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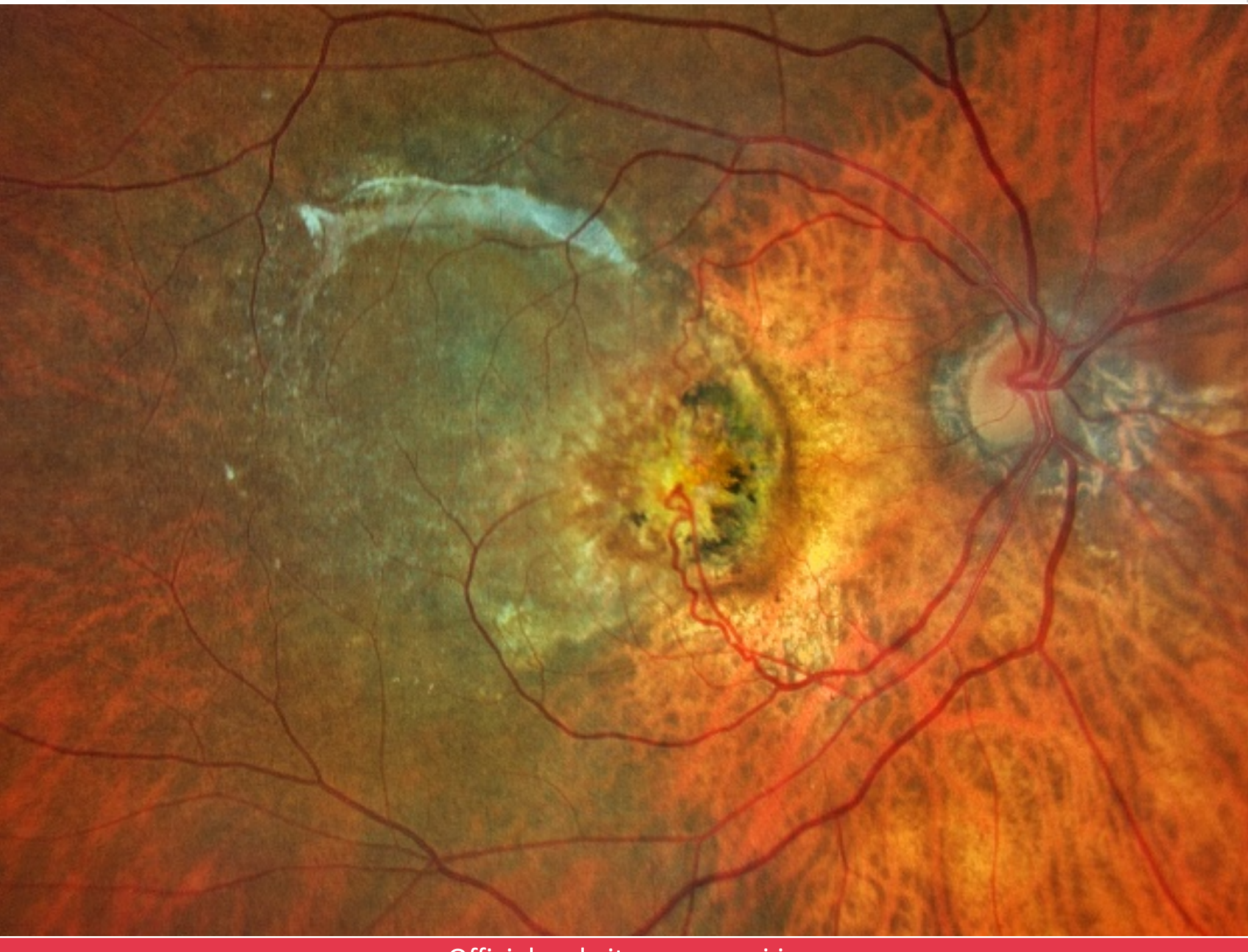
June 2023

The Official Newsletter of the

VITREORETINAL SOCIETY-INDIA



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FROM THE PRESIDENT'S DESK

Dear friends

Yet another issue of our VRSI newsletter is in your hands. The dedication of the team headed by Mahesh Shanmugam is evident by the quality of the contents and the timely release of these newsletters. This issue is also worthy of preserving for the content that focuses on AMD.

The 32nd annual meeting of VRSI will take place in Kovalam beach from December 1st to 3rd. Dr Mahesh is sure to come out with a unique program. The abstract submission is already open. Send in your best work for this meeting.

Our dynamic Secretary Dr Manisha will share the activities of the society in the past months.

Enjoy the issue !!

Dr N S Muralidhar

President, VRSI

FROM THE HONORARY SECRETARY'S DESK

Dear Friends,

VRSI is making best effort to spread awareness of blindness due to diabetic retinopathy (DR). As a part of this initiative the guidelines for DR screening by the Physicians is being worked on along with RSSDI. We have been conducting DR management skill transfer workshops in two tier cities thereby motivating Physicians to adopt a model of DR screening and General Ophthalmologists to contribute in screening and management of DR.

Various activities are being done including the profile update of the members, provision of the recordings of last year annual conference and multi-centric collaborative studies. We have been having regular newsletters and the Retina updates from our scientific Convenor Dr. Mahesh P. Shanmugam and the editorial team. They are being appreciated by all and found very useful. Recently an interesting webinar was conducted on AI and Chat GPT which was very informative to all the members.

This newsletter covers various aspects of managing age related macular degeneration (AMD) which is an important retinal pathology found in geriatric age

group of patients. This makes us as retina specialists deal with other aspects of patient care beyond medical care. The editorial team has put in great effort to compile this wonderful newsletter. Hope all of you enjoy reading this issue and find it useful for patient care.

This year annual conference is being hosted by Dr Unnikrishnan Nair at Trivandrum from 1-3rd Dec 2023. Kindly block your dates and we look forward to an active participation by all the members in the annual conference.

Regards

Dr Manisha Agarwal

Hon General Secretary VRSI

FROM THE CONVENER, SCIENTIFIC COMMITTEE'S DESK

Dear Friends,

Greetings!

Dr. Pradeep Sagar has curated this issue of the newsletter and the topic chosen is AMD. As in the previous issues, this has also turned out to be a keeper issue that details all about AMD – from contemporary to the future emerging trends and treatments.

Dr. Siddharth Narendran introduces us to the concept of inflammasomes, proteins that direct the inflammatory response and may be fuelling chronic inflammation in various age-related diseases, one of them being AMD. We may see therapies aimed at this pathway in the future and this article educates us on the role of inflammasomes in AMD and its future therapeutic potential.

Dr. Apoorva's article is a detailed review on the OCT biomarkers in nAMD. Dr. Aniruddha Agarwal's article details the role of OCTA in AMD, concise, yet complete. It is the OCTA that introduced to us the non-exudative neovascular AMD and Dr. Rama Kumar details its relevance in our clinical practice.

Current management of AMD is elegantly covered by 2 experts, Dr. Anand Rajendran and Dr. Jay Chhablani who opine of various aspects of AMD care, particularly the ones with no clear-cut guidelines, helping us formulate treatment

strategies in difficult situations.

Finally, we have a treatment option for geographic atrophy and Dr. Dilraj Grewal summarizes the results of trials with pegcetacoplan in dry AMD and where we may use them in treating our patients in the near future.

Replacing the diseased cells with new ones has always captured our imagination and the potential role of stem cells that can transform in to retinal cells has always been a promise, a promise that is yet to realize its potential. Ms. Rashmi Prabhu and Dr. Rajani Battu's article tell us more about the potential role of stem cells and how they can make a difference in the future.

The overall management of AMD has been summarized for easy reference by Dr. Sriram, concluding this issue of the newsletter.

The preparations for the forthcoming VRSI conference have begun and abstract submissions are open. Look forward to a great learning experience with support from all of you. The concept of the VRSI study group is slowly gaining roots and we hope to have meaningful collaborative studies in the near future.

Thank you for all your support and encouragement.

Dr. P. Mahesh Shanmugam

Convener, Scientific Committee, VRSI.

GUIDELINES:
MANUSCRIPT SUBMISSION FOR VRSI NEWSLETTER

Original Articles :

These include randomized controlled trials, interventional studies, studies of screening and diagnostic test, outcome studies, cost effectiveness analyses case-control series, and surveys with high response rate. The text of original articles amounting to up to 3000 works (excluding Abstract, References and Tables) should be divided into sections with the headings: Abstract, Key-words, Introduction, Material and Methods, Results, Discussion, References, Tables and Figure legends.

