INFLAMMATORY CHOROIDAL NEOVASCULAR MEMBRANE-INCIDENCE, VISUAL AND ANATOMICAL OUTCOMES AFTER INTRAVITREAL ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR THERAPY

Dissertation submitted to The Tamil Nadu Dr. M.G.R. Medical University in partial fulfilment of the requirements for the degree of

MS Ophthalmology

BRANCH - III

OPHTHALMOLOGY

THE TAMIL NADU

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CERTIFICATE

This is to certify that this dissertation entitled **"INFLAMMATORY CHOROIDAL NEOVASCULAR MEMBRANE-INCIDENCE, VISUAL AND ANATOMICAL OUTCOMES AFTER INTRAVITREAL ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR THERAPY"** submitted to Tamil Nadu Dr MGR Medical University is a bonafide work done by **Dr.TANYA BALAKRISHNAN** under the guidance and supervision in the department of Uvea, Aravind Eye Hospital and Post Graduate Institute of Ophthalmology in Madurai during her residency period from May 2017 to May to 2020.

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DECLARATION

I, **Dr. Tanya Balakrishnan** solemnly declare the dissertation titled **"INFLAMMATORY CHOROIDAL NEOVASCULAR MEMBRANE-INCIDENCE, VISUAL AND ANATOMICAL OUTCOMES AFTER INTRAVITREAL ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR THERAPY"** has been prepared by me. I also declare that this bonafide work or a part of this work was not submitted by me or any other for any award, degree, diploma to any other university board either in India or abroad. This dissertation is submitted to the **Tamil Nadu Dr.M.G.R. Medical University**, Chennai in partial fulfilment of the rules and regulation for the award of **M. S. Ophthalmology (BRANCH III)** to be held in May 2020.

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PART-I

1. INTRODUCTION

Choroidal neovascularization(CNVM) is the formation of new blood vessels beneath the retina, originating from the choroid. Various etiologies can cause CNVM, most common being age-related macular degeneration (ARMD) followed by pathological myopia and inflammatory CNVM.[1]

In uveitis, because of the association with various inflammatory conditions of the posterior segment, CNVMs formed are termed as "inflammatory CNVM".

Common causes of inflammatory CNVM in India are idiopathic, infectious causes like ocular tuberculosis, and Vogt-Koyanagi-Harada (VKH) syndrome,[2] some other etiologies being multifocal choroiditis, punctate inner choroidopathy (PIC), ocular histoplasmosis syndrome, etc.

Inflammatory CNVM is a rare but major vision threatening complication of active or inactive uveitis, with no uniform consensus for the treatment. CNV can occur in the sub-foveal, juxta-foveal or peri-papillary locations, with sub-foveal CNV having the most guarded prognosis[3], while variable outcomes are noted in the other two types.

CNV caused due to inflammatory causes are mostly Type 2 or classic CNV, which occupies the sub-neurosensory compartment between RPE and outer-segments of the retina.[4]

Various treatment modalities for inflammatory CNV are available, however no definitive evidence of superiority of one treatment over another is available due to the lack of randomized control trials. Some approaches currently available include observation, local and systemic corticosteroids, laser photocoagulation, photodynamic therapy (PDT), surgical removal of CNVM & intravitreal anti-vascular endothelial growth factor (Anti-VEGF) injection.

Over a five-year follow-up duration, Macular Photocoagulation Study showed that post laser therapy for CNVMs, there may be an enlargement of laser scar with subsequent involvement of the fovea, which necessitated other modalities like PDT, surgical excision, etc.[5] In submacular surgery trial research group, CNV recurred in 58% of surgically treated eyes, and 4% developed RD.[6]

Vascular endothelial growth factor (VEGF) is a cytokine, participating in multiple inflammatory processes. In uveitis, VEGF levels are increased in the vitreous and thus intravitreal VEGF inhibitors have been used for treating inflammatory CNV.

2. HISTORICAL PERSPECTIVE

Natural history

Brown et al reported 30% of patients having multifocal choroiditis and 40% having punctate inner choroidopathy to have CNVM over a course of 3 years. The eventual visual acuity in all subjects was less than or equal to 20/200.[7]

In a study done by Kleiner et al in patients with presumed ocular histoplasmosis (POHS), three fourth of the eyes with CNVM had a visual acuity to a level of 20/100.[8]

There is an increasing knowledge about the immunopathogenesis of CNVM, via animal models and experimental work, but still single effective treatment isn't available.

The following modalities have been used for treating inflammatory CNVMs till now:

a. LASERS

Immediate central visual loss occurs in sub-foveal CNVM after thermal laser photocoagulation. Macular photocoagulation study at 3 and 5 year follow-up showed improvement of visual acuity for cases of juxta-foveal CNVM in POHS, but nearly 8% of treated eyes had a vision drop of greater than or equal to 6 lines.[5]

Thermal photocoagulation is associated with enlargement of scars leading to scotomas and persistent and recurrent CNVM in about one-third of the cases.

b. SURGERY

Gass classified CNVM as Type 1 and Type 2. Inflammatory CNVM is mostly Type 2 where blood vessels grow beneath the sensory retina; thus surgery for this type of CNVM preserves the underlying RPE and choriocapillaris.

Even with initial success of submacular surgery with CNVM extraction, a high rate of recurrence of subfoveal CNVM postoperatively was seen. Macular translocation surgery has also been tried for inflammatory CNVM, however, there is inadequate information regarding prognosis.

c. CORTICOSTEROIDS

Use of corticosteroids for inflammatory CNVM has shown variable results. Stabilization of vision in 83% cases were seen with systemic steroids in 12 eyes with subfoveal CNVM due to MFC or PIC in a study done by Flaxel et al.[9]

In a comparative study between oral prednisolone and subtenon triamcinolone injection in patients with POHS, vision stabilized in 7 patients treated with prednisolone and 5 of the triamcinolone group. However, 72% had a visual acuity of less than 20/200.[10]

d. PHOTODYNAMIC THERAPY

In ocular histoplasmosis study, improvement in visual acuity after PDT was seen in 22 patients with subfoveal CNVM in 24 months. 45% eyes had gain in 7 or more letters while 18% had a loss of 8 or more letters.[11] However, most studies noticed choroidal hypoperfusion and RPE atrophy with collateral damage to surrounding tissue after PDT.

e. COMBINED THERAPY: PDT and CORTICOSTEROIDS

This has been seen to be more effective than PDT alone, success being due to dual mechanism of blocking the pathology of inflammatory CNVM and control of the intraocular inflammation. Complete improvement in vision was reported by Fong et al with combined treatment for CNVM IN PIC cases.[12]

f. ANTI-VEGF AGENTS

In a pro-inflammatory environment, release of VEGF-A due to activation of macrophages stimulated pathological angiogenesis.[13] Total resolution in 100% of the eyes of inflammatory CNVM treated with intravitreal bevacizumab was demonstrated by Adan et al.[14]

3. ANATOMY AND PHYSIOLOGY

The knowledge of the mechanism underlying the pathophysiology of the retinal and choroidal circulations is of fundamental importance for understanding the formation of CNVM.

3.1 RETINAL CIRCULATION

Outer four layers of the retina – pigment epithelium layer, layer of rods and cones, external limiting membrane and outer nuclear layer are supplied by choriocapillaris. These capillaries are branches of short posterior ciliary artery that also supplies the choroid.

Inner six layers of the retina – outer plexiform, inner nuclear layer, inner plexiform, ganglion cell layer, nerve fibre layer, and internal limiting membrane get their supply from the central retinal artery which is a branch of the ophthalmic artery. Fovea is an avascular area and is supplied by the choriocapillaris. Macula gets its supply from superior and inferior temporal branches of the central retinal artery. Arrangement of retinal capillary network in the extra macular area consists of 2 retinal capillary networks are present. The superficial network lies at the nerve fibre layer level, while the deep network lies between the inner nuclear and outer plexiform layer. The deep network is more dense and complex than the superficial network.

Retinal arteries are end arteries and do not anastomose with each other. But there is anastomosis between the retinal vessels and the ciliary system.

Inner blood-retinal barrier

Endothelial cells of the capillaries are closely bound together around the lumen by intracellular junctions known as the zona occludens. These junctions normally prohibit the flow of fluid and solutes from the lumen into the retinal interstitium, thus forming the inner blood-retinal-barrier.

The retinal blood is drained by the central retinal vein that leaves the eye through the optic nerve draining into the cavernous sinus.

3.2. CHOROIDAL STRUCTURE AND CIRCULATION

3.2.1. STRUCTURE

The choroid is a highly vascularised and pigmented layer that constitutes the posterior portion of uvea. The thickness of the choroid has been found to be 100-200 micrometres, with the thickness being greatest below the macula (500-1000 micrometres).

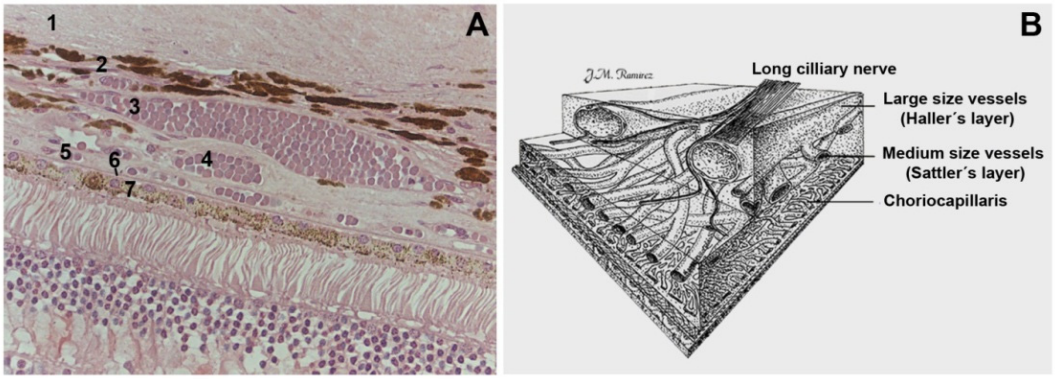

FIGURE 1: A: Histological section. B: Tridemensional scheme 1:Sclera, 2: Suprachoroid: 3:large sized vessel layer(Haller's Layer); 4:Medium sized vessel layer(Sattler Layer); 5: Choriocapillaris; 6: Bruch's membrane; 7: Retinal pigment epithelium

Microscopically it can be divided into four layers:

1) **Suprachoroidal lamina (lamina fusca)**: It is continuous anteriorly with supraciliary lamina of the ciliary body. The space between this layer and the sclera is called the suprachoroidal space which contains the long and short posterior ciliary arteries and nerves.
2) **Stroma of the choroid**: This consists of loose collagen and elastic fibres with plenty of macrophages, mast cells, plasma cells, lymphocytes. The degree of pigmentation observed ophthalmoscopically in the ocular fundus depends on the number of pigmented melanocytes in this layer choroid. While doing photocoagulation, the degree of pigmentation of the choroid must be considered as it influences the absorption of laser energy.
3) The main bulk is formed by vessels arranged in two layers, the outer layer of large vessels (**Haller's layer**) and the inner layer of medium vessels (**Sattler's layer**). The innermost vessels are arterioles which connect with the choriocapillaris. The veins are present in the outermost part next to the suprachoroidal lamina.
4) **Choriocapillaris**: It consists of rich capillary network which receives its blood supply from the medium and large vessels of the stroma. The outer layers of the sensory retina and pigment epithelium get their supply by these. It is formed by lobular

organization of wide capillaries that are well developed at the posterior pole and less regular at the ora serrata anteriorly. 8-16 precapillary arterioles feed the submacular choroid where marked inter-arteriolar anastomosis is present.

The vessels are very thin containing multiple fenestrations especially on the surface facing the retina. Zona occludens is not well developed as in the retinal capillaries and thus small molecules like fluorescein diffuse across the endothelium of the capillaries, while they do not leak through the medium and large choroidal vessels.

5) **Basal lamina (Bruch's membrane or lamina vitrae):** Approximately 2-4 mm in thickness, this is the innermost layer of choroid. It is multi-layered, lying between the choriocapillaris and pigment epithelium of retina. The Bruch's membrane is one of the most significant structures, in the predisposition, development and progression of CNVM. On electron microscope it is described to consist of 5 layers

- **Basement membrane of RPE**: It lies in continuity with the basal lamina of the ciliary epithelium. A 100 micrometer wide zone is what separates it from the RPE.
- **Inner layer of collagen**: It is 1 micrometer thick formed of interweaving collagen fibres.

- **Middle layer of elastic fibres sandwiched between collagen layers**: This is composed of dense cortex and homogenous core of interwoven band of elastic fibres.
- **Outer layer of collagen**: Its structure is similar to the inner zone
- **Basement membrane of choriocapillaris**: It is a discontinuous sheet of collagen across the Bruch's membrane.

3.2.2. BLOOD SUPPLY

The choroid is supplied by the long and short posterior ciliary artery along with the perforating anterior ciliary artery. Venous drainage is through the vortex veins. Blood flow to the choroid is higher than other tissues in the body. Thus the oxygen content in the venous blood is only 2-3% less than that in the arterial blood.

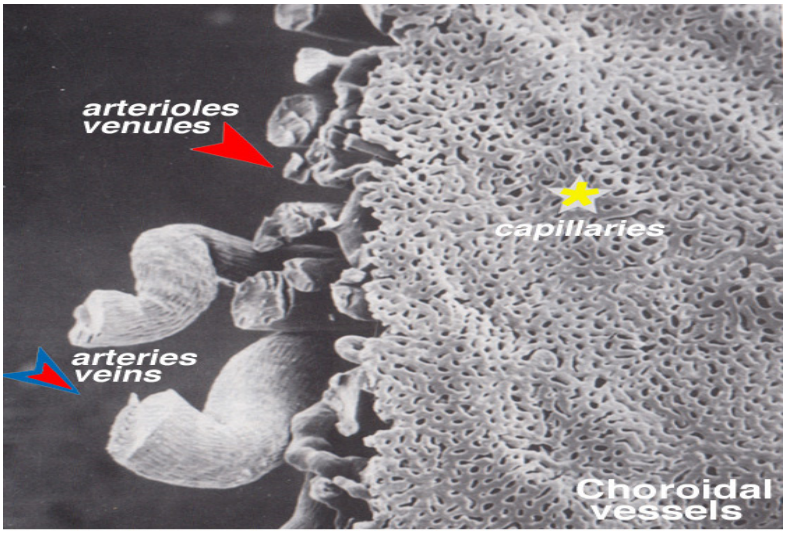

FIGURE:2 The 3 vascular layers in the choroid: outer arteries ans veins (red/blue arrow), medial arterioles and venules (red arrow) and inner capillary bed (yellow star)

Choroidal watershed zones

"Water-shed" zone is the border between the areas of distribution of any 2 end arteries. Choroidal vasculature has many such watershed zones, which are arranged as follows:

- Between posterior ciliary arteries
- Between short posterior ciliary artery
- Between the long and short posterior ciliary artery
- Between the posterior ciliary artery and anterior ciliary artery
- Between the choriocapillary nodules
- Between the vortex veins

The close proximity of the choroidal watershed zone to the peripapillary area and macula may indicate towards the possible role of choroidal blood flow changes in pathogenesis of macular ischemic lesions and ischemic optic neuropathy.

CNVM is characterized by the neovascular proliferation of the choriocapillaris which extends through the defects in the Bruch's membrane and invades the sub-pigment epithelial space. Histological reports suggest the presence of associated diffuse thickening of the inner aspect of Bruch's membrane, which predisposes the Bruch's membrane to

develop cracks through which the choriocapillaris can invade and proliferate.

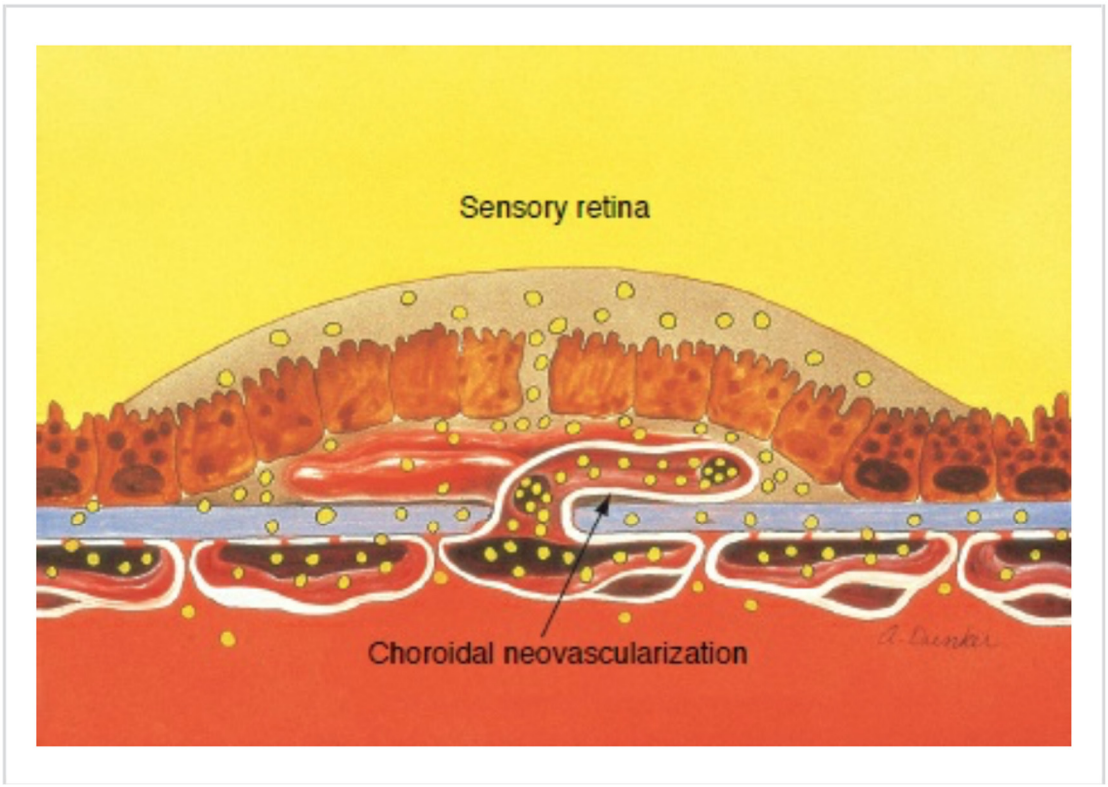

FIGURE 3: Schematic diagram of choroidal neovascularization originating from the choriocapillaris, breaking through the Bruch membrane, and proliferating in the sub pigment epithelial space.

