 PH 6/24	111	_	6/24 NIP	98	_	6/24 PH 6/18	97	_
Ameer	m	81234	RE-CNV	2/60 PH 6/60	278	+	3/60 PH 6/36	270	+	5/60 PH 6/36	234	_	6/60 PH 6/24	198	-	6/60 PH 6/18	188	_
Durairaj	m	56748	LE-CNV	1/60 PH 3/60	345	+	2/60 PH 4/60	340	+	3/60 PH 6/60	287	+	4/60 PH 6/36	234	_	4/60 PH 6/60	212	_
Berkman	m	76850	RE-CNV	2/60 PH 6/60	378	+	3/60 NIP	368	+	4/60 PH 5/60	311	+	6/60 NIP	267	=	6/60 PH 6/36	234	_
Saraswathy	f	63095	LE-CRVO	HM	246	+	1/60 NIP	246	+	3/60 PH 6/36	201	_	4/60 PH 6/24	189	_	4/60 PH 6/24	166	_
Santhanam	m	75803	RE-CNV	6/60 PH 6/36	255	+	6/60 PH 6/24	245	_	6/36 PH 6/24	203	_	6/36 PH 6/24	197	_	6/36 PH 6/24	169	_
Saraswathy	f	80587	RE-CNV	HM	398	+	CFCF	378	+	1/60 NIP	322	+	2/60 NIP	287	+	3/60 NIP	234	_
Baby	f	76894	LE-CNV	HM	467	+	CFCF	455	+	CFCF	389	+	CFCF	322	+	CFCF	289	+
Dhanam	f	60498	RE-CNV	3/60 PH 6/60	345	+	4/60 NIP	340	+	3/60 PH 6/60	340	+	4/60 PH 6/36	298	+	4/60 PH 6/36	277	_
Kannappan	m	86750	LE-CNV	2/60 NIP	453	+	1/60 NIP	435	+	2/60 NIP	435	+	2/60 NIP	367	+	2/60 NIP	370	+
Kumary	f	82635	RE-CNV	5/60 PH 6/36	267	+	6/60 PH 6/24	255	_	6/36 PH 6/24	222	_	6/36 PH 6/24	178	_	6/36 PH 6/24	166	_
Rameshwari	f	89463	LE-CNV	3/60 PH 6/60	346	+	2/60 PH 6/36	345	+	6/36 NIP	302	+	6/36 PH 6/24	278	+	6/36 PH 6/24	234	_
Krishnan	m	82176	RE-PDR	1/60 PH 2/60	378	+	/60 NIP	378	+	3/60 PH 4/60	342	+	4/60 NIP	302	+	4/60 NIP	355	+
Saroja	f	67580	LE-CNV	4/60NIP	8	+	5/60 PH 6/36	276	+	6/60 PH 6/36	245	_	6/60 PH 6/24	213	_	6/60 PH 6/24	194	_

KEY TO MASTER CHART

OCT	–	Optical coherence tomography
FFA	–	Fundus Fluorescein Angiography
PDR	-	Proliferative Diabetic Retinopathy
CRVO	–	Central retinal Vein Occlusion
CNV	–	Choroidal Neovascularization.
V/A	-	Visual acuity
PH	-	Pinhole

LIST OF SURGERIES PERFORMED

S. No.	Name	Age	Sex	IP no.	Diagnosis	Surgeries
1.	Kanniammal	60	F	684392	BE IMC	LE ECCE with PCIOL
2.	Maragatham	65	F	785391	RE IMC/LE MC	LE ECCE with PCIOL
3.	Elangovan	76	M	790160	RE IMC/LE MC	LE ECCE with PI
4.	perumal	70	M	690437	RE IMC/LE MC	LE ECCE with PCIOL
5.	Jayagopal	50	M	692899	BE IMC	RE ECCE with PCIOL
6.	Subramani	57	M	793525	RE IMC/LE MC	LE ECCE with PCIOL
7.	Kaliammal	68	F	783728	BE Nuclear Cat.	RE ECCE with PCIOL
8.	Annammal	60	F	674267	BE MC	LE ECCE with PCIOL
9.	Krishnaveni	50	F	725015	BE IMC	LE SICS with PCIOL
10.	Muniyammal	65	F	816095	BE IMC	LE SICS with PCIOL
11.	Dhanalakshmi	46	F	785885	BE IMC	RE SICS with PCIOL
12.	Ramasamy	65	M	826095	BE IMC	RE SICS with PCIOL
13.	Vasantha	38	F	656005	RE PSEUDO/ LE IMC	LE ECCE with PCIOL
14.	Gopal	65	M	776441	BE IMC	LE SICS with PCIOL
15.	Chandra	65	F	886336	RE MC/ LE PSEUDO	RE SICS with PCIOL
16.	Vellaiyan	55	M	847637	BE MC	LE ECCE with PCIOL
17.	Dasappan	35	M	87720	LE EXP. KERATITIS	LEMEDIAL TARSORRAPHY
18.	Etiappan	58	M	891721	LE-IMC	LE – SICS with PCIOL
19.	Mariappan	52	M	792726	LE-IMC	LE – SICS with PCIOL
20.	Shanthi	48	F	811986	BE IMC	RE SICS with PCIOL
21.	Varadhan	46	M	820826	RE CDC	RE DCR
22.	Sumathy	54	F	762091	LE CDC	LE DCT
23.	Baskar	52	M	83940	RE-Matur Cataract	RE – SICS with PCIOL
24	Venkatesh	56	M	78542	LE-IMC	LE – SICS
25.	Lakshmi	72	F	84286	RE CDC	RE - DCT