Case Reports / Challenging Case / Innovations / Instruments / Techniques:

New, interesting, challenging, rare cases, innovations, instruments and techniques can be reported. They should be unique and providing learning point for the readers. Manuscripts with clinical significance or implications will be given priority. These communications could be of up to 1000 words (excluding Abstract and References) and should have the following headings : Abstract (unstructured), Key-words, Introduction, Case, Discussion, Reference, Tables and Legends in that order. The manuscript could be supported with up to 10 references. Case Reports could be authored by up to four authors.

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COVERPAGE IMAGE

Dr. Shobhit Chawla

Dr. Priyanka Raj

Dr. (Maj) Vishal Gupta

Prakash Netra Kendr, Lucknow

Fundus image of the right eye of a 65 year old female showing a retinochoroidal anastomosis in stage III RAP (Retinal Angiomatous Proliferation) often recognised as a distinct form of neovascular AMD. Her BCVA remains 2/60 and has been stable without any Anti-VEGF therapy for over a year

PHOTO ESSAY: ANTERIOR MIGRATION OF THE BUCKLE ELEMENT EVIDENT ON AS-OCT

Dr. P Preethi

Mr. Karthick Jayavel

Dr. Muna Bhende

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Case report:

A 69 year old man underwent scleral buckle with encirclage in left eye for rhegmatogenous retinal detachment 25 years ago. He was a high myope and was on anti glaucoma medications. On a routine follow up examination his BCVA was no perception of light in right eye and 6/60 with N24 in left eye. Left eye showed anteriorly migrated encircling band reaching close to the inferior limbus (Figure 1). There was an inferior iris coloboma and posterior chamber intraocular lens (PCIOL). No exposure or intrusion of sutures or buckle elements were noted. Retina was well attached with scar at the macula and retinochoroidal coloboma sparing disc and macula. As the anterior border of the band was not visible, he was advised anterior segment optical coherence tomography (AS-OCT) (MS-39; Costruzione Strumenti Oftalmici (CSO), Firenze, Italy) which is a spectral domain OCT (16 mm corneal section) combined with placido disc. This showed the migration of the encircling band into the cornea at the inferior limbus (Figure 2). He was advised of the possibility of further intrusion and the need for close observation.

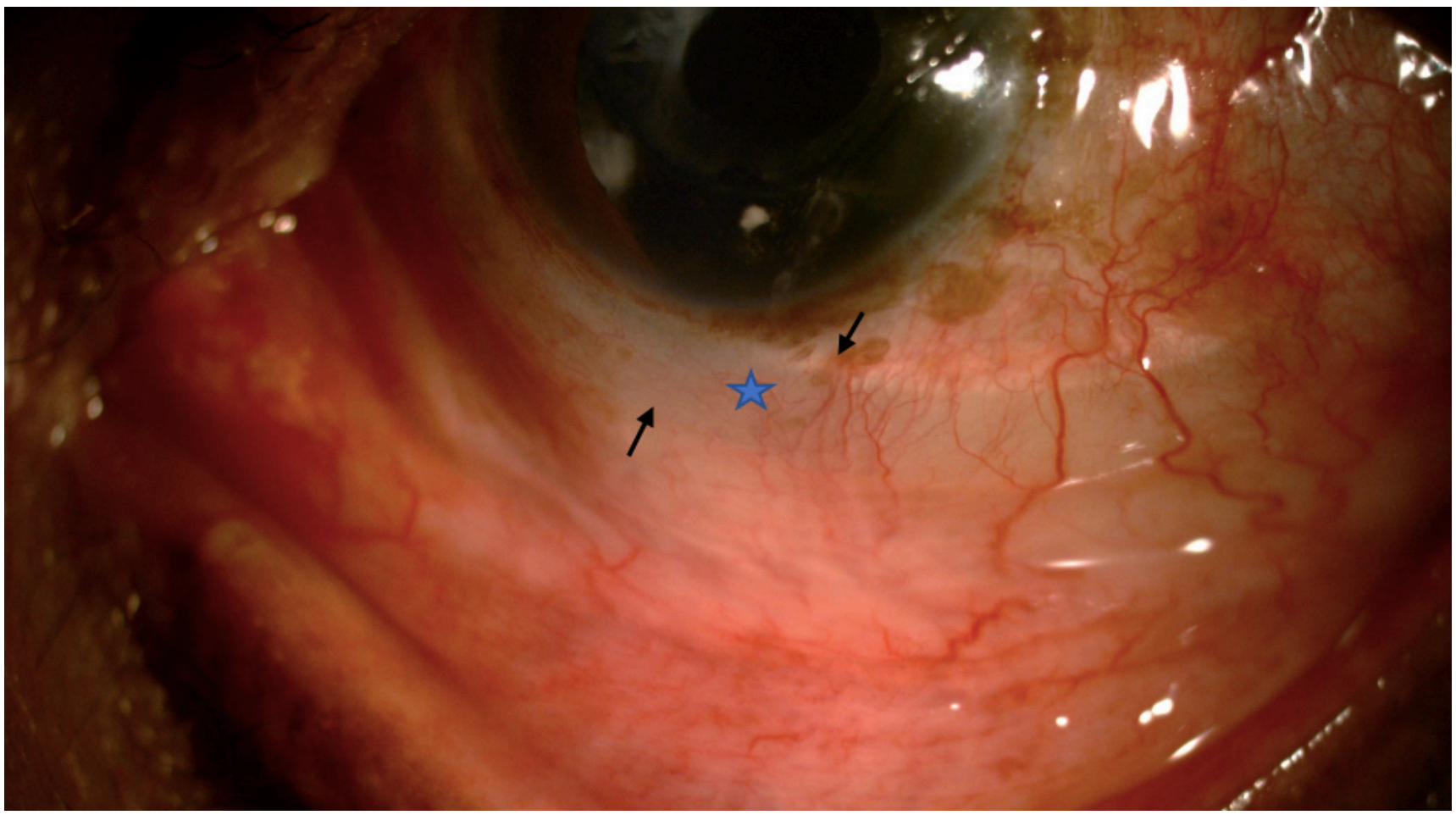

Figure 1- Anterior segment slit lamp image of the left eye: star show the anteriorly migrated encirclage and arrows shows the edges of the encirclage