4. AETIOLOGY OF CNVM

It is a common manifestation associated with multiple diseases affecting the posterior segment. Most common location of CNVM formation is the macular area, although it can occur in other areas of the posterior segment. Any disease disrupting the RPE and Bruch's membrane can result in choroidal neovascular membrane formation.

Some common conditions associated with CNVM are:

a. DEGENERATIVE

Age- related macular degeneration

Myopic degeneration

Angiod streaks

b. HEREDODEGENERATIVE

Vitelliform macular dystrophy

Fundus flavimaculatus

Optic nerve head drusen

c. INFLAMMATORY

Tuberculosis

Vogt-Koyanagi-Harada syndrome

Ocular histoplasmosis syndrome

Multifocal choroiditis

Serpiginous-like choroiditis

Toxoplasmosis

Toxocariasis

Rubella

Bechet disease

Sympathetic Ophthalmia

d. TUMOR

Choroidal nevus

Choroidal haemangioma

Metastatic choroidal tumours

Hamartoma of RPE

e. TRAUMATIC

Choroidal rupture

Intense photocoagulation

f. IDIOPATHIC

A quick overview of the inflammatory causes of CNVM are as follows:

OCULAR TUBERCULOSIS

It can manifest as either active infection or an immunologica; reaction to the organism. Primary ocular TB is where the eye is the primary portal of entry. Manifestation is mainly in the conjunctiva, cornea and sclera. Secondary ocular TB occurs by haematogenous or contiguous spread and uveitis is the most common manifestation. TB uveitis is

classically a granulomatous disease that affects the anterior and posterior segments. Signs include mutton fat keratic precipitates, iris nodules, posterior synechiae and secondary glaucoma. A waxing and waning course with accumulation of vitreous opacities and cystoid macular edema is seen. Posterior segment findings include disseminated choroiditis characterised by multiple, deep, discrete yellowish lesions which are located in the posterior pole, and associated with disc oedema, nerve fibre layer haemorrhages and vitritis. Alternatively, they can present as large focal elevated choroidal mass (Tuberculoma) and associated with neurosensory retinal detachment and macular star formation.

SERPIGINOUS CHOROIDITIS

It is a rare, progressive, chronic, recurrent inflammation of retinal pigment epithelium, choroid and choriocapillars of unknown etiology. It usually is bilateral, with asymmetric presentation as initially unilateral decrease in central vision, metamorphopsia or scotoma. This disease can be classified into: 1) peripapillary, 2) macular 3) ambiginous. Visual acuity depends on the involvement of fovea or para-fovea by lesions of secondary CNVM. On histology, atrophy of choriocapillaris, RPE and photoreceptor cells with moderate diffuse lymphocytic infiltrates all through the choroid are seen.

OCULAR HISTOPLASMOSIS

It is an infection caused by the yeast form of a fungus, *Histoplasma capsulatum*. The visual symptoms occur many years after the initial infection. It is also known as presumed ocular histoplasmosis syndrome (POHS) due to its causal relationship between the eye and the fungus. Findings show punched out small atrophic patches mostly in the posterior pole and mid-periphery. Linear peripheral atrophic tracks and chorioretinal scarring in the juxtapapillary region are seen which can be associated with CNV at the macula. 60% of the patients can have a bilateral presentation. Symptoms usually develop after the formation of CNV.

MULTIFOCAL CHOROIDITIS

It is an idiopathic inflammatory disorder. Presentation of this disease is bilaterally asymmetrical and more common in young women with myopia. Common symptoms include floaters, photopsia and enlargement of blind spot. On examination, multiple punched out, old atrophic lesions in the peripapillary, midperipheral and anterior equatorial region are seen as white-yellow (50-200 microns) dots, with vitreous inflammation and recurrent bouts of inflammation around the scars. The lesions are larger and more pigmented than PIC, and subretinal fibrosis and RPE clumping occurs more commonly than OHS. Complications include CME, epiretinal membrane (ERM), CNVM and cataract.

PUNCTATE INNER CHOROIDITIS

It occurs in healthy, white, young myopic women with presentation of metamorphopsia, paracentral scotoma and photopsia. Lesions seen are smaller (100-200 microns) compared to MCP and rarely extend to the mid-periphery and are never associated with vitreous inflammation. Recurrence around the lesions is rare. Complications like CME, ERM and cataract are uncommon with the exception of CNVM which may be more frequent than in MCP.

SARCOIDOSIS

It is a multisystem, granulomatous disorder of unknown etiology. 50% patients with systemic disease can have ocular involvement. Usually onset occurs between ages 20 and 50 years, but can also occur in older patients. It can affect any ocular tissue, including the adnexa and orbit. This may present as anterior uveitis, seen in the form of granulomatous mutton fat KPs, with Koeppe and Busacca iris nodules, posterior synechiae. This may also be associated with iris bombe and secondary angle closure. Snowballs (white clumps of cells in the anterior vitreous) or linear strands of vitreous cells called “string of pearls” can be seen. Posterior segment lesions are seen in 20% of cases as nodular granulomas along venules called “candle wax dripping”. Perivascular sheathing can also be seen. Clinically diagnosis is done using computed axial tomography of the chest

documenting hilar lymphadenopathy and characteristic pulmonary lesions. Increased serum calcium and ACE levels may also be indicative of the disease, but ultimately confirmatory diagnosis is reached with histological evaluation of biopsy tissue.

SYMPATHETIC OPHTHALMIA

It is a rare, asymmetric, bilateral, diffuse granulomatous non-necrotizing panuveitis that occurs after trauma or surgery to the fellow eye. Presentation is more severe in the exciting eye, at least initially. Both eyes on examination can have mutton fat KPs, posterior synechiae, thickening of iris from lymphocytic infiltration, and either elevated IOP or hypotony. Posterior segment findings include, mid-equatorial choroidal lesions called DALEN FUCHS nodules which are histopathologic findings of clusters of epitheloid cells located between Bruchs and RPE layer. These nodules are not specific to sympathetic ophthalmia and are present in one-third of the patients. The course of sympathetic ophthalmia is chronic with recurrent exacerbations and if left untreated it can lead to loss of vision or even phthisis bulbi. Structural complications include cataract, chronic CME, optic atrophy and peripapillary and macular CNV.

VOGT-KOYANAGI-HARADA SYNDROME

It is a presumed autoimmune, multisystemic disease, characterized by diffuse, chronic, bilateral granulomatous panuveitis associated with

auditory, neurologic and integumentary involvement. It is presumed that T-cell mediated autoimmune process against self-antigens associated with melanocytes is the pathophysiology behind this condition.

There are 4 stages of VKC syndrome 1) Prodromal, 2) Acute uveitic 3) Convalescent and 4) Chronic recurrent.

1) **Prodromal stage**: has flu like symptoms, focal neurological signs, tinnitus, meningismus etc.

2) **Acute uveitic stage**: diffuse bilateral non-necrotizing granulomatous anterior uveitis, with some vitritis, thickening of choroid, serous retinal detachment and hyperemia of disc is seen. Profound vision loss can occur in this phase.

3) **Convalescent stage**: this stage occurs after many weeks of acute disease with resolution of the exudative retinal detachment, the choroid gets depigmented gradually which results in an orange red discolouration – sunset glow fundus.

4) **Chronic recurrent stage**: repeated episodes of granulomatous anterior uveitis occur with KPs, posterior synechiae, iris nodules, iris depigmentation, etc. Sequelae such as posterior subcapsular cataract, glaucoma, CNV and subretinal fibrosis develop in this stage.

TOXOPLASMOSIS

It is the most common infectious cause of posterior uveitis both in adults and children, caused by toxoplasma gondii a single cell intracellular parasite. Infection can spread through infected food or water, transplacental route or through blood and organ transplantations. Congenital toxoplasmosis presents as Sabins tetrad of retinochoroiditis, intracranial calcifications, hydrocephalus or microcephaly and cognitive impairment. Acquired toxoplasmosis presents with blurred vision or floaters. Mild to moderate granulomatous anterior uveitis may be present, but classical presentation appears as focal retinochoroiditis with overlying moderate vitreous inflammation (“headlight in the fog”) which is often near a pigmented retinochoroidal scar. Kyrieleis arteriolitis is perivasculitis with diffuse venous sheathing and segmental arterial plaques seen in the vicinity of active lesion. It is a progressive and recurrent disease, with new lesions occurring at the margin of old scars. Complications include cataract, persistent vitreous opacities, CME, retinal detachment, epiretinal membranes, optic atrophy and CNV.

5. PATHOGENESIS OF CNVM

CNV appears as a neovascular sprout growing under or through the RPE through breaks in Bruch's membrane. Usually this occurs in association with evidence of fibroblasts, myofibroblasts, lymphocytes, and macrophages. Various growth factors are suspected to be involved in the development of CNV, such as vascular endothelial growth factor (VEGF).

The development of CNVM can result from either an inflammatory angiogenic drive or due to degenerative disruption in the Bruch's membrane- retinal pigment epithelium (RPE) complex. Following penetration of the inner aspect of Bruch's membrane, the new vessels proliferate laterally between the RPE and Bruch's membrane. As these neovascular twigs mature, they develop a more organized vascular system stemming from a trunk of feeder vessels off the choroid, as well as proliferation of fibrous tissue. The endothelial cells in the arborizing neovascular tufts lack the barrier function of more mature endothelial cells. Hence these new vessels can leak fluid (and fluorescein) in the neurosensory, subsensory, and RPE layers of the retina. Proteins and lipids may accompany this process and precipitate in any layer of the retina. In addition, the fragile vessels are prone to hemorrhage.

Ultimately, a fibrovascular scar results, usually causing disruption and death of the overlying sensory retinal tissue accompanied by severe visual loss.

The precise cellular process that results in abnormal vessel growth has not been elicited completely. Most likely, several diverse factors like myeloid cell (microglial) activation, VEGF, cytokine and chemokine production and complement activation must be present and together contribute to the development of CNVM.

- **Role of inflammation**

Recent studies have shown inflammation is pivotal in the pathogenesis of AMD[15]. Drusens found in AMD contain complement regulators, immunoglobulins, antigen presenting cells and macrophages.[16] Studies have compounded the possibility of systemic immune along with local ocular dysregulation, where there was elevated C- reactive protein (CRP) levels in patients with polypoidal vasculopathy and neovascular ARMD.[17]

Also in neovascular ARMD eyes higher levels of serum elastin derived peptides were found which degrades the elastin component of the extracellular matrix.[18]

Such features are similar to cases of inflammatory CNVM thus leading to the inference that leucocytes and chronic chorioretinal inflammation are critical for the formation of CNVM. Furthermore, very good evidence that supports the role of innate inflammation is the deposition of complement and immunoglobulin G (IgG) in RPE and choroid in patients with AMD.

- **Role of complement**

Complement system in constantly active at low levels in the normal eye to promote elimination of the potential pathogens without damaging the healthy tissue. Dysregulation of the complement pathways causes overactive complement activity thus causing immune mediated ocular damage. Complement dysregulation has been characterized in experimental autoimmune anterior uveitis, in which the specimens contained deposits of immune complexes such as IgG and complement 3 (C3), as well as tumour necrosis factor alpha and interleukin 1. Complement factor H (CFH) is a very important inhibitor of the complement pathway. Two pathways, the classical complement pathway which is initiated by the antigen antibody complexes and surface bound CRP, and alternative pathway activated by surface bound C3, converge at the point in which C3 is cleaved into C3a and C3b by the C3 convertase. This results in the formation of membrane attack complex by the C5

convertase. The CFH binds to C3b and acts as a cofactor to proteolyse C3b, thus causing inactivation of C3b molecule. Associations between lowered CFH and AMD emphasises the support for inflammatory pathogenesis of AMD. Thus, by triggering the complement cascade in a genetically predisposed individual, lowered CFH levels can increase the chances of development of AMD.

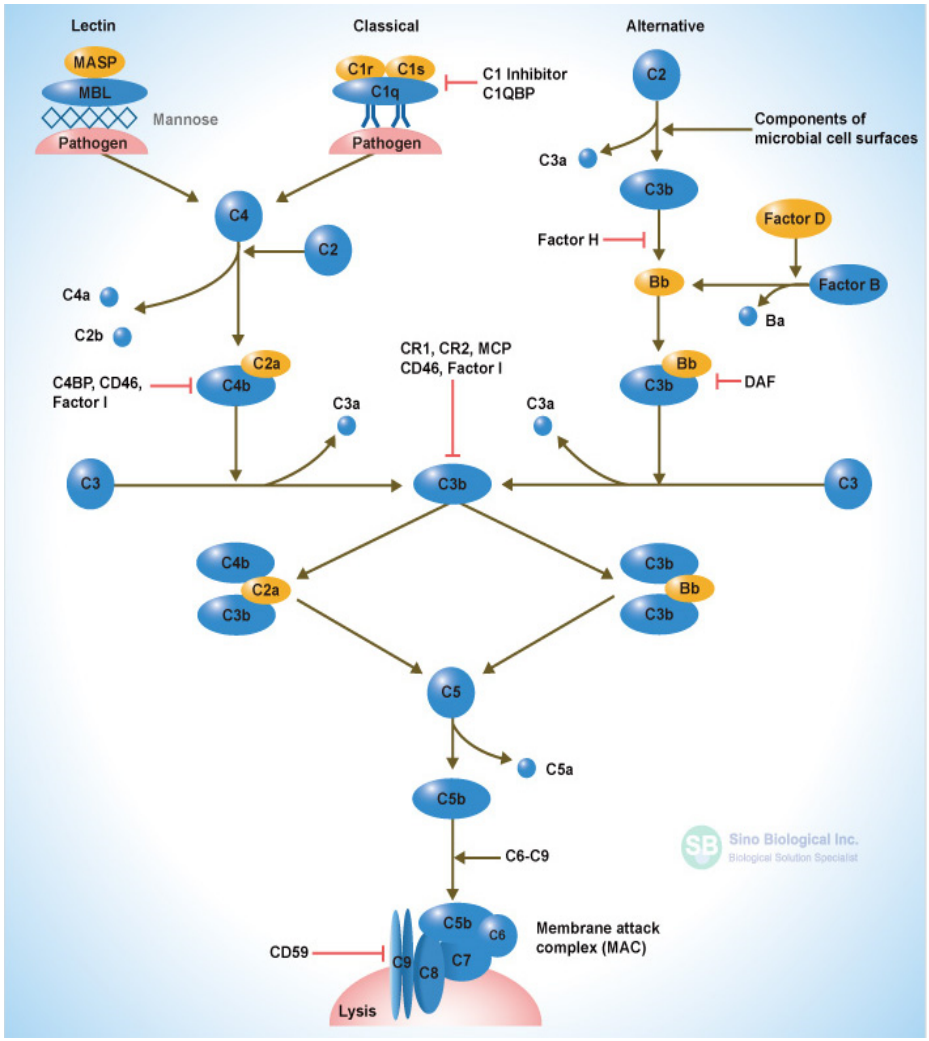

FIGURE:4 Diagrammatic representation of complement pathways

- **Role of macrophages**

Macrophages play an important role in granulomatous uveitis like VKH, sympathetic ophthalmia and sarcoidosis. Myeloid cell-mediated destruction of the retina is dependent on the integrity of the homeostatic mechanisms within the tissue to suppress T-cell activation and the cytokine response. CD200 provides down-regulatory signals to myeloid-derived cells and thus controls the activation of the myeloid cells. In the normal retina there is extensive expression of CD200. In mice that lack CD200, increased susceptibility to accelerated onset of tissue specific autoimmunity is seen.[19] Secondly pro-inflammatory cytokines (IL-1, IL-2, TNF- α) and chemokines are produced by the macrophages that are detected in uveitic eyes.[20] In histological specimens of patients with AMD, macrophages and multinucleate giant cells have been demonstrated in the regions of Retinal Pigment Epithelium (RPE) atrophy, breakdown of Bruch's membrane and CNVM.[21] Although many studies have elicited many mechanisms by which macrophages may have a role in the pathogenesis of CNVM, it still is unclear whether the macrophages accumulate near the CNVM because they play a causative role or because they serve as an adaptive response against the CNVM- associated pathology.

- **Role of Microglia (MG)**

In experimental autoimmune uveoretinitis (EAU), microglial migration and activation at the site of photoreceptors leading to generation of TNF-α before the infiltration of macrophages suggested that microglia might have a role in initiation of EAU.[22] Another theory shows that microglia migrate to the site of injury as a regulator and do not evoke inflammatory damage or act to suppress the excessive inflammation and tissue damage.

- **Role of growth factors**

Pigment epithelial derived growth factor (PEDF) appears to suppress the neovascularization. It is an endogenous molecule which has active effects in inhibiting the complications of neovascular disease of the eye. The vitreous of patients with CNVM is deficient of PEDF. Vascular endothelial growth factor (VEGF) on the other hand stimulates the growth of blood vessels and plays a critical role in the formation and progression of vascularization system, both in physiological and pathological conditions. PEDF as a treatment for AMD is being tested in animal models of CNVM through an adenoviral vector.[23,24]

6. DIAGNOSIS OF CNVM

CNVM can be diagnosed based on the following symptoms, signs and certain investigations:

6.1. SYMPTOMS

Symptoms arise due to subretinal or intraretinal fluid or blood accumulation, or damage to the photoreceptors and retinal pigment epithelium by fibrovascular tissue.

1) Reduction of visual acuity

2) Blurred vision, especially near vision

3) Metamorphopsia

4) Micropsia

5) Scotomas

5) Asymptomatic

Amsler grid can be used to map the distortion or scotomas.

6.2. SIGNS

1) Grey-green coloured elevation of tissue that is deep to the retina and the overlying detached neurosensory retina. The colour is due to hyperplasia of RPE in response to CNV.

2) Subretinal or intraretinal fluid, blood or exudate

3) Neurosensory detachment – can occur due to breakdown of the RPE pump or disruption of the tight junctions between the RPE cells

4) Pigment epithelium detachment (PED) or irregular elevation of RPE

5) Intraretinal blood and cystoid macular edema (CME) may indicate the presence of type 3 neovascularization, which originates from the deep capillary plexus of the retinal circulation.

6) Retinal pigment epithelium tears – more in serous or fibrovascular PED, at junction of attached and detached RPE

7) Disciform scars

8) Breakthrough vitreous haemorrhage

6.3. ANATOMICAL CLASSIFICATION OF CNV

J. D. Gass classified CNV into three types:

a. TYPE 1 CNVM: the new vessels originate from the choriocapillaris and through defects in the Bruch's membrane, growing into the sub-pigment epithelium space. Vascularized serous or fibrovascular PED can develop due to leakage or bleeding.

b. TYPE 2 CNVM: CNV is present in the sub-neurosensory compartment between the RPE and outer segments of the retina. On examination it appears lacy or grey green. Usually inflammatory CNVM is Type 2.

c. TYPE 3 CNVM or Retinal angiomatous proliferans (RAP): New vessels grow downwards towards the RPE from deep capillary plexus of the retina. They appear as small areas of red discolouration, associated with exudates.