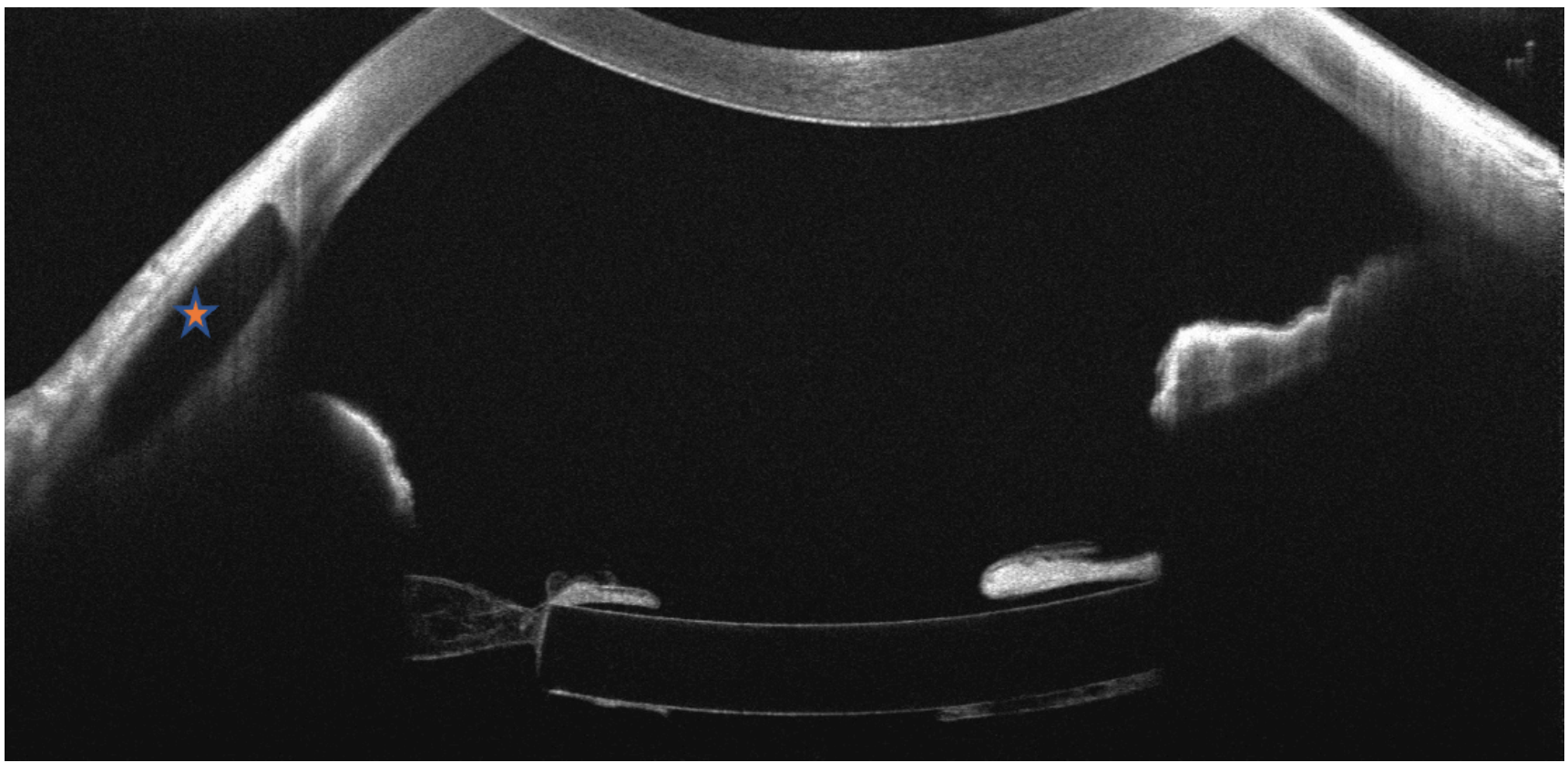

Figure 2: Anterior segment- optical coherence tomography image of left eye- star show position of encirclage in the corneal stroma

Discussion:

Scleral buckle surgery is one of the oldest and commonly done procedure for rhegmatogenous retinal detachment. Encirclage migration through the muscle insertion is an uncommon complication which can occur several years after successful surgery. Though mechanism of migration through the muscle insertion is unclear, it has been hypothesised that the silicon band can cheese wire the recti muscles and this slow process can give sufficient time for the muscles to reattach to its original insertion site.[1] Anteriorly placed buckle elements, superficial anchor sutures or tunnels, excessive cryopexy and high myopia are described risk factors.[2] Most cases are observed unless there is a further complication noted.[3]

Demonstration of the migrated element into the cornea has been described with ASOCT. However, in this case we used the investigation to identify the element that was not visible clinically.

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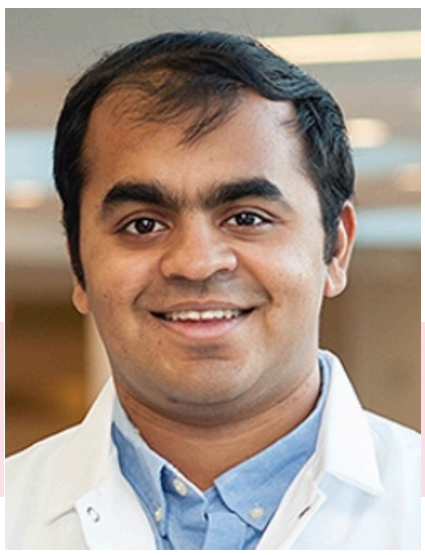
UPDATE ON AMD

INFLAMMASOMES IN FOCUS: NEW FRONTIER IN AGE-RELATED MACULAR DEGENERATION TREATMENT



Dr. Siddharth Narendran

Aravind Eye Hospital, Coimbatore

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Introduction

Age-related macular degeneration (AMD) is a series of complex disease processes involving multiple stressors, pathways, cell types, genetic susceptibilities, and environmental factors. Paralleling the dynamics seen in many aging-associated neurodegenerative diseases, chronic inflammation acts as a ubiquitous yet distinct catalyst, intricately interlaced within the pathobiology of both dry and wet forms of AMD. It significantly dictates their distinctive progression trajectories and exerts a profound influence on the scope of retinal deterioration and subsequent vision loss. Modulating chronic inflammation has emerged as a pivotal therapeutic strategy in AMD, providing substantial potential for prevention, halting, and decelerating disease progression, thereby fortifying the ramparts safeguarding vision.[1]

Inflammasomes, critical sentinels of the innate immune system, are intracellular multimeric protein complexes that assemble in response to a spectrum of danger signals, from stealthy pathogen intrusions to subtle metabolic shifts associated with

aging, thereby orchestrating an array of inflammatory responses. Due to their pivotal role in fuelling chronic inflammation that underpins a multitude of age-related diseases, inflammasomes have emerged as compelling therapeutic targets in several neurodegenerative diseases that share a pathobiological footprint with AMD, such as Alzheimer's disease. This assertion gains further momentum from the increasing number of clinical trials that are actively targeting inflammasomes in chronic neurodegenerative conditions, spotlighting the potential of such therapeutic strategies in managing these complex diseases.[2]

Among the members of the inflammasome family, the NLRP3 (NOD-, LRR- and pyrin domain-containing protein 3) inflammasome stands out as the most prominently implicated member in the pathogenesis of neurodegenerative diseases. The connection between AMD and inflammasomes was first unearthed in a groundbreaking study, revealing a compelling association between the NLRP3 inflammasome and geographic atrophy (GA).[3] This seminal discovery underscored the influence of *Alu* RNA (endogenous retrotransposons) accumulation in the retinal pigmented epithelium (RPE) due to DICER1 deficiency, which activated the NLRP3 inflammasome, heralding a new understanding of AMD pathogenesis. Subsequent research expanded our understanding by identifying multiple AMD-related stressors that activate the NLRP3 inflammasome, such as lysosomal destabilization, oxidative stress, accumulation of lipofuscin-like material, and amyloid oligomers.[4] Each of these factors contributed to AMD pathology in unique ways, culminating in NLRP3 inflammasome activation.

Inflammasomes' role in AMD also extends beyond NLRP3, with recent studies highlighting the pivotal and synergistic role of non-NLRP3 inflammasomes in the disease progression in both Choroidal Neovascularization (CNV) and GA.[5] Strengthening the link

between inflammasomes and AMD, recent research has spotlighted inflammasome proteins as promising biomarkers for AMD progression.[6]

Over the decade since the seminal paper, a substantial body of research has explored inhibiting the inflammasome as a potential therapeutic strategy for AMD. Interestingly, repurposed anti-HIV nucleoside reverse transcriptase inhibitors (NRTIs) have been found to exhibit inherent anti-inflammatory effects independent of their reverse transcriptase inhibitory activity.[7] This uncoupling alleviates the side effects typically associated with reverse transcriptase inhibition. Kamuvudines, modified NRTI analogs, have been recognized for suppressing inflammasome activation while maintaining antiretroviral inertness. This characteristic, namely their lack of reverse transcriptase inhibition and subsequent avoidance of related toxicities, presents a substantial advantage. In experimental models, Kamuvudines have demonstrated efficacy in treating both CNV and GA types of AMD.[8] Furthermore, clinical trials utilizing Lamivudine, an NRTI, and Kamuvudine have been initiated to address other inflammasome-dependent retinal degenerative diseases, such as diabetic macular edema.[9,10] In conclusion, harnessing the potential to inhibit inflammasome activity, especially targeting the pivotal NLRP3 inflammasome, could herald a transformative shift in our ability to combat AMD and related neurodegenerative disorders, opening a new horizon in the therapeutic landscape of these complex aging-associated diseases.