6.4. INVESTIGATIONS

6.4.1. OPTICAL COHERENCE TOMOGRAPHY (OCT)

It greatly helps in in-vivo analysis of retinal tissue for the diagnosis and management of retinal disorders and other conditions like glaucoma.

Principle of OCT:[25]

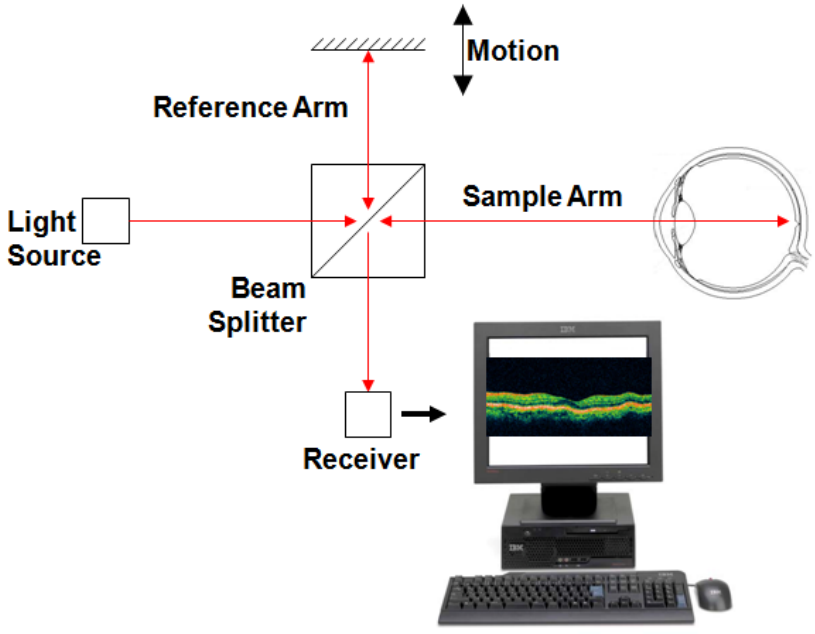

FIGURE 5: Diagrammatic representation of principles of OCT

It is based on interferometry, which is a technique to detect differences between two or more superimposing waves. Interferometery works in such a way that the two waves having same frequency and which

are in phase will add with each other, while two waves that are in opposite phases will subtract.

In OCT, light is directed onto a partially reflecting mirror which splits the beam into a reference and a measurement beam. The measurement beam is reflected from the specimen with different time delays based on the internal microstructure. A variable time delay is produced when light in the reference beam is reflected from a reference mirror at variable distance. A single echo from the reference mirror and multiple echoes from the specimen at a known delay are combined and detected. The detected signal contains information on the position of scatter within the sample, on their polarization, reflectivity, velocity properties. By these collection of depth scans (B scans) from the sample, a 3-dimensional construction of the cross-sectional image (C scan) is possible.

Evolution of OCT

1) Time domain OCT

The reflected beam of light is compared to a beam of light from the moving reference mirror, and the time delay between the 2 beams are measured using a photodetector.

- Scans generated sequentially one pixel at a time of 1.6 seconds
- Moving reference mirror takes images at 400 scans/second

- Resolution -10 micron
- Slower than eye movement.

2) Spectral Domain OCT

A spectrophotometer is used instead of a single detector. The difference in the wavelength between the light from a fixed reference arm and the light returning from the tissue is measured using the spectrometer.

There is no movement of the reference arm in spectral domain OCT, instead the reflected light is analysed using the spectrophotometer. The wavelength of light source used is 840 nm.

The advantage of the technology is high number of scans per second, which is approximately 27,000 A-Scans per second, making true three dimensional imaging possible.

Advantages

- Simple
- Reliable
- Sensitive (resolution of 5 microns)
- Reproducible

3) Swept Source OCT

A LASER source rapidly sweeps across the spectral frequency band. At the beam splitter, the reflected signals from the sample and reference

arm are combined and then directed at the detector after which an axial scan is constructed from the depth resolved spectral interference signals

SD-OCT PATTERNS IN CNV

OCT is a noninvasive procedure and most practical procedure for regular monitoring of the response of therapy by assessing regression of the neovascular membrane and resolution of sub or intraretinal fluid. SD-OCT is the most efficient and reliable test to diagnose and distinguish the different types of CNVM and monitor response to therapy.

TYPE 1 CNVM: PED or elevation of RPE is seen.

- Serous PED are dome shaped, sharply elevated with internal reflectivity and no intraretinal or subretinal fluid.
- Fibrovascular PED shows a lacy or polyp like hyperreflective lesion at the undersurface of RPE with or without signs of contraction.
- Chronic fibrovascular PED has a multi-layered appearance with a fibrovascular scar in the sub-PED compartment, with or without sub or intraretinal fluid.

TYPE 2 CNVM: In the subneurosensory space a hyperreflective plaque or band is seen with sub or intraretinal fluid.

TYPE 3 CNVM: These are best appreciated with SD-OCT as a hyperreflective focus from the deep capillary plexus of the retina, which can be associated with CME or PED.

6.4.2. FLUORESCEIN ANGIOGRAPHIC PATTERNS OF CNVM

Principle

Fluorescein ($C_{20}H_{10}O_5Na_2$) is an orange-red crystalline hydrocarbon which transmits through the vasculature and diffuses rapidly into the tissues when blood tissue barrier is disrupted. Principle is based on the property of certain molecules to emit light of a longer wavelength when stimulated by a shorter wavelength.

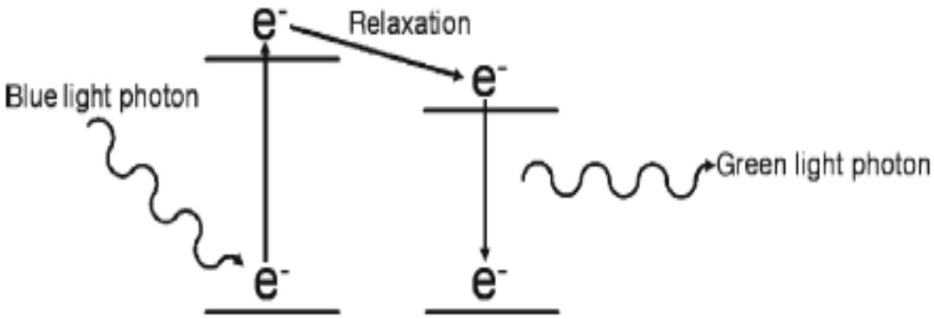

FIGURE 6: Property of fluorescence

Fluorescein fluoresces at 520-530-nm (green) when it is excited by light at 465-490 nm (blue).

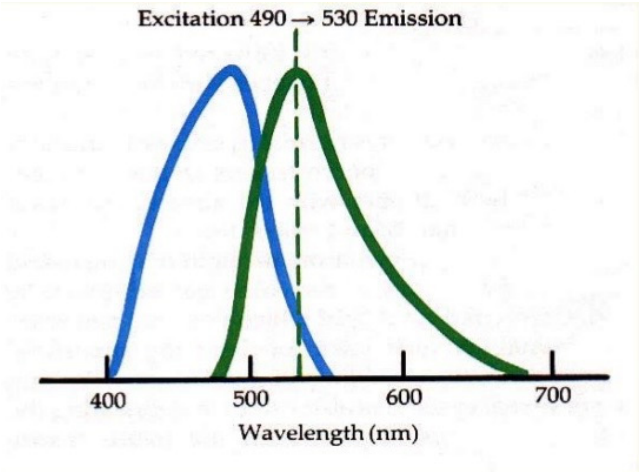

FIGURE 7

The retinal vasculature has dual blood supply; the retinal plexus derived from the central retinal artery supplies the inner retina and the endothelial cell tight junctions form the inner blood–retinal-barrier. Neither unbound nor bound fluorescein can pass through this barrier normally. The outer half of the retina is supplied by the choroidal circulation and the tight junctions of the RPE form the outer blood retina barrier. Unbound fluorescein can pass through the fenestrations of the choriocapillaris but do not pass through the RPE cells normally

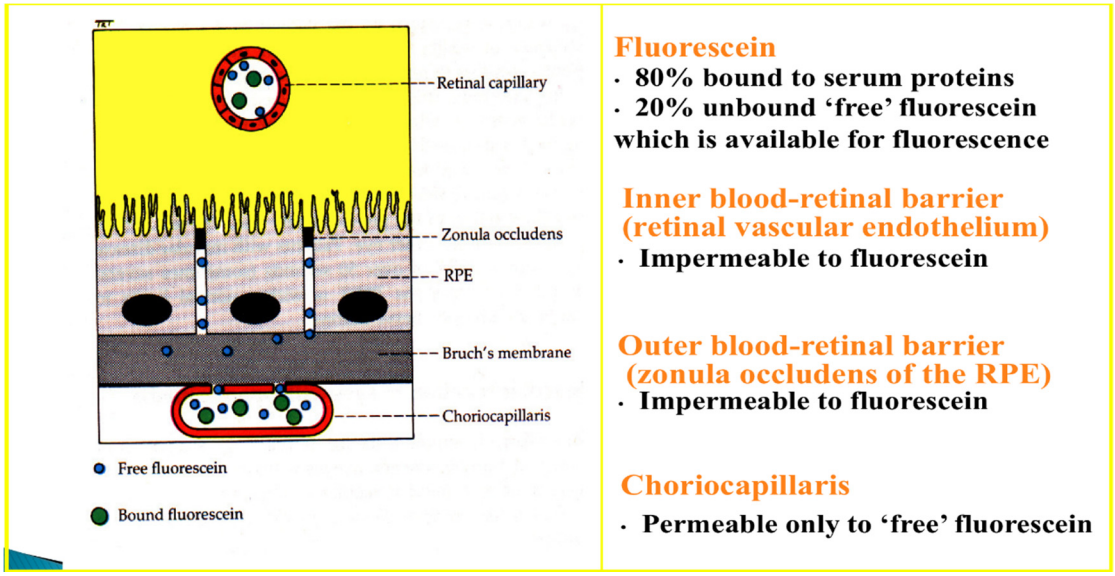

FIGURE 8: Diagramatic representation of fluorescein permeability in the retina and choroid

Technique

Dye is injected into the peripheral vein over 4-6 seconds in a concentration of either 5ml of 10%, 10ml of 5%, or 3ml of 20%. Serial

photographs are taken to document the various phases of arterial and venous filling. For the imaging special excitation and barrier filters are used. White light from the camera is passed through a blue filter; blue light in the retina stimulates the unbound fluorescein to emit a longer green wavelength and the reflected light from the eye is passed through a green filter so that only the green light emitted from the fluorescein is imaged.

Findings

The normal filling times are as follows

TABLE 1: Normal phases of FFA

		Phases of FFA
1	Choroidal phase (Flush)	8-12 sec after dye inj. (up to 20 sec)
2	Retinal Arterial filling	1-2 sec after choroidal phase
3	Venous Lamellar filling	2-3 sec after Arterial filling
4	Full venous circulation	< 11 sec after Arterial filling
5	Recirculation	30-150 sec after Injection
6	Late Phase	3-5 min after injection

Fluorescein leaks out only if there is a damage in the endothelium of the capillaries or when the RPE cells are abnormal.

Abnormalities on FFA can be grouped in 3 categories

- Autofluorescence
- Hypofluorescence
  - vascular filling defect
  - blocked fluorescence
- Hyperflourescence – leakage
  -staining
  - pooling
  - Window defect

Fluorescein angiography helps determine 1) Pattern (classic or occult) 2) Boundaries (well defined or poorly defined) 3) Composition and 4) Location

CNV patterns can be mainly of 2 types 1) Classic CNV 2) Occult CNV

1) **CLASSIC CNV**: It is an area of bright, lacy well– defined hyperflourescence pattern, that is identified in the early phase with progressive leakage, i.e increase in size and intensity in the late phase. Fluorescein may pool in sub-neurosensory retinal fluid overlying the classic CNVM. This angiographic description may be related to Type 2 CNV.

2) **OCCULT CNV**: This type can further be classified into

a) **PED**, which is either vascularized serous PED or fibrovascular PED, which is best seen with stereoscopic FFA views, usually 1-2 min after the dye injection. It shows irregular RPE elevation with stippled leakage. Homogenous ground glass appearance of pooling of dye in a serous PED with a hot spot indicating vascular tissue may be seen. Boundaries may or may not show leakage in late phase as the dye collects within the fibrous tissue or pools in the subretinal space overlying the PED.

b) **Late leakage of undetermined source**

It refers to late choroidal-based leakage where there is no clearly identifiable classic CNV or fibrovascular PED in the early or mid-phase of the angiogram. Boundaries cannot be precisely determined.

Description of occult CNV may be anatomically related to Type 1 CNVM.

CLASSIFICATION OF CNVM BASED ON LOCATION

1) PERIPAPILLARY CNVM

It is defined as a collection of new choroidal vessels, any portion of which lies within 1 disc diameter of the nerve head.

2) JUXTAFOVEAL CNVM

It is defined as well-defined choroidal neovascular lesions located 1-199 μ from the foveal centre.

3) SUBFOVEAL CNVM

It is defined as a choroidal neovascular lesion located under the fovea.

7. TREATMENT

1) LASER PHOTOCOAGULATION (thermal laser): It was the primary treatment especially for classic type extrafoveal CNV with well-defined borders upto the 2000s. Outcomes were poor, with high recurrence rates and hence now they are only used to treat extrafoveal lesions far from the foveal centre.

2) PDT: It was introduced in the 2000s and is less destructive than thermal laser. A photosensitive drug is administrated and light of a particular wavelength is used to incite a photochemical reaction at the affected tissue area. A reactive oxygen species is generated which leads to capillary endothelial cell damage and vessel thrombosis. Studies say progression of CNVM is slowed but significant vision loss cannot be prevented. Nowadays, it is rarely used except for recalcitrant cases or in eyes with polypoidal choroidal vasculopathy (PCV).

3) ANTIANGIOGENIC THERAPIES: New blood vessels formed by sprouting or splitting from the existing vessels is called angiogenesis. A cascade of events occurs, starting with vasodilation and increased vascular permeability of the existing vessels. This is followed by degradation of the extracellular matrix, helping in migration and proliferation of endothelial cells. These cells join together to form a lumen and make a new capillary. This is followed by maturation and remodelling to form a stable vascular

network. This cascade requires interplay of growth promoting factors like, Vascular endothelial growth factor (VEGF), Fibroblast growth factor(FGF), transforming growth factor alpha and beta (TGF-alpha, TGF-beta), angiopoietin-1 and angiopoietin-2, and growth inhibiting factors like pigment epithelium derived factor, thrombospondin etc.

All recent research has been on inhibition of VEGF. There are at least 4 major VEGF isoforms causative in AMD and $VEGF_{165}$ is thought to be dominant.

Pegaptanib, Ranibizumab, Aflibercept and Bevacizumab are the anti-VEGFs used as intravitreal injections so far.

- PEGAPTANIB: binds to human $VEGF_{165}$ with high affinity and specificity, and is a RNA oligonucleotide ligand. It was approved in 2004 but has now been replaced by far more effective agents.
- RANIBIZUMAB: it is a recombinant humanized antibody fragment that binds to VEGF, which binds to all active isoforms of VEGF-A.

FIGURE 9: Representation of Lucentis molecule.

The MARINA study (minimally classic/occult trial of the Anti-VEGF antibody Ranibizumab in the treatment of Neovascular AMD) showed 95% visual acuity improvement or stabilization vs 62% of sham treated patients, approximately 40 % eyes had visual acuity improvement [26]

Another study ANCHOR (Anti-VEGF antibody for treatment of predominantly classic choroidal neovascularization in AMD) 95% of eyes treated with ranibizumab vs 64% of eyes treated with PDT maintained or improved vision at 12 months.[27]

Other studies like PIER and EXCITE had similar results.

Two treatment schemes have been accepted, one being “treat-and-observe” or “treat-and-extend” approaches. The treat-and-observe method gives regular treatment until macula is dry followed by injections only on signs of recurrence during maintenance phase. The treat-and-extend regimen administers injections even after the CNV is inactive, after regular monthly injections till macula is dry treatment continues at gradually increasing intervals. Several clinical trials evaluated the as-needed approaches like PrONTO (Prospective optical coherence tomography imaging of patients with neovascular AMD treated with intraocular ranibizumab), SUSTAIN and SAILOR. All these studies used 3 monthly injections followed by various as-needed regimens based on clinical and

OCT guided criteria and showed outcomes comparable to or reduced from those obtained with MARINA and ANCHOR studies.[28,29,30]

- **AFLIBERCEPT:** also known as VEGF-trap is a soluble protein that acts as a VEGF receptor decoy. It binds to both VEGF and placental-derived growth factor and penetrates all retinal layers.

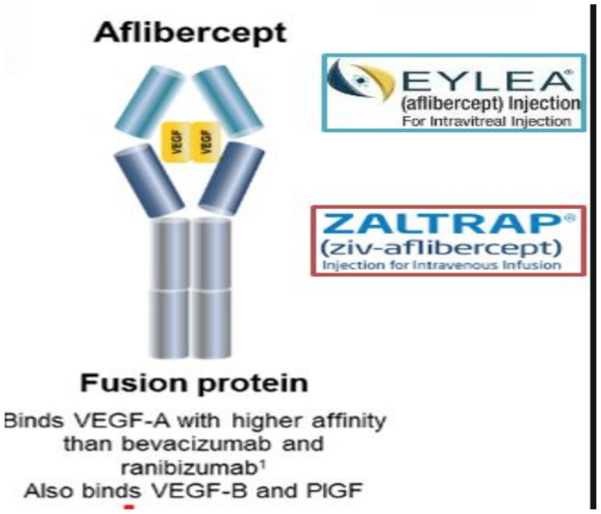

FIGURE 10: Representation of aflibercept molecule

In studies VIEW 1 and 2, aflibercept was compared with ranibizumab injections and results showed non-inferiority compared to the monthly ranibizumab treatment.[31] VIEW 2 indicated that after 3 monthly doses, aflibercept could be administered every 2 months with similar efficacy to ranibizumab administered monthly.

- BEVACIZUMAB: It is a full length monoclonal antibody, which was approved for the treatment of metastatic colon cancer by FDA and is used as an “off label” drug for AMD. It is a larger molecule

with 2 antigen binding domains and has a longer half-life (approximately 21 days) compared to ranibizumab.

FIGURE 11: Representation of bevacizumab molecule

- CATT (comparison of Age Related Macular Degeneration Treatment Trials) was the largest multicentre, randomized clinical trial comparing efficacy and safety of ranibizumab with bevacizumab. The results showed bevacizumab to be non-inferior to ranibizumab therapy over 2 years in monthly or as-needed delivery schedules. [32]

Intravitreal injections are occasionally associated with minor local complications like local irritation and subconjunctival haemorrhage. Severe complications like vitreous haemorrhage, retinal detachment and endophthalmitis are very low. Systemic arteriothrombotic events can occur

with ranibizumab but no study has conclusively proved this. RPE tears can occur post-injection in eyes with fibrovascular PEDs.

4) COMBINED TREATMENT: Trials like DENALI (Safety and efficacy of Verteporfin PDT Administered in Conjunction With Ranibizumab Versus Ranibizumab Monotherapy in Patients With Subfoveal CNV Secondary to AMD) found visual outcomes with combined therapy with PDT were inferior than monotherapy but retreatment rates were reduced[33]. Studies show benefit of combined therapy in cases of PCV recalcitrant to anti-VEGF therapy.

5) SURGICAL TREATMENT: CNV is removed from under the fovea and fovea is moved to healthier RPE –macular translocation surgery, but the visual outcomes were poor and thus abandoned

6) LOW VISION THERAPY: In spite of good results with intravitreal Anti-VEGF, many number of patients can develop central blindness. Newer low visual aids like implantable miniature telescopes have been approved by the FDA. Chances of corneal decompensation and corneal transplant must be considered for the same. [34]

7) REHABILITATION: Any degree of vision loss can have a profound effect on the day-to-day activities of a patient. Quality of life should be improved with the use of optical and non-optical devices like magnification

lenses, enhanced contrast sensitivity and improved lighting. In case of central scotomas due to disciform scarring, training to use eccentric foci shifted out of the central scotoma can be given. Thus prompt referrals to low vision centres must be considered to improve the quality of life of the patients.

8. REVIEW OF LITERATURE

Palmeera et al [2] in a retrospective case series of 15 cases of newly diagnosed inflammatory CNVM assessed the long –term visual and anatomical outcomes after intravitreal anti VEGF injections bevacizumab or ranibizumab. All cases had classic CNVM confirmed on angiography with 8 out of 15 (53.3%) located in the peripapillary area, 4 (26.7%) juxtafoveal and 3 subfoveal (20%).Complete resolution of CNVM was seen with 2.6 ± 1.2 injections per eye with a mean follow-up of 6-48 months. Visual acuity improved from mean of 20/123 (Snellen equivalent) to mean of 20/58, and the central macular thickness at the final visit reduced to mean of 262.1 ± 108.7 microns from a mean thickness of 435.9 ± 190.2 microns. Recurrence was seen in only 4/15 cases which regressed with single injection. Ocular TB (6/15) and idiopathic cases (6/15) were most common causes, followed by Vogt-Koyanagi-Harada syndrome (2/15) and 1 case of toxoplasmosis. In the bevacizumab and ranibizumab groups no statistically significant difference was noticed. In one case with peripapillary CNVM submacular fibrosis extending subfoveally occurred.

Ahmad et al[1] assessed the role of bevacizumab in inflammatory ocular neovascularization in a retrospective, multicentre consecutive case series. 84 eyes out of which 34 were juxtafoveal, 34 subfoveal, 8

peripapillary and 11 had neovascularization of disc or elsewhere. At 3 month follow up with a mean no of injections of 1.3, BCVA improved by 6 lines in 14.2%, 4-6 lines in 16.7%, 1 line in 34.5%, unchanged in 23.8% and worsened in 10.7%. Central macular thickness decreased from 346 to 252 microns, 43.2% had complete regression while 6.8% (5) eyes had no response. The most common causes for CNVM were multifocal choroiditis and punctate inner choroidopathy, 15 eyes each, 13 eyes of ocular histoplasmosis, 10 idiopathic uveitis 5 eyes each for VKH, Serpiginous choroiditis and retinal vasculitis and few cases of ocular TB, toxoplasmosis and sarcoidosis. There was no correlation of visual acuity and CNV size, location or age of patient. Although visual improvement was seen in all disease categories, multifocal choroiditis, punctate inner choroidopathy and VKH showed significant improvement. Only complication was macular haemorrhage in 1 eye.

Alfredo et al [14] retrospectively assessed the effects of intravitreal becacizumab injection as primary treatment in 9 patients with inflammatory CNVM. Regression was seen in 100% cases improvement in visual acuity in 8 eyes (88.8%) and stable in 1 eye (11.2%). One case had recurrence and needed a second injection. A reduction in mean central foveal thickness from 360 microns to 220 microns was seen. 4/9 eyes had

subfoveal CNV, 3 juxtafoveal and 2 extrafoveal CNV. No injection or drug related complication was seen.

Thi ha chau tran et al[38] assessed the safety and short term efficacy of intravitreal bevacizumab injection in 10 patients with refractory CNVM secondary to uveitis unresponsive to immunosuppression with or without PDT. All cases were classic CNVM, 8/10 were subfoveal, while 2 were juxtafoveal. Vision improved from a mean of 20/55 (Snellen equivalent) to 20/40 in one month and was stable in the follow-up period mean of 7.5 months. Central macular thickness reduced to 267 ± 28 at last visit from 326 ± 95 preinjection. Most common etiology 6/10 patients was multifocal choroiditis. Intravitreal injection was the 2nd or 3rd line of management. 7/10 eyes needed 2 or more injections to maintain visual acuity. No intravitreal injection related complication was noted, but 2 eyes with sympathetic ophthalmia and 1 eye with VKH developed submacular fibrosis.

Howard et al[35] in a retrospective study of 6 eyes described the treatment of CNV associated with multifocal choroiditis with intravitreal bevacizumab and /or ranibizumab. An average of 2.3 injections with a mean followup of 41.5 weeks showed visual improvement in 5 eyes improved to 20/30 or better. 1 eye had a subfoveal rip of the retinal pigment epithelium and visual acuity decreased to 20/400. Previous therapies were

subtenon or intravitreal corticosteroids, PDT or thermal laser, 1 patient underwent trabeculectomy for presumed steroid-induced glaucoma post subtenon injection of triamcinolone acetonide.

Gaurav et al[36] evaluated the role of anti-VEGF in treatment of CNVM secondary to ocular toxoplasmosis in a 13 year old female. Examination showed visual acuity of 6/15 and N10 with juxtafoveal scarred toxoplasmosis lesion with subretinal haemorrhage and fluid at the foveal edge of the scar suggestive of CNVM. 1 month post injection, the visual acuity improved with OCT showing regressing CNVM; FFA showed active leak hence 2nd injection was given. Final visual acuity was 6/9, N6 with scarred CNVM adjacent to the toxoplasma scar with no signs of activity up to last follow up at 10 months.

Ahmad et al [40] assessed the long term role of bevacizumab in inflammatory ocular neovascularization with follow up every 6 months upto 2 years post injection. It was a multicentric consecutive case series of 99 eyes. Long term mean visual acuity improved to > 2.2 lines with significant foveal flattening to 77 microns at 2 years.No injection related complication was noted, but 5 bevacizumab drug related complications were seen: 1 case of mild ocular hypertension, 1 macular haemorrhage immediately after the injection for juxta foveal CNVM, 4 eyes of submacular fibrosis, 1 of which had pre-existing submacular fibrosis which

increased following intravitreal injection. All 4 cases had no regression of CNV after intravitreal injection.

Shree Kurup et al[37] described 2 patients with posterior uveitis complicated by neovascularization who were treated with intravitreal bevacizumab and efficacy was noted. 1st patient had ocular sarcoidosis and developed peripapillary CNV with visual acuity of hand movements. Intravitreal bevacizumab was given and patient was also treated with oral corticosteroids and methotrexate; visual acuity improved to 20/40 over 2 months with resolution of subretinal fluid and intraretinal haemorrhage. The other patient with lupus underwent PRP with intravenous methylprednisolone and oral cyclophosphamide, still eventually developed NVE and vitreous haemorrhage and was treated with intravitreal bevacizumab which regressed and no recurrence of bleeding was seen at 3 months follow up.

Reema et al[39] evaluated the diagnostic challenges in cases with inflammatory CNVM. A retrospective analysis of 73 eyes with CNVM was done where 12 eyes had a delayed diagnosis CNVM. Most common causes included Vogt-Koyanagi- Harada disease (n-5, 35.7%), tubercular uveitis (n=5, 35.7%), idiopathic (n=3, 21.4%) and sympathetic ophthalmia (n=1, 7.1%). The mean delay in diagnosing CNVM was 9.8 ± 7.98 months. Treatment comprised of intravitreal bevacizumab (n=57) eye, oral

corticosteroids in 7 eyes, observation in 8 eyes and transpupillary thermoplasty in 1 eye. In groups 1 and 2 (with timely diagnosis of CNVM) the BCVA improved in 33.9% eyes by >0.3 logMAR units as compared to improvement of 7.1% eyes in group 3 (delayed diagnosis). A significant visual deterioration was seen in 5 cases from Group 3 as the CNVM was undetected and continued to progress.

PART-II

1. OBJECTIVES

- **PRIMARY**

To analyse the incidence of inflammatory choroidal neovascular membrane and measure the visual and anatomical outcomes post intravitreal anti-VEGF injections in the treatment of patients with inflammatory CNV.

- **SECONDARY**

2. To analyse the outcomes of various treatment modalities that are cost effective for the patient
3. To assess the outcomes of Anti-VEGF injections among different locations of inflammatory CNV

2. METHODOLOGY

2.1. STUDY DESIGN

-This was a tertiary care centre-based prospective, non-randomized, observational clinical study

2.2. PLACE OF STUDY

-The study was conducted in the Department of Uvea, Aravind Eye Hospital and Post Graduate Institute of Ophthalmology, Madurai, Tamil Nadu.

2.3. STUDY POPULATION

Patients of uveitis with evidence of inflammatory CNV treated with intravitreal anti-VEGF injection

2.4. SAMPLE SIZE

-All patients newly diagnosed with inflammatory CNV and/ or treated with intravitreal anti-VEGF injection coming to the Uvea department during the study period were included.

2.5. DURATION OF THE STUDY

-Recruitment period: 01/01/2018 – 31/12/2018 (1 year)

-Follow up period of 6 months since first visit

2.6. INCLUSION CRITERIA

All cases of uveitis with evidence of inflammatory CNVM undergoing anti-VEGF injection therapy

2.7. EXCLUSION CRITERIA

- Choroidal neovascular membrane due to other causes like

    1) Age related macular degeneration

    2) Pathological myopia

    3) Angioid streak

- Patients denying treatment with anti-VEGF
- Patients not willing to give consent
- Other macular diseases causing loss of vision
- Significant cataract precluding imaging

2.8. BASELINE EXAMINATION

This is a tertiary care centre-based, prospective, observational study. The patients of this study were recruited from the Uvea department, Aravind Eye Hospital, Madurai. Each patient with uveitis who presented to the department were evaluated for the presence of inflammatory CNVM. A detailed history of new patients was taken to help in the diagnoses of uveitis etiology, and detailed history of treatment for past uveitis and new symptoms was taken from chronic uveitis patients that newly developed inflammatory CNVM. The uncorrected (UCVA) and best corrected visual acuities (BCVA) were checked used Snellen chart at 6 meters.

Ocular examination of both eyes consisted of a preliminary examination using slit lamp biomicroscopy. Conjunctiva, episclera, sclera, cornea and pupils were examined. Using the Standardization of Uveitis Nomenclature(SUN) Working Group Grading Scheme, anterior chamber reaction was graded. Intraocular pressure was recorded using Non contact tonometer. After pupillary dilation, lens and fundus examination using a slit lamp biomicroscopy with 90D lens and indirect ophthalmoscope using 20 D lens was done to note the status of vitreous, pars plana, retina, choroid, optic nerve and macula. This was done to evaluate for intermediate and posterior uveitis and the presence of CNVM.

Diagnosis and prognostic evaluation of CNVM was done by Optical Coherence Tomography (OCT). Central macular thickness and presence of intra/ subretinal fluid or haemorrhage was noted for all patients. Fundus Fluorescein Angiography (FFA) being an invasive procedure was done only in doubtful cases.

Anatomical Location of inflammation was assigned based in the International Uveitis Study Group (IUSG) criteria. A list of possible etiologies was considered as differential diagnosis and further investigations were done to confirm the diagnosis.

Systemic investigations like total blood cell count, differential count, ESR, CRP, Mantoux test, CT scan of chest and abdomen ere done to help diagnose the etiology of uveitis based on suspicion of symptoms and signs.

2.9. TREATMENT PROTOCOL

Active uveitic cases were treated with oral and/or topical steroids, immunosuppressant or antibiotics based on the cause of uveitis. While CNVM was treated with intravitreal Anti-VEGF injections, either ranibizumab or bevacizumab, based on patient choice. Before injection, informed consent was taken and patient identity, eye and medication were confirmed. Pupil was dilated and topical anaesthetic drops were instilled.

10% povidone iodine was used to clean the skin and periocular area, while 5% povidone iodine drops were instilled in the conjunctival cul-de-sac. Sterile drape was placed and lid speculum used to isolate eye lashes and keep the eye open. Inferotemporal quadrant was preferred and distances of 3.5 mm or 4 mm posterior to the limbus for pseudophakic and phakic eyes respectively was marked. Valvular entry tract was made with needle directed towards centre of globe, with minimal movements inside the eye. Globe was fixed with swabstick. Needle checked in pupillary area before injecting. Single dose sterile injections were used; 0.05 ml of drug containing 1.25 mg of bevacizumab or 0.5 mg of ranibizumab was instilled. Tamponade was applied to needle track and conjunctiva with sterile cotton tipped applicator as the needle was withdrawn. Indirect ophthalmoscopy was performed to check for retinal tears, RD and perfusion status of central retinal artery.

Follow-up examinations

Every monthly follow-up till 6 months following 1st injection was done for every patient. At each visit, complete ophthalmic examination, visual acuity and OCT were done. Based on OCT findings, CNVM was graded as regressing, resolved or recurrent, and accordingly decision of observation or repeat injection was taken. Recurrence was defined as repeat activity of CNVM on OCT in the form of reappearance of subretinal or

intraretinal fluid after initial complete resolution following treatment.

2.10. OUTCOME ASSESMENT

The treatment outcome was assessed based on visual acuity, central macular thickness and regression of subretinal fluid/ haemorrhage on OCT. Data of 1, 3, & 6 months follow-up for the above outcome measures was evaluated for statistical analysis.

2.11. STATISTICAL METHODS

All the statistical analysis was done using statistical software STATA Ver. 14.1 (Texas, USA). Demographic variables were described using frequencies (percentage) or mean +/- standard deviation. Categorical variables were compared using the chi square test for parametric data or Fisher's exact test for non-parametric data. Pre- and post-injection changes in quantitative variables were compared using the paired t test for parametric data and Freidman's test for non-parametric data. A 2-tailed p value < 0.05 was considered as statistically significant.

CLINICAL PICTURES

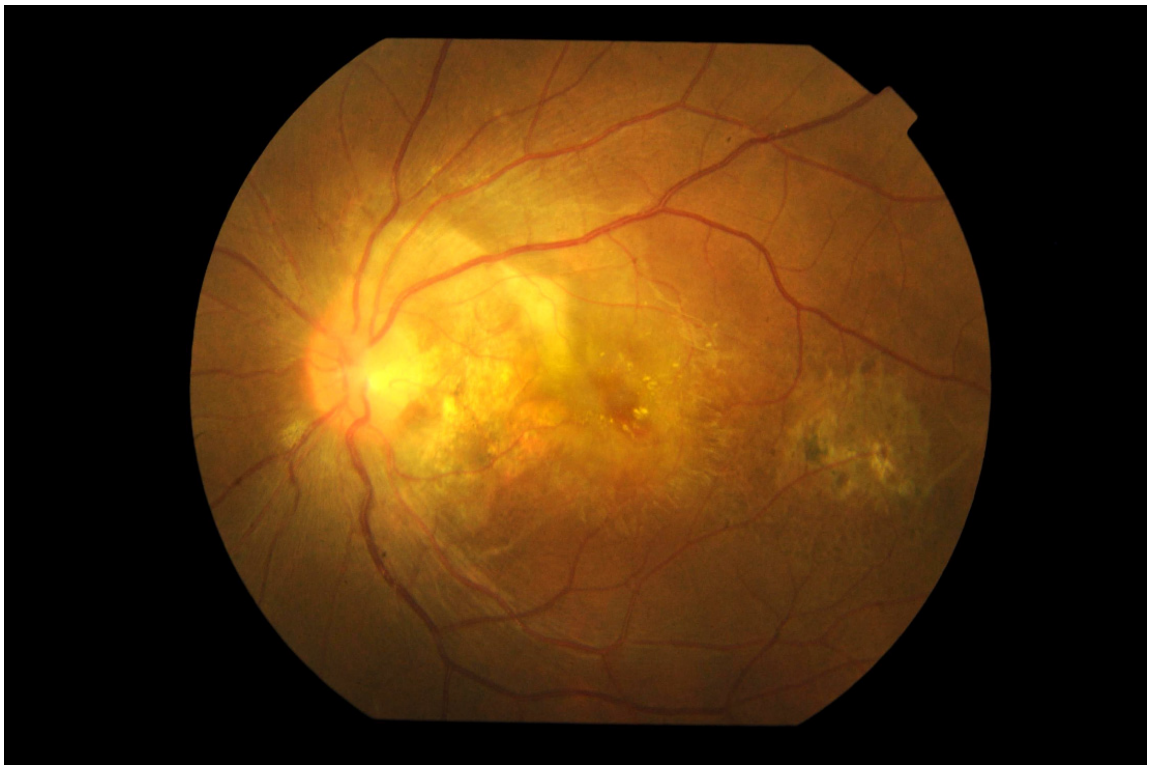

FIGURE 1: Fundus photo of case number 2 showing peripapillay CNVM with healed choroiditis scar temporal to macula.