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OPTICAL COHERENCE TOMOGRAPHY BIOMARKERS IN NEOVASCULAR AMD

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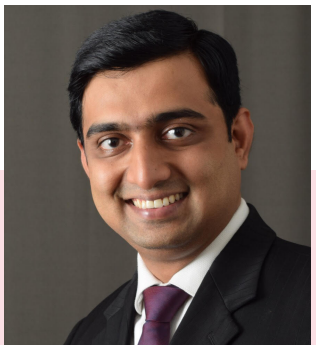

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Introduction

Multimodal imaging including optical coherence tomography (OCT), fluorescein angiography (FA), indocyanine green angiography (ICGA) and optical coherence tomography angiography (OCTA) should be used for the diagnosis and follow up of neovascular age related macular degeneration (nAMD). However, OCT alone can be extremely useful in the diagnosis and evaluation of treatment response in cases of nAMD. It is used widely by most ophthalmologists in their clinics. OCT is quick, user-friendly, non- invasive and provides high-resolution, ultrastructural detail of chorioretinal anatomy and vasculature. [1]

A biomarker is defined as morphological and structural alterations that can provide information about disease staging.[2] OCT biomarkers can help in retinal conditions by providing important details for prognostication at baseline and during follow ups. Biomarkers can be divided into two categories.

1. Based on retinal distribution of fluids- Intraretinal fluid (IRF), subretinal fluid (SRF) and sub- retinal pigment epithelium (RPE)- sub- RPE fluid.
2. Structural biomarkers- based on the presence or absence of specific features in the
    i. Retina- photoreceptor layer integrity, hyperreflective dots, outer retinal tubulations, subretinal hyperreflective material, RPE tears, multi-layered PED
    ii. Choroid- Pre-choroidal cleft, choroidal caverns, choroidal vascularity index
    iii. Vitreomacular interface- vitreomacular adhesion, vitreomacular traction

This brief review highlights the various OCT biomarkers in nAMD that have value in initial diagnosis and treatment responses during follow ups.

Intraretinal fluid (IRF)

It is defined as the presence of cystoid spaces in the inner retinal layers typically associated with retinal thickening. IRF/ Intraretinal cysts (IRC) is seen in association with macular neovascularization (MNV) type 2 and 3 and in later stages of type 1. [3] (Figure 1)

The presence of IRF at baseline forms the bulk of the predictive value for vision loss. It is the most important negative prognostic marker associated with high risk for macular atrophy (MA) and fibrosis.[4] Many studies have concluded that IRF is associated with poor baseline visual acuity (BCVA) as well as lower visual improvement after treatment initiation especially if it persists in the first 3 months of treatment. When IRF persists after 12 injections, the incidence of atrophy and fibrosis is higher. [5]

Specifically, the presence of inner nuclear layer cysts (INLc) is associated with gross sub foveal choroidal thickness reduction and decreased BCVA at 24 months.[6] Persistent small spaces after 1 year of treatment indicate that the persistent cysts are more likely to be due to cell- death rather than due to VEGF- driven mechanisms.[7]

The horizontal extension and eccentricity of IRC from the fovea are also important for prognostication. [8] The CATT study found the presence of IRC in 60% eyes at the end of 5 years, wherein, mean VA was worse in foveal IRC compared to extrafoveal IRC. [9]

Prevalence of IRF is 5- fold higher in eyes that receive injections vs. eyes that do not undergo treatment, indicating low tolerance for IRF in both patients and retinal physicians. IRF without associated visual loss is seen only in 7.4% of total injection visits. [10] Although, there is no difference in anti- VEGF efficacy between eyes with IRF and those without, higher absolute values of IRF at the point of switching predicted a better response to a switch in treatment. [11]

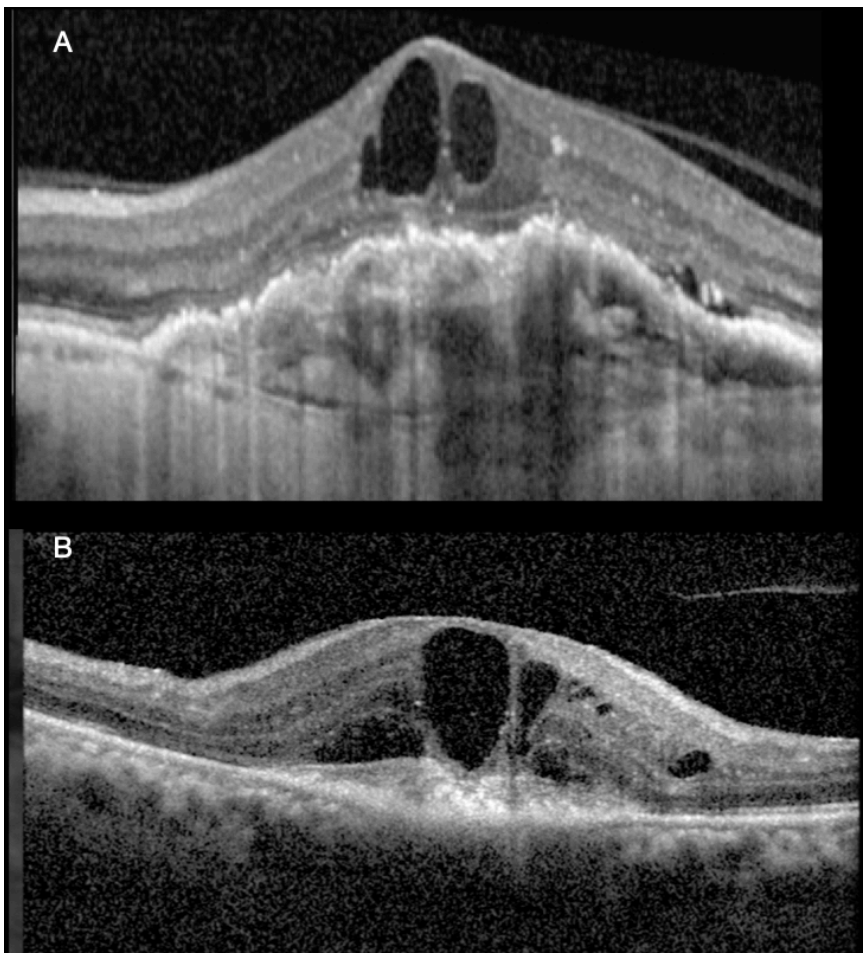

Figure 1: A- Intraretinal fluid in a case of type 1 MNV, 1B- Persistent large IRF spaces unresponsive to treatment in a scarred MNV

Subretinal fluid (SRF)

It is defined as fluid exudation between outer retina and RPE. (Figure 2) SRF is associated with higher values of baseline VA and better visual outcomes after treatment. [12] Post hoc analysis of VIEW showed that eyes with SRF at baseline had higher mean BCVA at baseline and through treatment, compared to eyes without SRF at baseline.[13] Rapid improvement in SRF is associated with better visual outcomes. However, greater fluctuations of SRF in the first 12 months may result in lower BCVA.[14] Chatrizalli et al reported the highest values of VA at baseline in eyes with SRF compared to eyes without SRF. Final visual acuity was comparable in eyes with SRF alone and those without SRF. Hence SRF associated with IRF and PED determined the final VA rather than the presence of isolated SRF. [15]

CATT study showed that VA was better in eyes with foveal SRF at 5 years than in those without SRF. [16] A post- hoc analysis of the randomized HARBOR study showed that the absence of SRF at baseline was associated with an increased risk of macular atrophy and low VA. It was postulated by the study workers that SRF is probably protective against MA *OR* that the presence of a low- activity MNV supported RPE metabolism.[4] In CATT study, SRF was proposed to protect the photoreceptors from potential toxicity due to

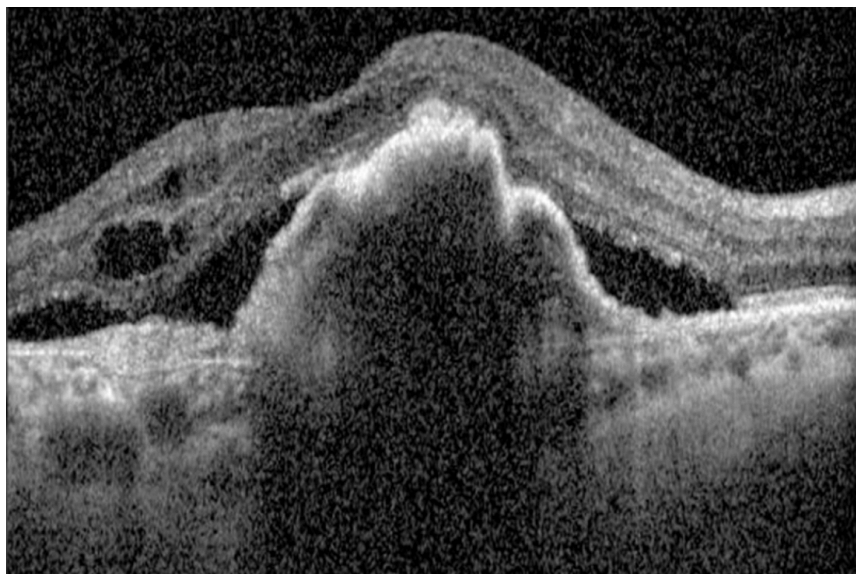

Figure 2- Predominant SRF with a few IRF spaces overlying a fibrovascular PED

direct contact with underlying diseased RPE. SRF may also provide a pool of neuroprotective factors providing trophic support to the overlying photoreceptors. [16] The FLUID study evaluated the outcomes of ranibizumab treatment in two groups, viz. ≤ 200 microns of fluid tolerated subfoveally vs. resolved SRF. Both groups had similar outcomes, however, in eyes with residual SRF there was progressive reduction in sensitivity on microperimetry. [17]

Pigment epithelial detachment

PED is defined as an RPE detachment due to exudation of fluid, hemorrhage or because of a membrane. It is separation of the RPE from the inner collagenous layer of the Bruchs membrane. (Figure 3)

It has an inconsistent relationship with visual acuity and is hence less important for visual acuity prognosis. It is not significantly associated with progression to advanced AMD, except when seen concomitantly with SRF and IRC. [18]

A post- hoc analysis of VIEW revealed a better VA at baseline in presence of a PED compared to eyes without, however this reduced in significance during treatment. [13]

HARBOR trial showed that eyes with PED at baseline and at 2 years showed better VA. [19]

The CATT study showed that eyes with a foveal PED had in fact a higher visual acuity at the 5th year. [16] The postulation is that a PED may provide trophic support to the outer retina and hence treating a PED to full resolution may be detrimental to visual

outcomes. [20]

PED characteristics such as height, width, volume, dome vs. peak shaped, RPE rip or cholesterol bands (onion sign) had no relation to final anatomical or visual outcomes. [18]

A serous vascularized PED (shows hyperreflective structures underneath the RPE that occupy only a part of the PED) has however shown an increase in > 5 letters post treatment. The reduction in PED height is also more in serous vascularized PED than in a fibrovascular PED. [21]

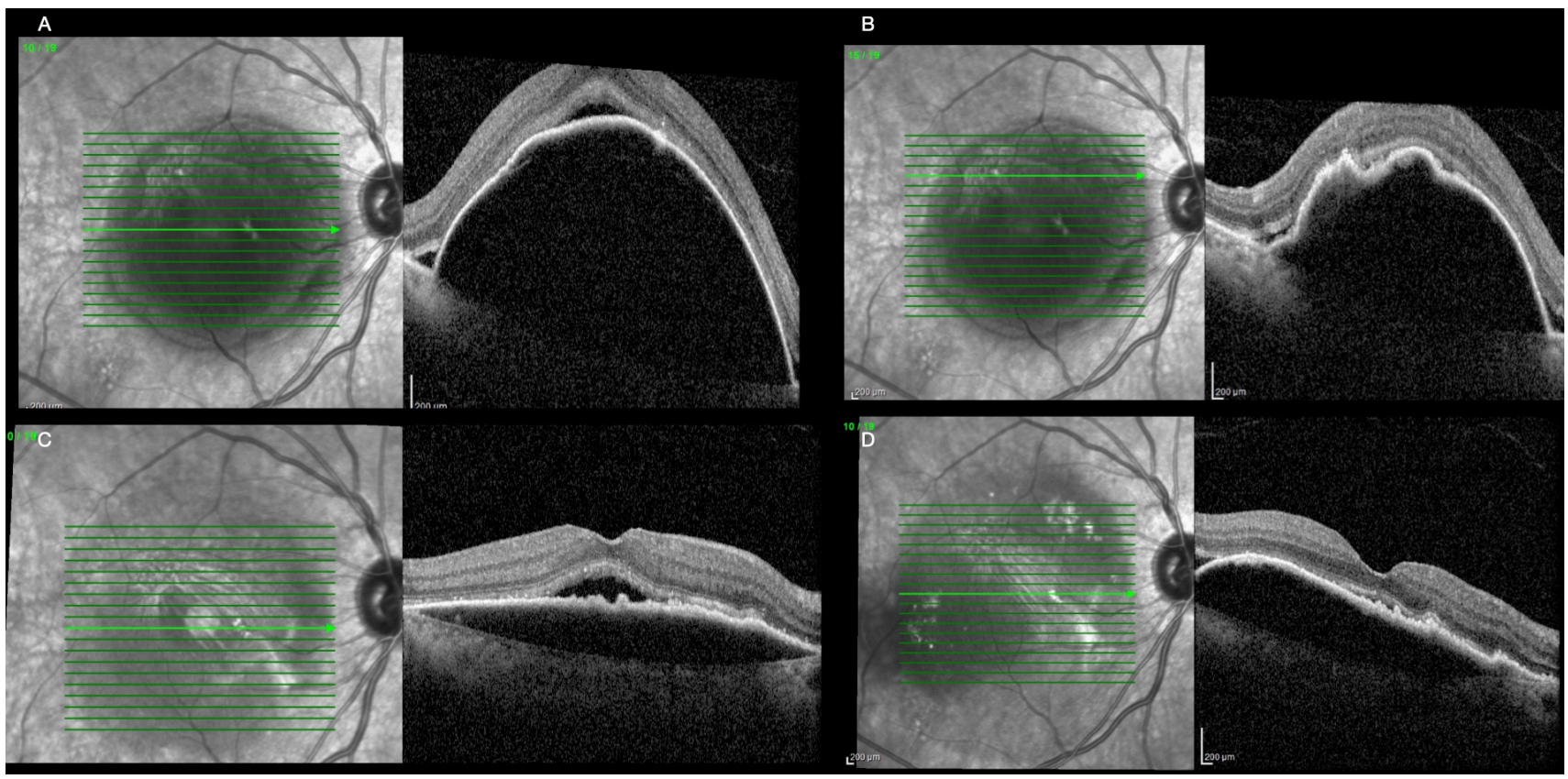

Figure 3: A- Foveal line scan in the right eye of a 75-year-old man showing a large serous PED, B- line scan through the fibrovascular component showing rippling of the RPE with a hyper reflective membrane on the under surface of the RPE. C and D- Reduction in PED height after injection no.1 and injection no. 3 respectively.

Subretinal hyperreflective material (SHRM)

Defined as hyperreflective material between the neurosensory retina and RPE. (Figure 4)

It can be composed of fluid, fibrin, blood, scar or MNV. [22]

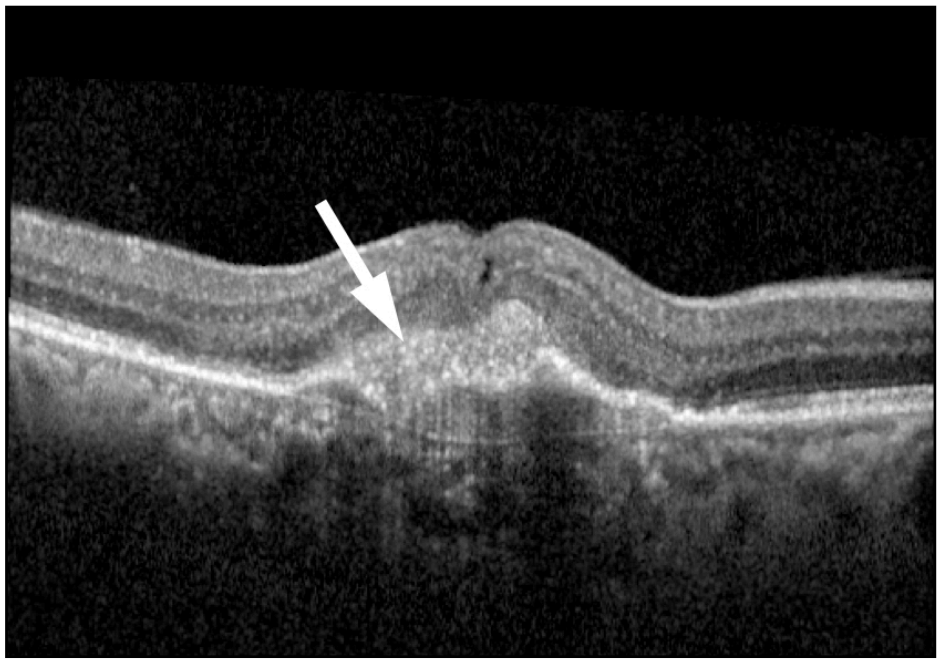

Figure 4- Undefined SHRM- in a type 1 MNV (White arrow)