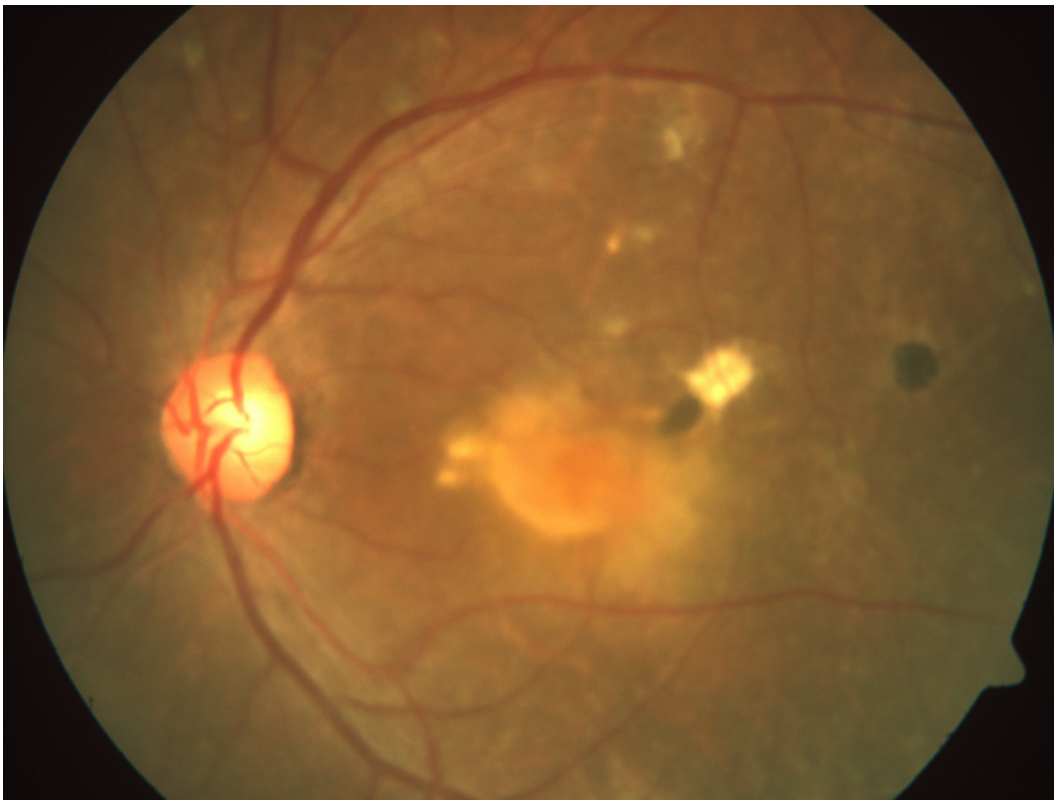

FIGURE 2: Fundus photo of case number 7 showing subfoveal CNVM with pigmented scarring and satellite lesion temporally suggestive of healed toxoplasmosis retinochoroiditis lesion

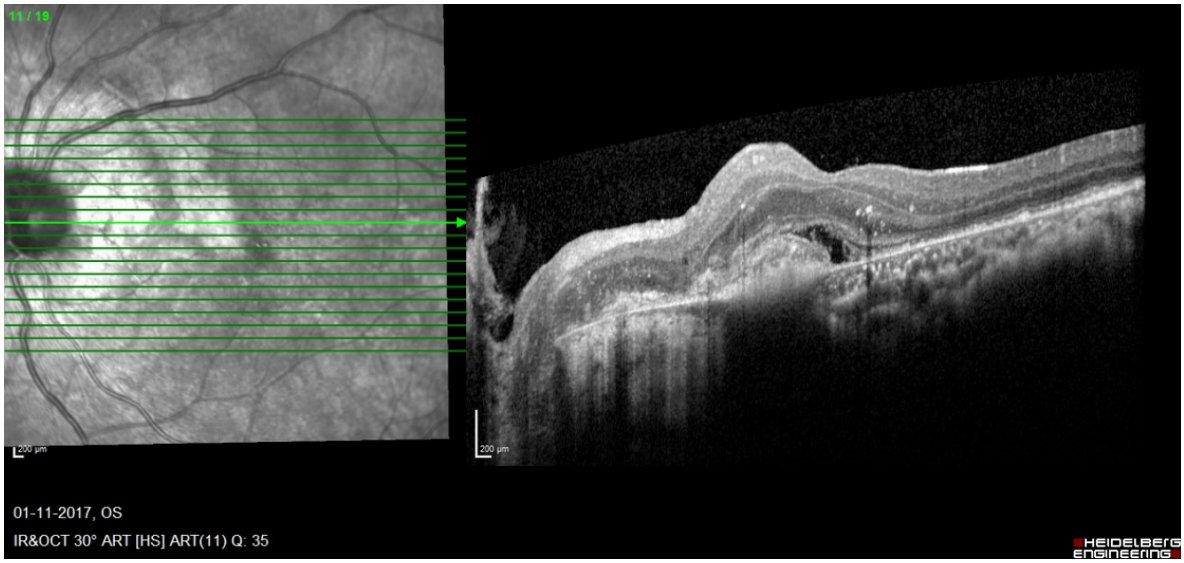

FIGURE 3: Baseline OCT showing break in the Bruch's membrane with peripapillary hyperreflective lesion with hyporeflective subretinal fluid in the outer layers of retina and increased retinal thickness.

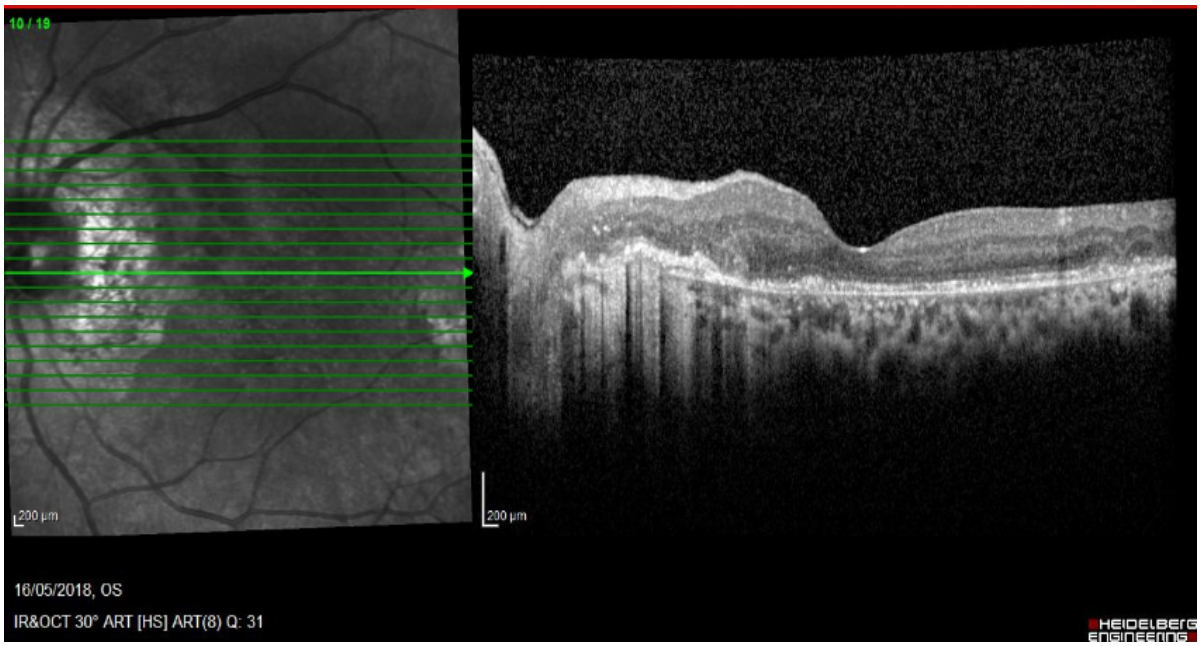

FIGURE 4: Final OCT at 6 months follow-up showing complete resolution of subretinal fluid in the outer layers of retina suggestion of resolution of CNVM.

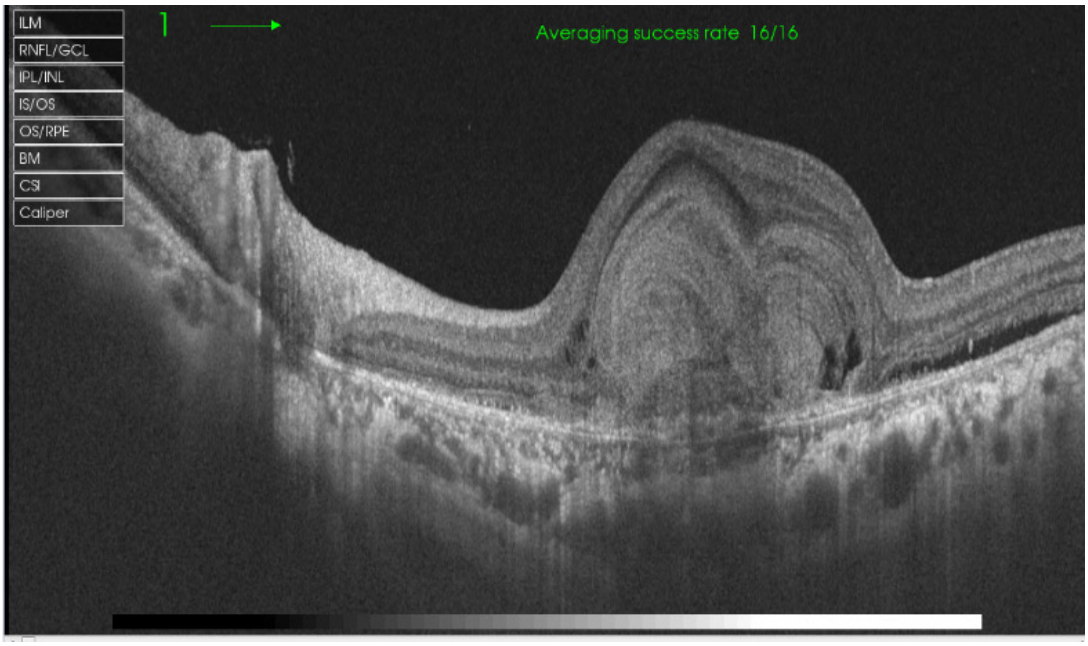

FIGURE 5: OCT showing increase in retinal thickness with elevated foveal contour, subfoveal hyperreflective lesions suggestive of scarring and hyporeflective spaces suggestive of subretinal fluid

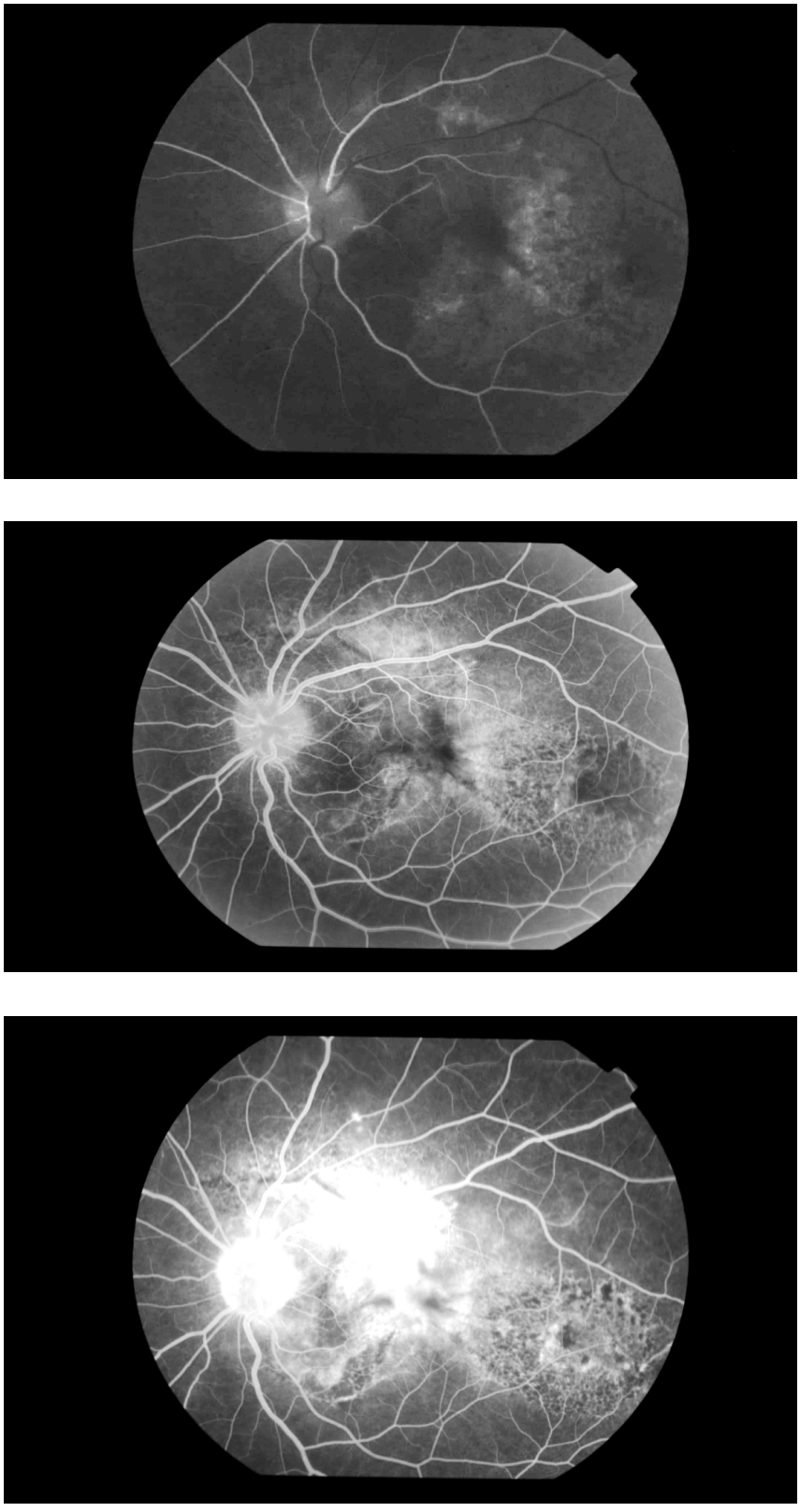

FIGURE 6: Sequential FFA photographs showing hyperfluorescent lacy pattern in early phase that are increasing in size and intensity in late stages, with disc leakage

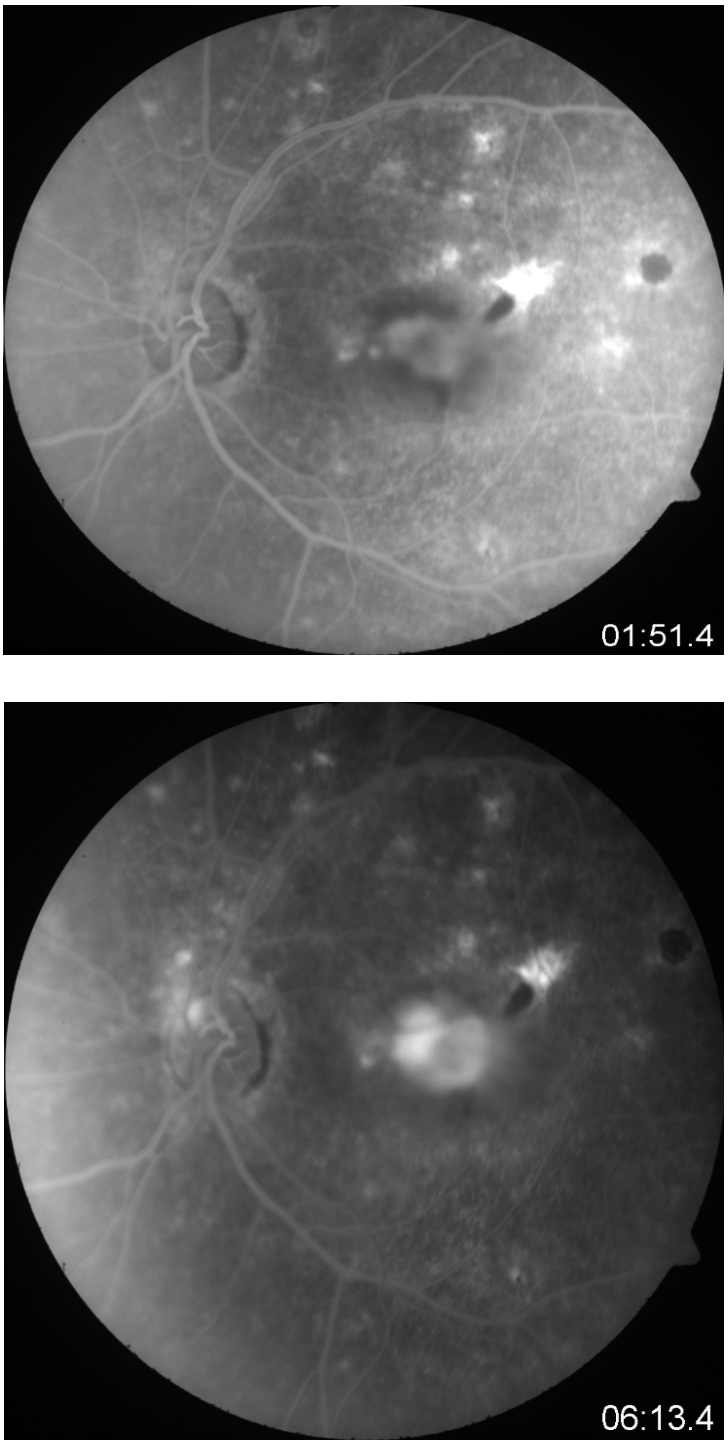

FIGURE 7: Sequential FFA photographs showing hyperfluorescent lesions increasing in size and intensity in late phase

3. RESULTS

A total of 2104 patients came to the Uvea department of Aravind Eye Hospital, Madurai from 1st January to 31st December 2018, who were diagnosed as having intermediate, posterior or pan-uveitis. Out of these patients 18 cases were diagnosed to have active inflammatory CNVM and treated with intravitreal anti-VEGF injections. 6 patients were lost to follow-up at the end of 6 months and thus we had 12 patients who completed the expected follow-up duration of the study.

3.1. INCIDENCE OF INFLAMMATORY CNVM

In a span of 1 year (January to December 2018), 2104 New and Old patients with the diagnosis of Intermediate/Posterior/Panuvietis were evaluated in the Uvea department of Aravind Eye Hospital, Madurai. Out of these patients 18 eyes were diagnosed to have Inflammatory CNVM and were treated with Intravitreal Anti- VEGF injections. Thus the incidence of Inflammatory CNVM in our hospital for the year 2018 was 0.85%.

3.2. AGE DISTRIBUTION

The age of patients in the study population ranged from 17 to 58 years with a mean of 40.94 ± 12.84 years.

TABLE 1: Age distribution of cases with inflammatory CNVM

Variable	N	Mean (SD)	Range
Age in years	18	40.94 (12.84)	17 - 58

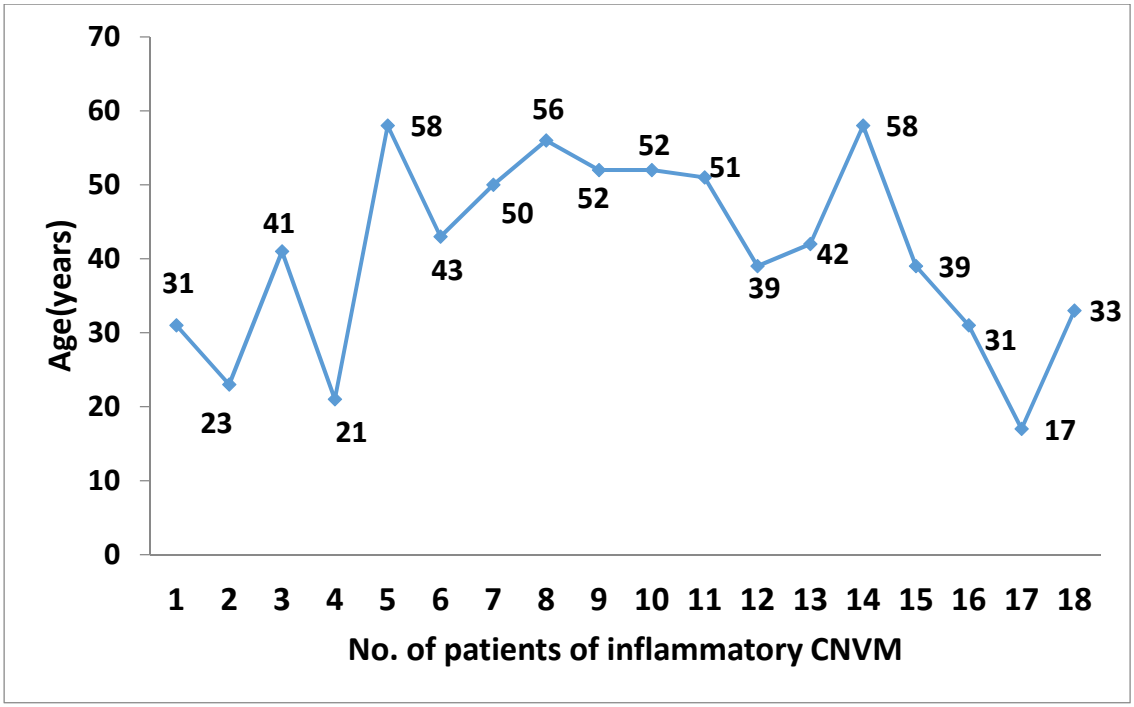

FIGURE 1: Line graph of age distribution.

3.3. GENDER

We found in our study that 12 patients (66.67%) were females and 6 patients (33.33%) were males. Thus there was a female preponderance in our study.

TABLE 2: Gender distribution of cases with inflammatory CNVM

Gender	N (%)
Male	6 (33.33)
Female	12 (66.67)
Total	18 (100)

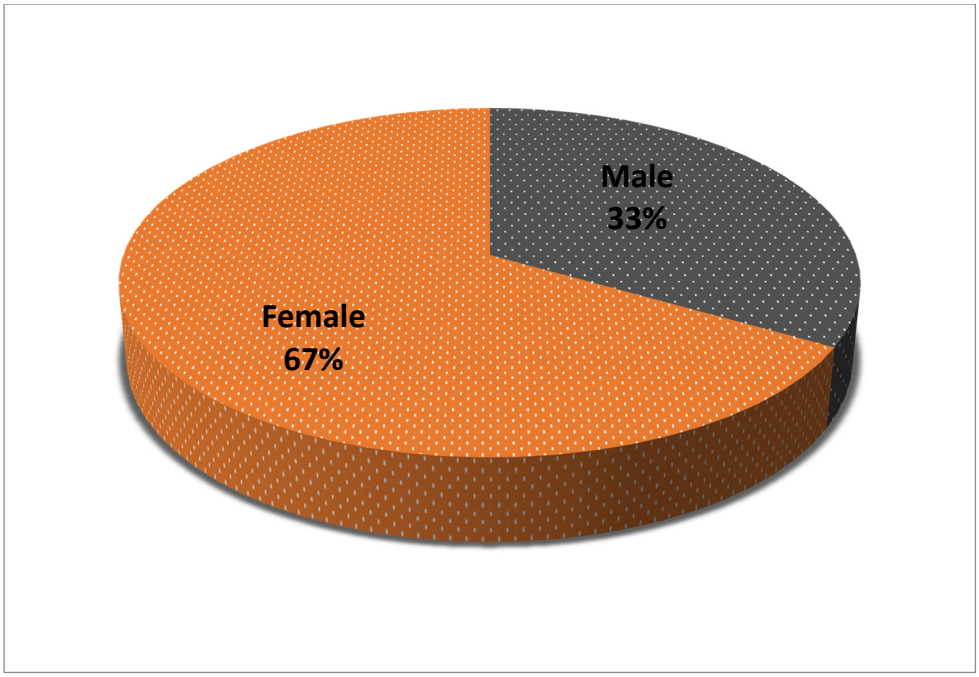

FIGURE 2: Pie chart for gender distribution

3.4. ANATOMICAL DIAGNOSIS

Patients of intermediate uveitis (n=1, 6%), posterior uveitis (n=13, 72%), panuveitis (n=4, 22%) were included in the study, with posterior uveitis being the most common cause and intermediate uveitis the least common cause for Inflammatory CNVM to develop in. No cases of inflammatory CNVM were seen in anterior uveitis.

TABLE 3: Anatomical Diagnosis of uveitis based on IUSG criteria.

Diagnosis	No of cases	%
Intermediate uveitis	1	6%
Posterior uveitis	13	72%
Panuveitis	4	22%

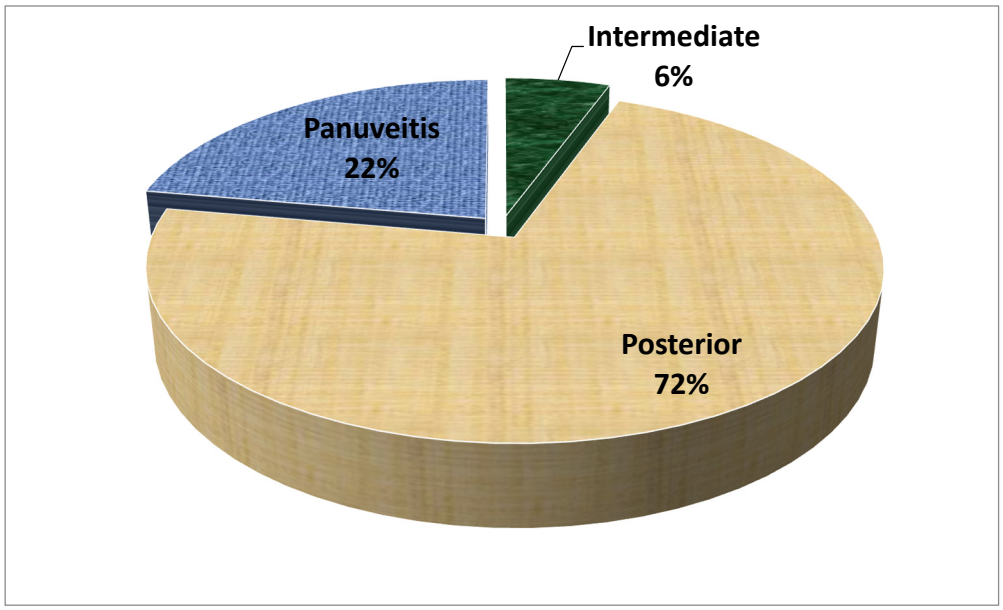

Figure 3: Pie chart for anatomical diagnosis of uveitis

3.5. SPECIFIC ETIOLOGY

The most common uveitic causes for Inflammatory CNVM to develop were Ocular Tuberculosis (n=5, 27.7%), and Sarcoid (n=5, 27%). Other causes were idiopathic (n=3), ocular toxoplasmosis (n=2), VKH (n=1), white dot syndrome (n=1), multifocal choroiditis (n=1).

TABLE 4: Specific etiology of uveitis

ETIOLOGY	Number	%
Ocular TB	5	27.78
Sarcoid	5	27.78
Idiopathic	3	16.67
Ocular Toxoplasmosis	2	11.11
VKH	1	5.56
White dot syndrome	1	5.56
Multifocal choroiditis	1	5.56

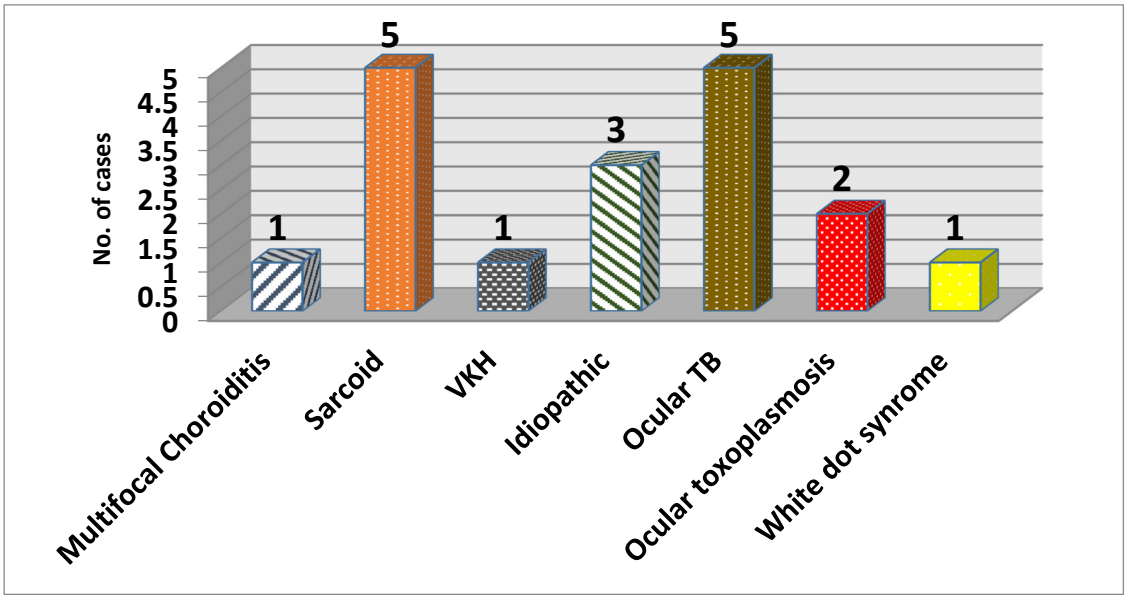

FIGURE 4: Bar diagram for specific etiology of uveitis

3.6. ACTIVITY OF UVEITIS

In our study inflammatory CNVM developed in 9 (50%) active uveitic cases, while 9 (50%) were inactive at the time of presentation of CNVM with signs/ records of old uveitis resolved with treatment.

TABLE 5: Activity of uveitis

ACTIVITY	NO	%
Active inflammation	9	50%
Inactive inflammation	9	50%

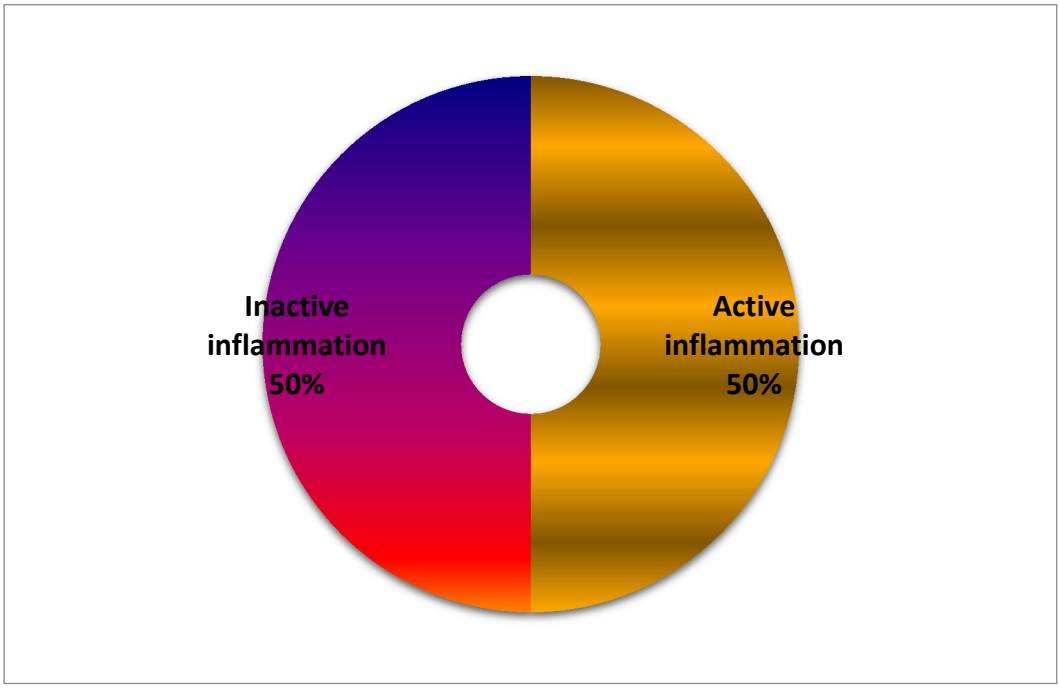

FIGURE 5: Doughnut chart showing activity of uveitis

3.7. LOCATION OF CNVM

In our study 11 cases (61.11%) were peripapillary, 5 cases(27.77%) were subfoveal, and 2 cases (11.11%)were juxtafoveal in location.

TABLE 6: Location of CNVM

Location	Number	%
Peripapillary	11	61.11
Subfoveal	5	27.77
Juxtafoveal	2	11.11

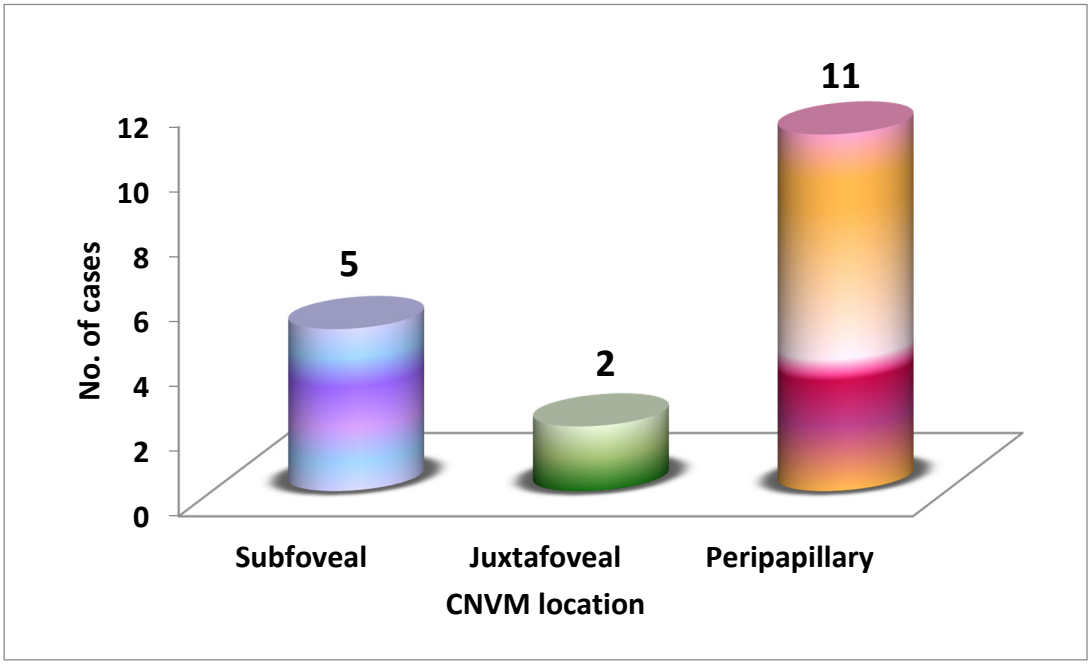

FIGURE 6: Bar diagram showing location of CNVM

3.8. TOTAL NUMBER OF INJECTIONS

During the 6 month followup period, 5 cases (27.7%) received only 1 injection, 3 cases (16.67%) received 2 injections, 5 cases (27.7%) received 3 injections , 4 cases (22.22) received 2 injections and only 1 case (5.56%) received 5 injections in total.

TABLE 7: Mean number of injections given in 6 month follow-up

No. of injection	N	Mean (SD)	Range
	18	2.61 (1.28)	1 to 5

TABLE 8: Total number of injections given per eye

No. of injection	no	N (%)
1	5	(27.78)
2	3	(16.67)
3	5	(27.78)
4	4	(22.22)
5	1	(5.56)
Total	18	(100)

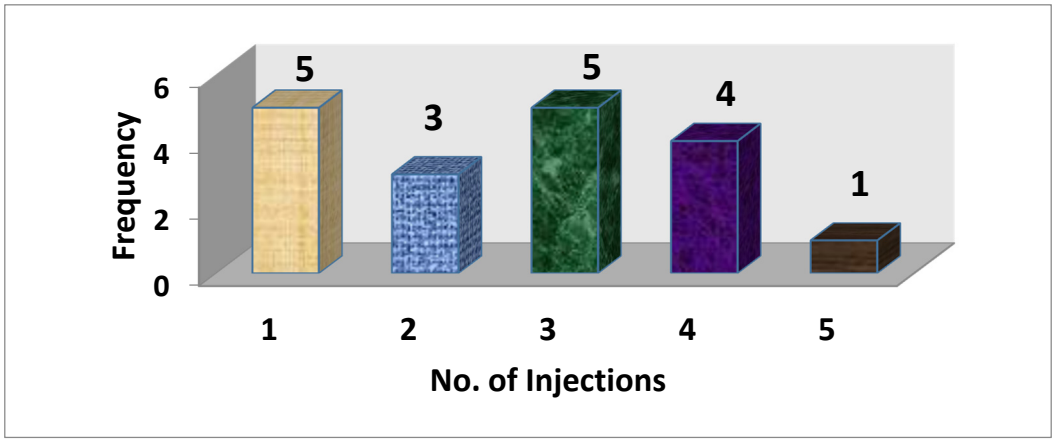

FIGURE 7: Bar diagram for total number of injections given

3.9. BCVA PRE AND POST TREATMENT

Visual acuity was one of the primary outcome measures in our study. Although there seemed to be an improvement in the logMAR BCVA over the follow-up period, it did not achieve statistical significance. However, on sub-group analysis, a significant statistical difference was found between the pre-treatment BCVA and final BCVA at 6 months (P value being 0.009<0.05).