SHRM is associated with poor baseline visual acuity than eyes without SHRM. Higher VA was noted at month 12 with no SHRM and the lowest VA was recorded with undefined SHRM. [23]

SHRM with associated IRF form the bulk of the predictive value on outcomes with presence of SHRM at baseline being the most significant predictor. [24]

Pigmentary SHRM due to migration of RPE is associated with progression to advanced AMD (MA/ MNV). [25] Alex et al noted that the worst visual outcome was when foveal SHRM exceeded 0.24 mm^2. [26]

The subset of SHRM that is diffuse and located in the subretinal space is a result of inflammation in AMD. Well- defined SHRM has a better visual acuity at month- 12, compared to undefined SHRM. Undefined SHRM suggest a re-activation at month- 12 and hence has a poorer visual acuity. [23]

Vascularized SHRM has IRF at baseline and is associated with external limiting membrane (ELM) disruption. Vascularized SHRM is a predictive factor for less response to anti- VEGF treatment.[27] Baseline characteristics of SHRM such as layered appearance, hyperreflective spots, SHRM separation from outer retina and larger size have a negative impact on outcomes. The decrease in reflectivity of SHRM over follow- ups is associated with better VA.[28] When SHRM is associated with less response to anti VEGF- it indicates an angio- fibrotic switch. This can occur as early as 3 months during treatment. [29]

Drusen

Associated with development of late AMD. Baseline drusen volume of approximately 0.03 mm^2 is a significant predictor of late AMD (MA or nAMD) even in fellow eyes. [30] HARBOR trial showed that an increase in mean drusen thickness of about 30 microns at the foveal centre had an increased risk of developing MNV and mean drusen thickness of about 17 microns at foveal centre was associated with increased risk of macular atrophy. [19] Drusen at foveal centre are seen to be associated with MNV and parafoveal drusen with macular atrophy. [31] Dot- subretinal drusenoid deposits (SDDs) are independently associated with MNV and confluent SDD with GA. [32]

Photoreceptor layer integrity

The integrity of ellipsoid zone (EZ) and external limiting membrane (ELM) is closely associated with VA. In nAMD, foveal ELM band and foveal EZ band disruption has been associated with poor VA at baseline and after anti-VEGF therapy. Coscas et al have described that baseline foveal ELM and EZ integrity are predictive of final photoreceptor layer integrity and final VA. [33] Restored foveal ELM band after anti- VEGF therapy shows a correlation with better VA. [34]

RPE atrophy

A leading consensus group has defined RPE atrophy in terms of outer retinal, RPE and choriocapillaris atrophy and has coined the terms iRORA (incomplete RPE and outer retinal atrophy), cRORA(complete RPE and outer retinal atrophy, iORA (incomplete outer retinal atrophy), cORA (complete outer retinal atrophy). iRORA has been shown to have the highest incidence of MNV followed by cORA, iORA and cRORA. [35] RPE atrophy has also been shown to be the primary factor predicting visual deterioration in type 3 MNV.

Outer retinal tubulations (ORT)

These are biomarkers located in the outer nuclear layer and was first described by Zweifel et al. ORTs are uncommon at baseline, appearing only in later stages of treatment (Figure 5). These are hypo reflective circular structures surrounded by a hyperreflective band. They represent a rearrangement of photoreceptors as a consequence of chronic retinal hypoxia and are associated with worse visual acuity when compared to eyes without ORT.[9] Anti-VEGF treatments neither prevent nor cause any regression of ORTs. [37]

***Hyperreflective foci*(HF)**

These can occur due to lipid exudation, inflammatory aggregates or migratory RPE cells. [38] Coscas and colleagues showed that poor BCVA at baseline was significantly associated with persistence of HF after anti-VEGF therapy. In responders, HF quickly decreased after the first injection. [39]

RPE rip or RPE tears

These are complications of nAMD and represent a breach in the RPE monolayer causing an area of RPE denudation and scrolling of RPE. (Figure 6) They can occur spontaneously or because of laser, PDT, or anti- VEGF treatments. [40] Tears are from a fibrovascular PED more commonly (80.6%), followed by hemorrhagic PED (16.2%) and serous PEDs (3.2%). [41] PED height > 400 microns, a large PED basal diameter, small MNV/ PED size ratio are risk factors for RPE tear following intravitreal anti VEGF injection. [42] The OCT shows a wide area of RPE loss and the scrolled- up RPE shows back- shadowing. The denuded area shows hyper transmission. Rips are associated with a sudden increase in SRF.

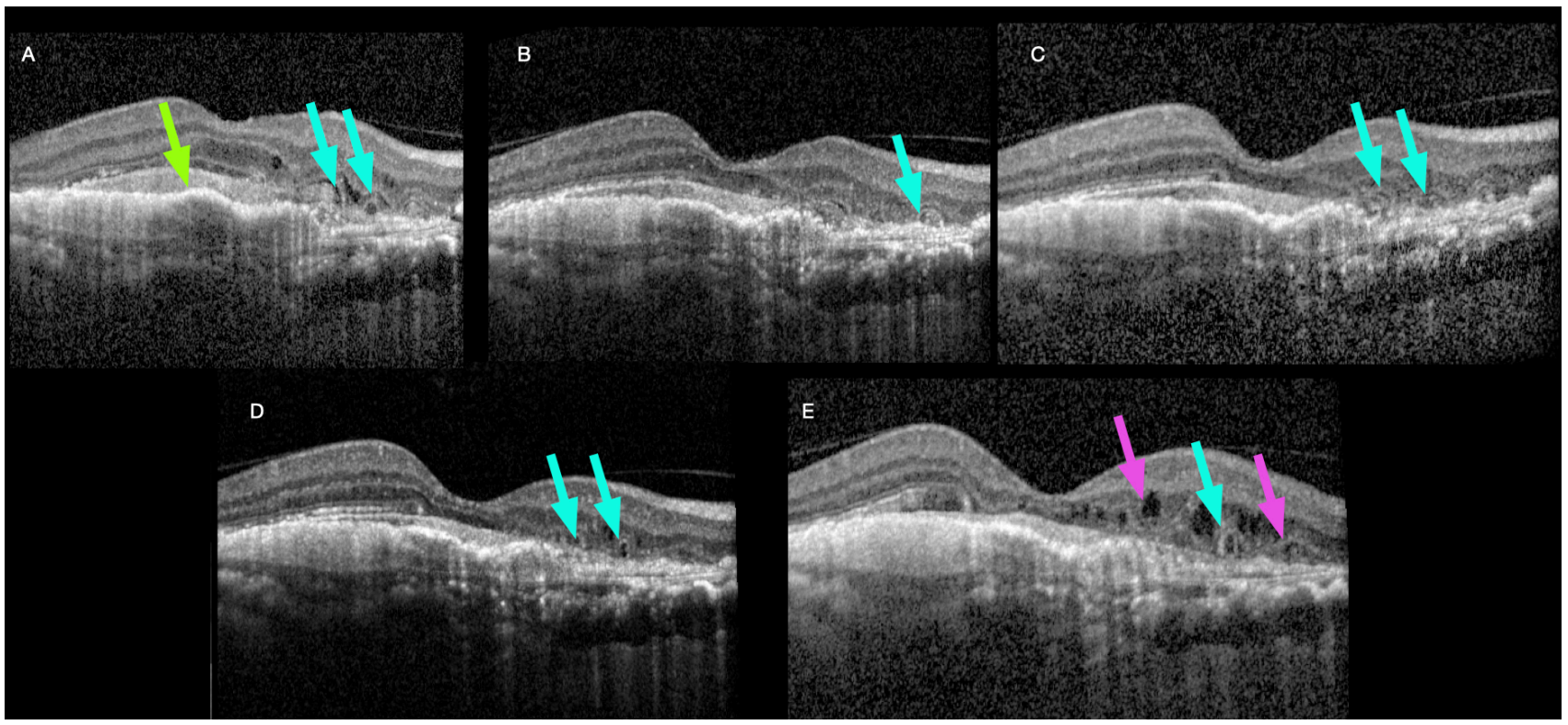

Figure 5- Evolution of an ORT in the right eye of a 65-year-old woman

A- Baseline - Type 1 MNV with overlying SHRM (green arrow) and few cysts in outer retina (blue arrows).