TABLE 9: Best corrected visual acuity of cases at baseline and during follow-up

BCVA	n	Mean (SD)	Median	P-Value*
BCVA Pre treatment	18	.701(.423)	.6	0.2037
BCVA I Month	16	.538(.267)	.6	
BCVA 3 Months	15	.402(.275)	.3	
BCVA 6 Months	12	.295(.195)	.18	

*-Friedman test

TABLE 10: Comparison of improvement BCVA between baseline and each follow-up

BCVA	P –VALUE*
BCVA Pre treatment Vs BCVA I Month	0.916
BCVA Pre treatment Vs BCVA 3 Months	0.068
BCVA Pre treatment Vs BCVA 6 Months	0.009

*-Bonferroni test

3.10. CENTRAL MACULAR THICKNESS(CMT) PRE AND POST TREATMENT

The second outcome measure was measuring the reduction in central macular thickness after the anti-VEGF injection due to reduction in the intraretinal/subretinal fluid or haemorrhage. In this study an overall reduction in the CMT was found during the follow-up period, however it was not statistically signficant. On sub-group analysis, we found a statistically significant difference between the pre-treatment CMT and at 1 month followup. (P=0.006<0.05) This difference again went non-significant after the 1st month.

TABLE 11: Central macular thickness of cases at baseline and during follow-up

CMT	n	Mean (SD)	Median	P-Value*
CMT Pre treatment	15	448.86(97.71)	445	0.0747
CMT I Month	13	313.46(50.53)	341	
CMT 3 Months	12	341.41(103.81)	323.5	
CMT 6 Months	10	347.5(145.40))	284.5	

*-Friedman test

TABLE 12: Comparison of reduction in CMT at baseline and during each follow-up

CMT	P –VALUE*
CMT Pre-treatment Vs CMT I Month	0.006
CMT Pre -treatment Vs CMT 3 Months	0.053
CMT Pre -treatment Vs CMT 6 Months	0.109

*-Bonferroni test

3.11. REGRESSION ON OCT

The third outcome measure was evaluating the regression of intraretinal/subretinal fluid or haemorrhage on OCT in the serial follow-ups after treatment with multiple Intravitreal Anti-VEGF injections until complete resolution was achieved. In our study 13eyes (81.25%) out of 16 eyes (2 patients lost to follow-up after the first visit) had complete resolution of the intraretinal/subretinal fluid or haemorrhage on OCT. Out of these 13 eyes, 2 eyes developed recurrence and had active CNVM at the end of our study period of 6 months. 3/16 eyes (18.75%) had resolving CNVM with treatment compared to initial OCT, but did not completely resolve at the end of our study period of 6 months.

TABLE 13: Regression of CNVM at baseline and final follow-up

Activity	**Baseline N (%)**	**Final visit N (%)**
Active	18 (100)	0
Resolving	0	3 (18.75)
Resolved	0	13 (81.25) #
Total	18 (100)	16 (100) *

*- Two patients were lost to follow up; #-Recurrence was seen in 2 patients

3.12. COMPARISSON OF RANIBIZUMAB to BEVACIZUMAB

In our study only 2 eyes were treated with Ranibizumab, while 16 eyes were treated with Bevacizumab. The mean no of injections were 2.6± 1.3 and 3.5± 0.7 for Bevacizumab and ranibizumab respectively. There was no statistical difference noticed in the improvement of BCVA and CMT in the Ranibizumab and Bevacizumab groups individually.

TABLE 14: Mean number of injections in each group

Intravitreal Anti-VEGF	N	Mean (SD)
Bevacizumab	16	2.5 (1.31)
Ranibizumab	2	3.5 (0.7)

TABLE 15: Comparison of BCVA at baseline and each follow-up in each group

BCVA	Bevacizumab Mean (SD)	Ranibizumab Mean (SD)
Baseline	0.64 (0.38)	1.19 (0.83)
1 Month	0.53 (0.27)	0.54 (0.33)
3 Months	0.42 (0.27)	0.24 (0.33)
6 Months	0.324 (0.19)	0.15 (0.212)
P value #	0.2172	0.3173

#-Friedman test

TABLE 16: Comparison of Central macular thickness at baseline and each follow-up in each group

CMT	Bevacizumab Mean (SD)	Ranibizumab Mean (SD)
Baseline	456.46 (101.61)	399.5 (64.34)
1 Month	318.27 (44.73)	287 (94.75)
3 Months	356.2 (105.47)	267.5 (72.83)
6 Months	370.87 (153.55)	254 (57.98)
P value #	0.1563	0.3173

#-Friedman test

3.13. RECURRENCE OF INFLAMMATORY CNVM IN CASES WITH ACTIVE INFLAMMATION

CNVM can occur in both active and inactive uveitic cases. Following regression of the CNVM with anti-VEGF injections we evaluated if recurrence was more common in the cases with active inflammation. Recurrence occurred only in total 2 cases (2/16, 12.5%). Both these 2 cases had uveitic activity out of total 8 with active uveitis. No recurrence was seen in the inactive uveitic cases. However, it was found that there is no association between the active inflammations and recurrence result. It is also not statistically significant. (P=0.467 > 0.05)

TABLE 17: Comparison of recurrence of CNVM in active and inactive uveitis

Active Inflammation	Recurrence			P value
	Yes N (%)	No N (%)	Total	
Yes	2 (100)	6 (42.86)	8 (50)	0.467 (NS)
No	0	8 (57.14)	8 (50)	
Total	2 (100)	14 (100)	16 (100)	

3.14. SUBGROUP ANALYSIS TO COMPARE VISUAL AND ANATOMICAL OUTCOMES IN SUBFOVEAL, JUXTAFOVEAL AND PERIPAPILLARY

BCVA improved in all the subgroups pre and post treatment, with a small statistical significance in BCVA gain in the subfoveal group. Reduction of CMT was seen in all three subgroups but no statistical difference was noted among the three groups. There was complete resolution of CNVM on OCT in 100% juxtafoveal cases, 60% peripapillary cases and 60% of the subfoveal cases at the last follow-up. 20% of the peripapillary cases had complete resolution followed by recurrence, which had active CNVM at the 6 month follow-up.

TABLE 18: Subgroup analysis of BCVA at baseline and each follow-up in the three groups based on location

BCVA	OCT Location		
	Subfoveal Mean (SD)	**Juxtafoveal Mean (SD)**	**Peripapillary Mean (SD)**
Baseline	0.87 (0.44)	0.89 (0.15)	0.58 (0.48)
1 Month	0.67 (0.29)	0.69 (0.12)	0.456 (0.26)
3 Months	0.59 (0.36)	0.6 (0)	0.306 (0.23)
6 Months	0.3*	0.48*	0.276 (0.21)
P value#	0.0498 (S)	0.2482	0.4360

*-Only one observation, so SD does not exist; #-Friedman test

TABLE 18: subgroup analysis of CMT at baseline and each follow-up in the three groups based on location

CMT	OCT Location		
	Subfoveal Mean (SD)	Juxtafoveal Mean (SD)	Peripapillary Mean (SD)
Baseline	418.2 (43.47)	447 *	466.11 (121.82)
1 Month	307.66 (76.6)	344.5 (2.12)	307.87 (48.72)
3 Months	310 (132.93)	354.5 (78.48)	346 (114.78)
6 Months	213 *	273 *	373.62 (151.74)
P value #	0.5637	0.99	0.1748

*-Only one observation, so SD does not exist; #-Friedman test

TABLE 20: Subgroup analysis of activity of CNVM at the end of 6 month follow-up in the three groups based on location

ACTIVITY	SUBFOVEAL	JUXTAFOVEAL	PERIPAPILLARY
ACTIVE	0	0	2(20%)**
RESOLVING	1(20%)	0	2(20%)
RESOLVED	3(60%)	2(100%)	6(60%)
TOTAL	5*	2	11#

*1 case lost to follow-up , # 1 case lost to follow-up

** 2 cases resolved &had recurrence

4. DISCUSSION

Intravitreal anti- vascular endothelial growth factor (ANTI-VEGF) is nowdays commonly used in the treatment of Choroidal neovascular membrane (CNVM) caused due to Age related macular degeneration. Inflammatory CNVM has no uniform consensus for treatment due to lack of large randomized controlled trials. The aim of our study was to prospectively study the effects of anti-VEGF when used for the management of inflammatory CNVM. No such studies have been done in the past, according to our knowledge.

4.1. AGE DISTRIBUSTION

In previous studies done both in India and in the western population the mean age of presentation was 40 years [1,2,14]. Palmeera et al [2] reported a range of 11-70 years who were previously or concurrently treated for uveitis and now presented with Active CNVM. In our study the mean age was 40.94 years ±12.84 years with a range of 17-58 years(Table1).

4.2. GENDER DISTRIBUTION

In most of the studies there was no gender predilection in the incidence of inflammatory CNVM [2,38,39] . Reema et al studied 60 patients having inflammatory CNVM and found no gender predilection, with

number of male being 28 and females 32. In our study 66.67% of the patients were females and 33.33% were males(Table 2). There was an obvious female preponderance with the ratio of male to female population being 1:2.

4.3. ANATOMICAL DIAGNOSIS

There is a difference in location of inflammation reported in various studies. Reema et al [39] reported the most common cause for inflammatory CNVM to be panuveitis (47.9%) followed by posterior uveitis (46.6%) and (5.5%) eyes had intermediate uveitis. Palmeera et al[2] reported maximum cases to be due to posterior uveitis (n=7), and 4 cases each of panuveitis and intermediate uveitis to develop inflammatory CNVM. None of the studies done so far have documented inflammatory CNVM occurring in cases with anterior uveitis. In our study most cases had posterior uveitis (72%), followed by panuveitis and only 1 case of intermediate uveitis presenting with inflammatory CNVM was documented(Table 3). None of our cases had anterior uveitis as has been previously studied.

4.4. SPECIFIC ETIOLOGY

The etiology of uveitis varies drastically between the western population and in Indian settings. The most common causes of inflammatory CNVM in western literature was multifocal choroiditis, punctate inner choroidopathy, serpiginous choroiditis [14,1,38]. In previous

studies done in India showed the most common causes to be ocular Tuberculosis, Idiopathic and Vogt Koyanagi Harada (VKH)[2,39]. Our study showed maximum cases to be due to Ocular Tuberculosis and Sarcoid, followed by idiopathic and toxoplasmosis (Table 4). Thus in a developing country like ours, ocular Tuberculosis is a common cause of inflammatory CNVM, probably due to higher prevalence of tuberculosis associated uveitis in endemic countries compared to nonendemic countries.

4.5. ACTIVITY OF UVEITIS

Inflammatory CNVM can occur both in active and inactive uveitic states. Previous studies have shown that for the development of CNVM concurrent active inflammation is not essential [1,2]. In a study by Ahamad et al[1] out of 84 eyes, in 61 eyes uveitis was inactive or absent and only 23 eyes had active inflammation at the time of development of CNVM. In our study 50% of the patients had active uveitis(Table 5). Thus the role of local steroids is limited. Steroids and immunosuppressants can be used for the treatment of the active uveitis state but isn't necessary for the resolution of CNVM.

4.6. LOCATION OF CNVM

Based on the macular photocoagulation study the location of CNVM was classified as Peripapillary, subfoveal and juxtafoveal. In a large multicentric study[1], most common location of CNVM was found to be

subfoveal (49 eyes) followed by juxtafoveal (38 eyes) and peripapillary (6 eyes). In the Indian population, Palmeera et al[2] found peripapillary (8 eyes) to be most common followed by juxtafoveal (4eyes) and subfoveal (3 eyes) locations, similar to a study done by Reema et al[39] in 73 eyes, where the most common location was peripapillary (33 eyes) followed by subfoveal (21 eyes) and juxtafoveal (9 eyes). In our study we found similar results compared to the previous case series done in India. We had 11 cases in peripapillary location, 5 were subfoveal and 2 were juxtafoveal(Table 6).

4.7. TYPE OF CNVM BASED ON FFA

In the study done by Palmeera et al[2] and Tran et al[38] all cases had classic type of CNVM on angiography. Bansal et al[39] noted 55 eyes (75.3%) had classic CNVM while 18 eyes (24.7%) had occult CNVM. In our study angiography was done only in 5 of the 18 patients. Similar to the previous study, all the 5 cases had Classic type of CNVM on angiography, which is generally seen in cases of Inflammatory CNVM.

4.8. NUMBER OF INJECTIONS

The mean number of injections in the study done by Palmeera et al [2] was 2.6 ± 1.2 during a mean follow-up period of 20.53 ± 14.53 months with complete resolution of subretinal fluid. In a large multicentric study by Mansour et al [1] the mean number of injections given was 1.3. Similar to the previous studies the mean number of injections given in our study was

2.6 ± 1.2 in the stipulated follow-up period of 6 months (Table 7). There was complete resolution of subretinal fluid in 81.25% of the cases with recurrence of CNVM in 2 cases following complete resolution.

4.9. BEST CORRECTED VISUAL ACUITY(BCVA) – PRE AND POST TREATMENT

In the studies done both in India and Western population, there was an improvement in the post treatment BCVA[1,2,14,38]. In the largest case series Mansour et al[1] assessed 99 eyes for 6 months and 27 eyes for 2 years , a visual improvement of >2.2 lines was achieved by treatment. Tran et al[38] followed up 10 patients for 7.5 months and documented an improvement in logMAR BCVA from 0.62 to 0.45 at 1 month, which was stable during the follow-up period. In a study of CNVM in multifocal choroiditis by Howard et al[35] 5 out of the 6 eyes improved to a acuity of 20/30 or better at the end of 6 months. The study done by Palmeera et al[2] found an improvement in mean BCVA from pretreatment logMAR 0.79±0.76 to post treatment logMAR of 0.46±0.43. In our study the pretreatment BCVA of log MAR 0.701±0.432 improved to logMAR 0.295±0.195 at the end of 6 months follow-up (Table 9).There was a statistical difference between BCVA pre- treatment and post treatment at 6th month follow-up (Table 10) (P value is 0.009 < 0.05).

4.10. CENTRAL MACULAR THICKNESS (CMT) – PRE AND POST TREATMENT

Reduction of CMT following treatment was seen in previous studies [14,2,38]. In a study by Adan et al [14] mean central thickness improved to 220µm (191-288µm) from 360µm (226-442µm), with a statistical difference (P= 0.051). The mean CMT preinjection of 435.9±262.13 µm decreased to a mean CMT of 262.13 ±108.70 µm at the final visit in the study by Palmeera et al[2]. Tran et al[38] studied the effects of intravitreal bevacizumab for refractory choroidal neovascularization secondary to uveitis, where the CMT of 326±95 µm pre-treatment improved to 260±84 µm with treatment at the last visit.

In our study the mean baseline CMT was 448.86±97.71 µm which reduced to a mean of 347.5 ±145.4 µm at the end of 6 months (Table11) with a statisticallly significant difference between the CMT pre-treatment and at 1 month follow-up (Table 12) (P=0.006<0.05).

Thus it was found that after a reduction of CMT at 1 month, anti-VEGFs helped stabilise the disease process till 6 months, with or without need of repeat injections. Moreover, visual acuity also seemed to improve till the end of the 6 months period.

4.11. REGRESSION ON OCT – PRE AND POST TREATMENT

Adan et al [14] and Palmeera et al[2] found complete resolution of the subretinal fluid in all their 9 and 15 cases respectively at the last follow-up. In a multicentric study by Mansour et al[1] 32eyes (43.2%) had complete resolution, 27 eyes (36.5%) had partial regression, 5 eyes(6.8%) had no response to the treatment. In our study with a follow-up period of 6 months, 13 eyes (81.25%) had complete resolution of CNVM, while 3 eyes (18.75%) had partial resolution. Of the 13 cases, 2 eyes had complete resolution at the 1st and 3rd month follow-up respectively which developed recurrence of CNVM that was still active at the end of 6 months in spite of intravitreal injections. Both these eyes also had active uveitis (Table 13).

4.12. COMPARISON OF RANIBIZUMAB TO BEVACIZUMAB

Ranibizumab and Bevacizumab were compared in the study done by Palmeera et al [2]. While improvement was seen in the BCVA and reduction of the CMT occurred in both groups, no statistical significance was reached. In our study, the mean BCVA showed improvement from baseline logMAR 0.64± 0.38 and 1.19±0.83 to logMAR 0.32±0.19 and logMAR 0.15± 0.21 at the final visit in Bevacizumab and Ranibizumab groups respectively, but the change was not statistically significant (Table 15) (P=0.217 and P=0.317 respectively). The CMT reduced from baseline 456.46 ± 101.61 µ and 399.5 ±64.34 µ to final 370.87±153.55 µ and 254±

57.98 μ in the Bevacizumab and Ranibizumab groups respectively, however no statistical significance was reached (Table 16) (P=0.15 and p=3.17 respectively). This could be due to a low sample size and unequal distribution of the 2 groups with Ranibizumab having only 2 cases and Bevacizumab group having 16 cases.

4.13. RECURRENCE OF INFLAMMATORY CNVM

In the study done by Palmeera et al [2] recurrence was noted in 4 out of the 15 cases (26.7%) out of which 3 cases were peripapillary and 1 case was juxtafoveal in location. Out of the 4 cases 1 had active inflammation and 3 cases inactive uveitis. In our study 2 (12.5%) out 16 cases had recurrence. Both cases were peripapillary in location and had active inflammation at the initial presentation of CNVM(Table 17). However there was no statistically significant association between the active inflammations and recurrence result. (P=0.467 > 0.05).

4.14. SUBGROUP ANALYSIS TO COMPARE VISUAL AND ANATOMICAL OUTCOMES IN SUBFOVEAL, JUXTAFOVEAL AND PERIPAPILLARY

In two studies done by Adan et al[14]and Palmeera et al[2] subgroup analysis among the three groups subfoveal, juxtafoveal and peripapillary showed no statistical significance in the pre and post injection CMT reduction. The final visual acuity gain was slightly better in the

peripapillary group compared to the subfoveal group in both the studies. In our study there was reduction of CMT in all 3 groups but no statistical significance was seen when comparison between baseline and final followup was done in each group(Table 18). Complete resolution of CNVM on OCT was seen in 100 % of juxtafoveal cases, and 60% each subfoveal and peripapillary eyes at the end of 6 month followup (Table 20). Unlike the previous studies we noted a statistically significant visual acuity gain between baseline and final followup in the subfoveal group (Table 18) (P=0.049).

4.15. OCULAR AND SYSTEMIC COMPLICATIONS OF INTRAVITREAL

Some complications noticed in previous studies have been Retinal pigment epithelium rip, submacular fibrosis, submacular haemorrhage, ocular hypertension and spread of chorioretinal atrophy. In a long term follow up study done by Masnsour et al[40] 3 eyes developed submacular fibrosis, 1 eye had macular haemorrhage immediately after the intravitreal injection, and 1 eye developed ocular hypertension all following bevacizumab injections. No injection related complication like endophthalmitis, retinal detachment or cataract was noted. In our study of 18 patients with a follow-up period of 6 months, no ocular or systemic complications was noted in either the Bevacizumab group or Ranibizumab group.

5. CONCLUSION

Inspite of the fact that inflammatory CNVM is a rare complication, being a referral centre, we encountered 18 patients in one year (January - December 2018) accounting for 0.85% cases of inflammatory CNVM in cases of intermediate, posterior or pan-uveitis.

Even though there was apparent improvement in the BCVA and reduction in CMT following treatment, we could not arrive at any significant statistical difference because of the very small sample size as inflammatory CNVM is a very rare complication. The other limitations were that the study was a non-randomized non-controlled study.

The follow-up period of the study was only 6 months, which showed good improvement in the outcome measures. Long term observation study is needed to note the stability, recurrence and complication following treatment. Based on our study we can suggest treatment of inflammatory CNVM with Intravitreal Anti-VEGF injections along with appropriate treatment of the active uveitis such as steroids, immunosuppressants or antibacterials, based on the etiology. However a larger controlled study with long term follow-up is needed to compare the intravitreal anti-VEGF therapy to other treatment options for management of Inflammatory CNVM.

ANNEXURE

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ABBREVIATIONS

CNVM	-	Choroidal neovascularization
ARMD	-	Age related macular degeneration
VKH	-	Vogt-Koyanagi-Harada syndrome
PIC	-	Punctate inner choroidopathy
VEGF	-	Vascular endothelial growth factor
PDT	-	Photodynamic therapy
POHS	-	Presumed ocular Histoplasmosis
RPE	-	Retinal pigment epithelium
MFC	-	Multifocal choroiditis
TB	-	Tuberculosis
KPs	-	Keratic precipitates
CRP	-	C- reactive protein
CFH	-	Complement factor H
IL-1	-	Interleukin 1
IL-2	-	Interleukin 2
TNFα	-	Tumour necrosis factor alpha
EAU	-	Experimental autoimmune uveoretinitis
PEDF	-	Pigment epithelial derived growth factor
CME	-	Cystoid macular edema
PED	-	Pigment epithelial detachment

RAP	-	Retinal angiomatous proliferans
OCT	-	Optical coherence tomography
SD-OCT	-	Spectral domain optical coherence tomography
FFA	-	Fundus fluorescein angiography
PCV	-	Polypoidal choroidal vasculopathy
FGF	-	Fibroblast growth factor
TGFα and β	-	Transforming growth factor alpha and beta
BCVA	-	Best corrected visual acuity
SUN	-	Standardization of uveitis nomenclature
CMT	-	Central macular thickness
IUSG	-	International uveitis study group criteria
ESR	-	Erythrocyte sedimentation rate

PROFORMA

INFLAMMATORY CNVM STUDY

Case No: _____

NAME: _____ UID NO:_____ MR NO:_____ DATE of CNVM: _____

AGE: _____ GENDER: M/F CONTACT NO :_____

ADDRESS: _____

EYE AFFECTED: (Right=1, Left=2) ☐

SYSTEMIC HISTORY: (DM=1, HTN=2, cardiac=4, others=4, nil =8) ☐

COMPLAINTS: (Sudden loss of vision=1, Metamosrphopsia=2, Blurring of vision=3, Scotomas=4, others=5) ☐

Others: _____

Anatomical Diagnosis: (Anterior=1, Intermediate=2, Posterior=3, Panuveitis=4) ☐

Specific diagnosis: _____ Date of diagnosis: _____

Active Inflammation : (Yes=1, No=2) ☐

Visual acuity (VA):_____ VA with PH/ BCVA:_____
IOP:_____ ☐

Anterior Segment: (KPs=1, Cells=2, Flare=3, Others=4)

Others: _____

Posterior Segment: (Yes=1, No=8, Not examined=9)

MEDIA : (Vitreous haze(0,1+,2+,3+<4+)=1, Vitreous opacity=2, Avf cells=3, other=4, No=8) ☐

Others: _____

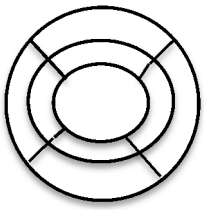
DISC AND MACULA: (Hyperemic disc =1, disc edema=2, foveal scarring=3, hmg s/o CNVM=4, others=5, No=8) ☐

Others: _____

BACKGROUND AND VESSELS: (Choroiditis=1, resolved/scarred choroiditis=2, Retinitis=3, Chorioretinitis=4, Scarring=5, Sheathing of vessels=6, Exudated=7, No=8, other =9) ☐

Others :_____

1) OCT FINDINGS: a) Central Macular Thickness: _____



b)Location: (Subfoveal=1, Juxtafoveal=2, Peripapillary=3) ☐

c)Activity: (Active=1, Resolving=2, Resolved=3) ☐

2)FLUORESCEIN ANGIOGRAPHY: (Disc leak=1, classic CNVM=2, occult CNVM =3) ☐

3)FUNDUS PHOTO: (CR Scars=1, Vitreous haze=2, Vascular sheath=3, Subretinal scar=4, Not taken =8) ☐

TREATMENT

1) INTRAVITREAL ANTI-VEGF: (Bevacizumab=1,Ranibizumab=2) ☐

(Phakic=1, Pseudophakic=2) ☐

Date:_____

2) REPEAT INJECTION: (Yes=1, No=2) ☐

2nd Injection on:_____

3rd injection on:_____

3)Any other treatment after CNV diagnosis: (Oral corticosteroids=1, Intravitreal steroids=2, Subtenons steroids=3, Immunosuppresants =4,systemic antibiotics=5) ☐

Others:_____

4)Treatment given for uveitis: (Oral corticosteroids=1, Immunosuppresants=2,AKT=3, Others=4, No=8)

Others: _____ ☐

FOLLOW UP

	BCVA	**IOP**	**CMT**	**OCT(Active=1, Resolving=2, Resolved=3)**
AT PRESENTATION				
1 MONTH				
3MONTH				
6MONTH				

RECURRANCE: (YES=1, NO=2) ☐

COMPLICATION OF ANTI VEGF: (Subfoveal retinal pigment epithelial rip=1, Submacular fibrosis=2, Submacular hmg=3, Ocular hypertention=4, Reactivation of uveitis=5, Spread of chorioretinal atrophy=6, Endophthalmitis=7, others=8) ☐

Others: _____

Systemic complications of ANTI-VEGF: _____

INFORMED CONSENT FORM TO PARTICIPATE IN THE STUDY

STUDY: INFLAMMATORY CHOROIDAL NEOVASCULAR MEMBRANE-INCIDENCE, VISUAL AND ANATOMICAL OUTCOMES AFTER INTRAVITREAL ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR THERAPY

Protocol Number:

Subject's Name: _____Subject's Initials: _____

Subject ID No: _____

Date of Birth / Age: _____

I confirm that I have understood the information about the study, procedures and treatments for the above study and have had the opportunity to ask questions and I received satisfactory answers to all of my questions. I have been given a copy of the informed consent form to take home	[ ]
I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. However, this is may not be possible for certain surgical procedures	[ ]
I understand that the Investigator of the study can access my health records for the research purpose. However, I understand that my identity will not be revealed in any information released to third parties or published.	[ ]
I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s)	[ ]
I agree to take part in the above study.	[ ]

Signature (or Thumb impression) of the Subject: _____

Date: _____/_____/_____

Subject's Name: _____

Signature (or Thumb impression) of Legally Acceptable Representative (LAR):

_____ Date: _____

Signature of the Investigator: _____

Date: _____/_____/_____

Investigator's Name: _____

Signature of the Witness _____

Date:_____/_____/_____

Name of the Witness: _____

ARAVIND MEDICAL RESEARCH FOUNDATION
Institutional Ethics Committee
(REGISTRATION NO. ECR/182/INST/TN/2013 DATED 20.04.2013)

20th December 2017

To
Dr.Tanya Balakrishnan
MS Resident
Aravind Eye Hospital
Madurai

Dear Dr. Tanya Balakrishnan,

Thesis Title: Inflammatory Choroidal Neovascular Membrane - Incidence, Visual and Anatomical outcomes after Intravitreal Anti-Vascular Endothelial Growth Factor Therapy.

IEC Code: IEC201800251

Thank you for submitting your thesis and seeking the approval from the ethics committee. The documents provided by you for consideration which include the thesis protocol and informed consent forms were reviewed for the research methodology and scientific content. The Ethical committee did not find any correction and has recommended the thesis to go ahead in the present form.

Thanking you

Yours Sincerely,

Dr.R.Sharmila
Member Secretary
Institutional Ethics Committee

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE
ARAVIND MEDICAL RESEARCH FOUNDATION
No.1, Anna Nagar, Madurai-625 020

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URKUND

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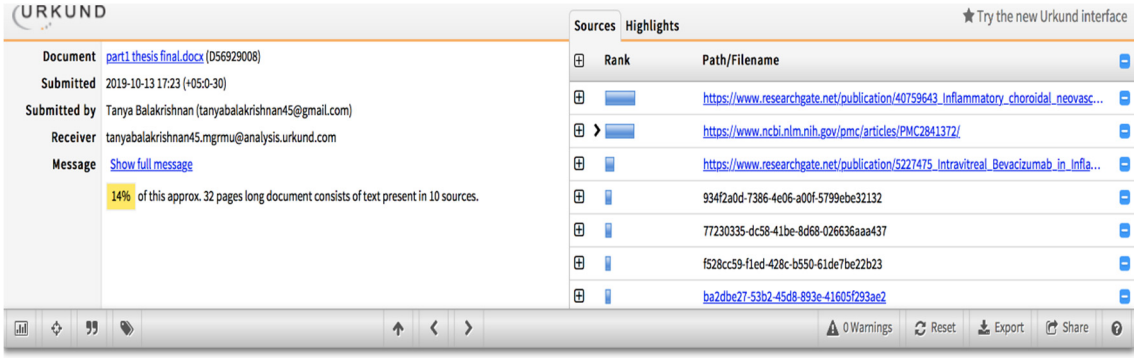

PART 1 S.NO TITLE PAGE NO. 1 INTRODUCTION 2 HISTORICAL PERPECTIVE 3 ANATOMY AND PHYSIOLOGY 4 AETIOLOGY 5 PATHOGENESIS 6 DIAGNOSIS 7 TREATMENT 8 REVIEW OF LITERATURE

PART 2 S.NO TITLE PAGE NO 1 AIMS AND OBJECTIVES 2 MATERIALS AND METHOD 3 RESULTS 4 DISCUSSION 5 CONCLUSION 6 ANNEXURES Bibliography Abbreviations Proforma Consent form Institutional Review Board approval Plagiarism Report Master chart

PART 1

1. INTRODUCTION Choroidal neovascularization(CNVM) is the formation of new blood vessels beneath the retina, originating from the choroid. Various etiologies can cause CNVM, most common being age-related macular degeneration (ARMD) followed by pathological myopia and inflammatory CNVM. In uveitis, because of the association with various inflammatory conditions of the posterior segment, CNVMs formed are termed as "inflammatory CNVM". Common causes of inflammatory CNVM in India are idiopathic, infectious causes like ocular tuberculosis, and Vogt-Koyanagi-Harada (VKH) syndrome, some other etiologies being multifocal choroiditis, punctate inner choroidopathy (PIC), ocular histoplasmosis syndrome, etc. Inflammatory CNVM is a rare but major vision threatening complication of active or inactive uveitis, with no uniform consensus for the treatment. CNV can occur in the sub-foveal, juxta-foveal or peri-papillary locations, with sub-foveal CNV having the most guarded prognosis, while variable outcomes are noted in the other two types. CNV caused due to inflammatory causes are mostly Type 2 or classic CNV, which occupies the sub-neurosensory compartment between RPE and outer-segments of the retina. Various treatment modalities for inflammatory CNV are available, however no definitive evidence of superiority of one treatment over another is available due to the lack of randomized control trials. Some approaches currently available include observation, local and systemic corticosteroids, laser photocoagulation, photodynamic therapy (PDT), surgical removal of CNVM & intravitreal anti-vascular endothelial growth factor (Anti-VEGF) injection. Over a five-year follow-up duration, Macular Photocoagulation Study showed that post laser therapy for CNVMs, there

Sr. No	MR NO	NAME	AGE	GENDER	ADDRESS	DATE OF DIAG	EYE	COMPLAINTS	ANAT DIAG	SPECIFIC I	ACTIVE INFLAM	SYST HIST	UCVA	BCVA	IOP	ANT SEGMENT	MEDIA	DISC &MACULA	BACKGROUND	CMT	OCT location	FFA	ANTIVEGF	LEN STATUS	NO OF REPEAT	OTHER TREAT	TREAT FOR UVEITIS
1	4623871	Kavitha	31	F	3	15-09-2017	2	3	3	toxo	2	8	1. / 60	1./60	20	8	8	4	5	354	3	3	2	1	3	8	4
2	4604148	Aiswarya	23	F	1	01-11-2017	2	3	3	ocular TB	2	8	5./60	6./36	17	2	8	2	2	445	3	1,3	1	1	3	1	1&3,4
3	4637045	Manickan	41	M	1	05-02-2018	2	3	3	ocular TB	1	8	6./24	6./12	20	8	2,3	2,4	9	313	3	8	1	1	2	1	1&3
4	3799870	Sahithya d	21	F	1	03-02-2018	1	3	4	VKH	1	8	6./36	6./24	12	1,4	8	5	9	507	3	8	1	1	3	1,4	1,2
5	4516224	Sujatha	58	F	2	03-11-2017	2	3	3	Sarcoid	1	1	6./24	6./24	16	8	8	4	9	732	3	8	1	1	5	1	1,4
6	4645284	Mahamud	43	F	1	26-10-2017	2	3,5	3	white dot s	1	8	6./18	6./9	13	4	8	5	1,9	394	3	8	1	1	4	1	8
7	4641238	Kalaiarasi	50	M	1	22-03-2018	2	3	3	idiopathic	2	8	2./60	2./60	15	8	8	8	5	420	1	3	1	1	1	8	8
8	4549834	Shameem	56	F	1	13-04-2018	2	3	4	ocular TB	1	1,3,4	6./36	6./9	18	8	8	4,5	8	522	3	8	1	1	3	1	1,3
9	4894652	Jothi Sund	52	F	1	13-02-2018	2	3	3	sarcoid	2	1,2	5./60	5./60	13	8	1,3,4	8	2	430	3	8	1	2	2	8	1
10	4894652	Jothi Sund	52	F	1	13-02-2018	1	3	3	sarcoid	2	1,2	6./18	6./18	20	8	8	1,3,5	1,2	420	3	8	1	2	1	8	1
11	4673913	Rajeshwar	51	F	1	19-02-2018	1	3	3	Multifocal	1	8	6./36	6./36	14	8	8	4	1	370	2	3	1	1	4	1,3	1,2
12	4768543	Amutha Eswari	3	F	1	07-06-2018	2	3	3	sarcoidosis	1	8	6./18	6./18	14	8	8	2peripap SRF	8	492	3	3	1	1	4	1,3	1
13	4750603	Jahir Huss	42	M	1	30-06-2018	1	3	2	ocular TB	2	8	6./12	6./12	12	4(PS	3 occ cc	8	8	367	1	8	1	1	1	1	1,3
14	1381161	Anthony I	58	M	1	21-07-2018	1	3	3	ocular TB	2	tb	6/.60	6./24	12	8	4old av	8	5?	445	1	8	2	1	4	1	3
15	4678759	Subash	39	M	1	06-09-2018	1	3,5 floaters	4	sarcoidosis	1	8	6./12	6./12	16	4 pig on ALC &	1	1,4?5 pre ret hmg	df NODULES	436	3	1,3	1	1	1	1	1,2
16	4883151	aJEEM nl	31	f	1	31-10-2018	2	3	4	idiopathic	1	1,4	6./60	6./60	12	2,3	1,3	1,3	5	385	1	8	1	1	1	1	8
17	4845857	liya mol s	17	f	3	27-07-2018	2	3	3	ocular toxo	2	8	6./60	6./60	11	8	8	4	5	474	1	8	1	1	2	1,5	8
18	1958911	Velmurga	33	M	1	10-08-2018	1	3	3	idiopathic	2	8	6./60	6./60	15	8	8	8	5,6	447	2	3	1	1	3	9	8

	bcva 1	bcva3	bcva6	iop1	iop3	iop6	cmt1	cmt3	cmt6	Oct-01	Oct-03	Oct-06	recurrence
patient1	6./12	6./6	6./6	18	16	16	354	319	295	2	2	3	2
2	6./9	6./9	6./9	17	16	16	305	272	272	2	3	3	2
3	6./9	6./12	6,/9	15	19	17	268	596	707	3	1	1	1
4	6./36	6./18	6./18	15	18	18	302	283	274	2	2	3	2
5	6./24	6./24	6./9	16	16	16	385	343	356	2	3	1	1
6	6./9	6./9	6./9	14	17	16	252	406	385	1	1	2	2
7	LOST TO FOLLOW UP												
8	6./36	6./36	6./24	18	19	18	341	328	455	1	2	3	2
9	6./36	6./9	6,/9	18	14	10	320	211	161	2	2	3	2
10	6./18	6./9	6./9	17	16	10	340	213	172	2	3	3	2
11	6./24	6./24	6./18	14	18	17	346	299	273	1	2	3	2
12	6./12	6./9	6./24	20	20	14	256	221	245	2	2	2	2
13	6,/12	6,/12	lost to follow	12	11	lost to follow	261	243	lost	3	3	lost	2
14	6.36	6,18	6.12	14	15	14	220	216	213	2	2	2	2
15	lost tO FOLLOW UP												
16	6,/60	6,/60	lost to follow	15	18	lost to follow	362	404	lost	2	3	lost	2
17	6./.24	lost	lost to follow	13	lost	lost to follow	341	lost	lost	3	lost	lost	2
18	6./36	6./24	lost to follow	14	15	lost to follow	343	410	lost			lost	2