B- After one anti- VEGF injection, minimal reduction in SHRM, and reduction in hypo reflective cysts seen, although mounds of outer retinal hyper reflective material have appeared (blue arrow). Foveal ELM loss noted.

C- After 2nd injection, organised SHRM, loss of foveal ELM band and whorling with unformed ORTs seen. (Blue arrows)

D- After 3rd injection, cavitation of foveal outer retina. Formed ORTs now seen (blue arrows). Anti- VEGF treatment stopped.

E- At 12- months follow up, persistent formed ORT (blue arrow) and more unformed ORTs appeared (purple arrows). VA remained unchanged.

There are no guidelines on the management of rips, although there are studies that advocate half- dose and frequent injections. However, the consensus is, that anti- VEGF treatment should be continued, since there is higher incidence of disciform scar

formation, lest the rips remain untreated. The prognosis after RPE rip is variable and depends on the pattern of RPE healing. Excessive and persistent SRF can lead to thick SHRM formation and poor prognosis. Early resolution of SRF shows better outcomes. [43]

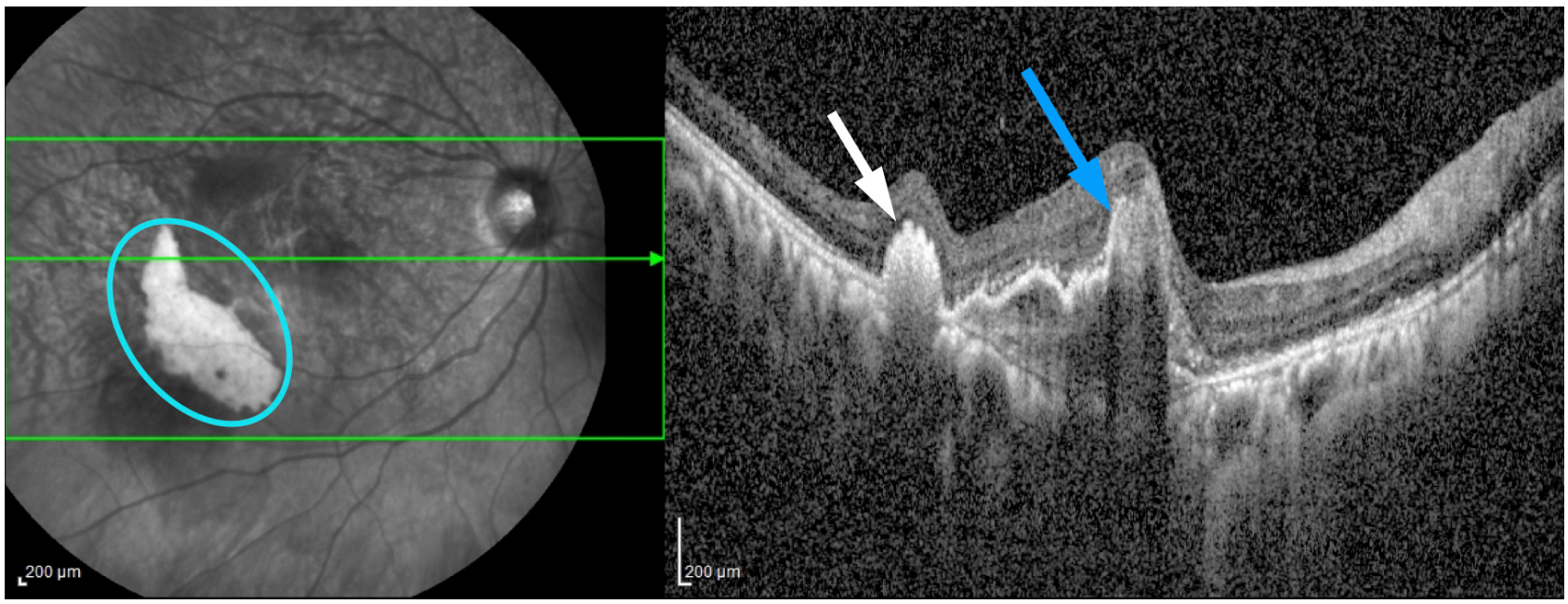

Figure 6 - Blue oval - showing area of scrolled up RPE.

Blue arrow- Hyper reflective mound with back shadowing indicating layered RPE. White arrow also indicates a RIP on the opposite end of the fibrovascular PED. This is a line scan showing two mounds of RPE because of a bi-directional rip.

Vitreomacular interface abnormalities

Patients with vitreomacular adhesion (VMA) may develop a resistance to anti- VEGF treatment. The partial detachment of vitreous may affect the availability of drug and prevent achievement of the target concentration. [44] Vitreomacular traction (VMT) is different in that, persistent traction results in chronic inflammation that causes progression of nAMD activity. A surgical removal of VMT could potentially reduce the traction and inflammatory effects of VMT and improve the diffusion of cytokines and VEGF from the macular to vitreous. [45]

Pre choroidal clefts

These are pockets of fluid underneath a multi-layered PED and are above the Bruchs membrane, seen in cases of chronic fibrovascular PEDs (Figure 7). Pre choroidal cleft may sometimes be the only evidence of activity in cases of lack of fluid in other compartments of the retina. The series of hyperreflective lamella are due to remodelling of sub RPE neovascular lesions. The cicatrizing process in these cases are confined to the sub RPE space and hence have good visual acuity. These eyes are also less prone to macular atrophy, probably due to the trophic support provided by the neovascular tissue to the outer retina. Multi-layered PEDs are also less prone to RPE rips. [46] [47]

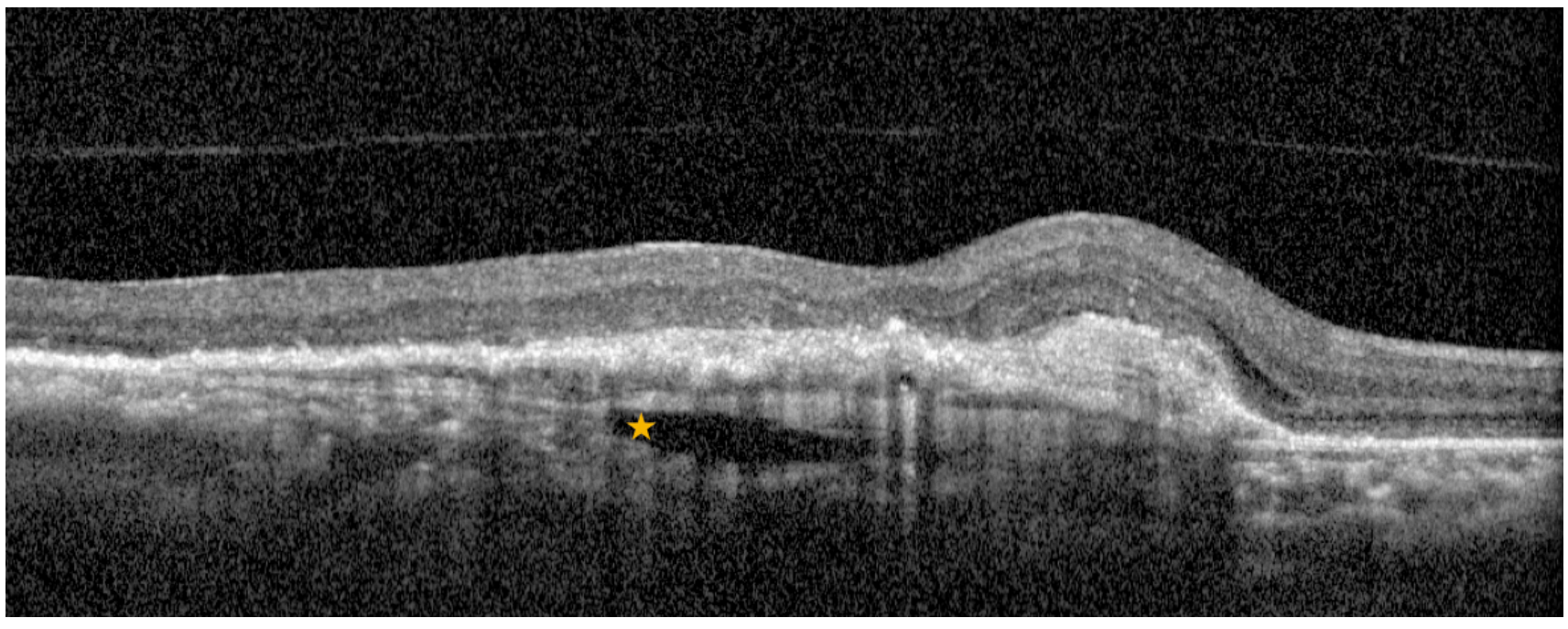

Figure 7- Yellow asterisk- prechoroidal cleft, convex outwards, situated underneath the multilayered RPE. There are no other fluid compartments like IRF, SRF or serous PED.

Quantitative metrics

Central macular thickness (CMT) or central subfoveal thickness (CSFT) does not consider retinal fluid and neural tissue separately. It is a poor marker since, it does not distinguish between SRF, IRF and disregards PEDs. It also ignores extramacular fluid. Central retinal thickness also has poor sensitivity for detecting change in VA. However, progressive increase in central subfield thickness is associated with poorer BCVA. Baseline central

retinal volume correlates significantly with BCVA at baseline, 3 months and 12 months and the correlation increases with increase in follow- up duration. [14]

Sub foveal choroidal thickness –Although choroidal hypoperfusion has been implicated in causation of exudative AMD, a significant correlation between sub foveal choroidal thickness and VA recovery in nAMD has not been noted. Thin SFCT is however correlated with baseline macular atrophy.[48] Choroidal vascularity index (CVI) has been devised with a binarization method of separately viewing the choroidal tissue and vascular lumen. CVI is defined as the proportion of the lumen area over the total analysed area of the scan. Several studies have correlated the reduction in CVI with reduction in luminal area, in comparison with the stromal area.[49]

Artificial intelligence – An objective approach to OCT biomarkers in nAMD

Machine learning has made it possible to process routine SD- OCTs and precisely ascertain the location and severity of macular fluid in various retinal tissue compartments. The software generates quantitative data related to SRF, IRF and PED volumes. This circumvents subjective biases by clinicians about qualitative descriptions such as “trace IRF” or “minimal IRF”. Such descriptions have poor inter-grader consistency. Hence, instead of using a heat map, where just macular thickness is compared spatially with reference values, the large volumetric data provided by SD- OCT can be used, by employing AI- generated deep learning models. Keenan et al used this concept to quantitatively assess retinal fluid volumes using Vienna fluid monitor or Notal OCT analyzer applied to macular cube scans in eyes with nAMD. The fluid volumes were expressed in nanolitres. Nanoliter (nL) was noted to be a convenient unit for consistency between studies. AI accurately monitored fluid characteristics in different AMD

populations at baseline and during follow ups. [50] There are distinct advantages in adopting these quantitative metrics in clinical practice and research.

Conclusions

The identification of specialized biomarkers at baseline can help in long- term prognostication even before starting treatment. Biomarkers not only, evaluate progression and treatment response, they do so regardless of changes in visual acuity. In fact, variations in the biomarkers during treatments can be effective in communicating prognosis to patients to set realistic expectations from therapy. OCT biomarkers can be studied longitudinally and can be used to decide to reduce or stop treatment such as in cases of ORTs, persistent IRF, loss of photoreceptor layers in patients with no further visual improvement. A reduction in IRF, persistent SRF or PED can prompt physicians to continue treating. With the vast quantity of volumetric data available in virtually every retinal physician's out- patient clinic, machine learning can be used to glean information about disease activity and treatment response and a highly- individualized approach can be used to address different disease- courses.

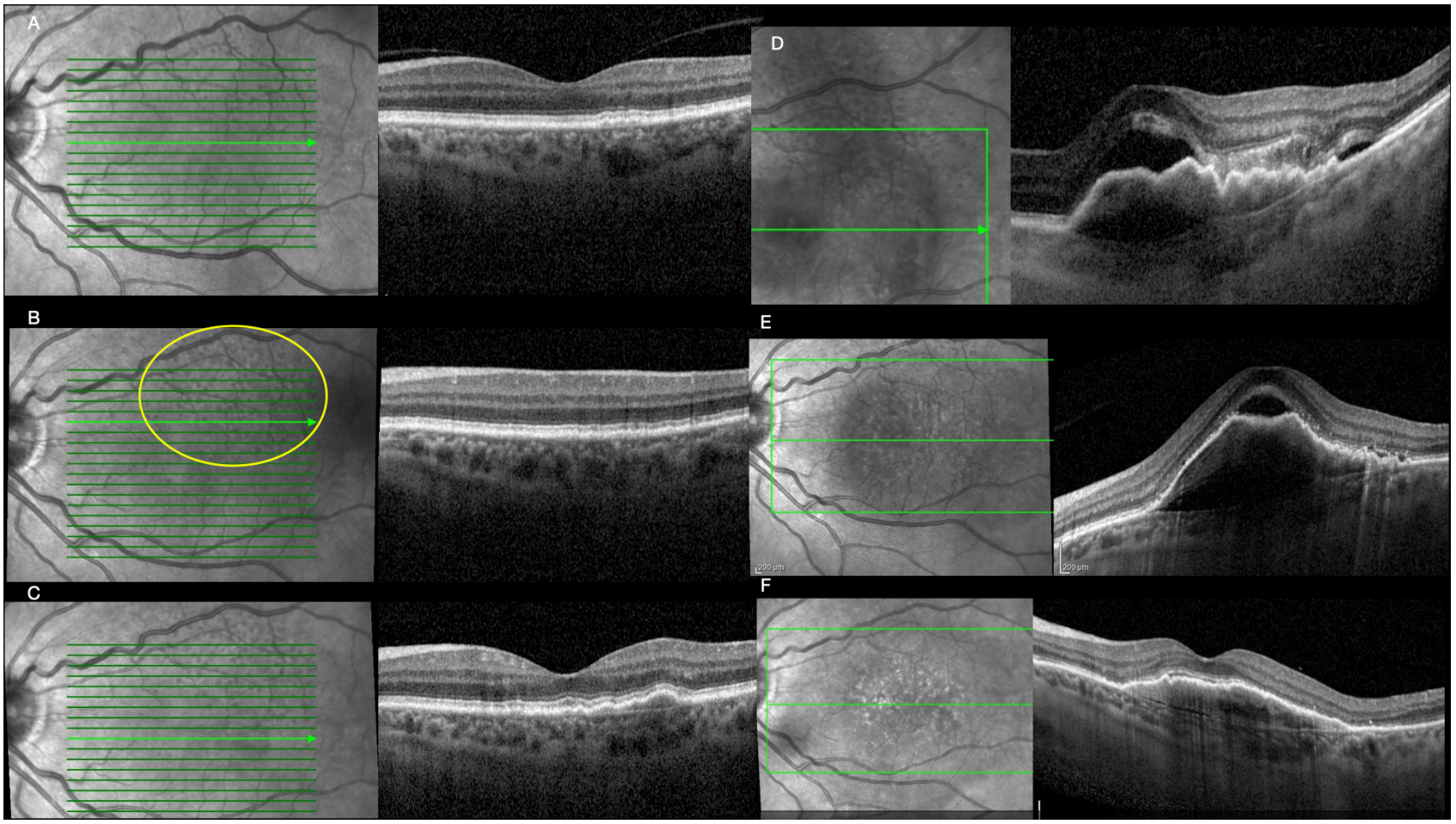

Figure 8- Case example of a patient with predominantly PED and SRF with good visual outcomes.

62- year- old woman with right eye type 1 MNV taking frequent anti- VEGF injections. Timeline of left eye shown as a case example.

A- Jan 2018- Dot SDD seen in superior macula on routine scanning

B- July 2019 (19 months)- increase in the number of dot-SDD seen. (yellow oval)

C- Dec 2019 (24 months)- flat irregular PED corresponding to a network. Patient refused treatment due to treatment burden in the other eye and no signs of activity in this eye (6/6 N6).

D- Presented with DOV- 6/24, N18. - Large, serous vascular PED (svPED) with pre-choroidal cleft, overlying SRF and parafoveal SHRM.

E- After 3 loading doses, SRF reduction, SHRM resolution and reduction in horizontal extent of PED seen, although increase in height

F- After monthly injections (n= 8), resolved SRF, SHRM, reduced height of PED with multilayering, along with reduction in subfoveal choroidal thickness

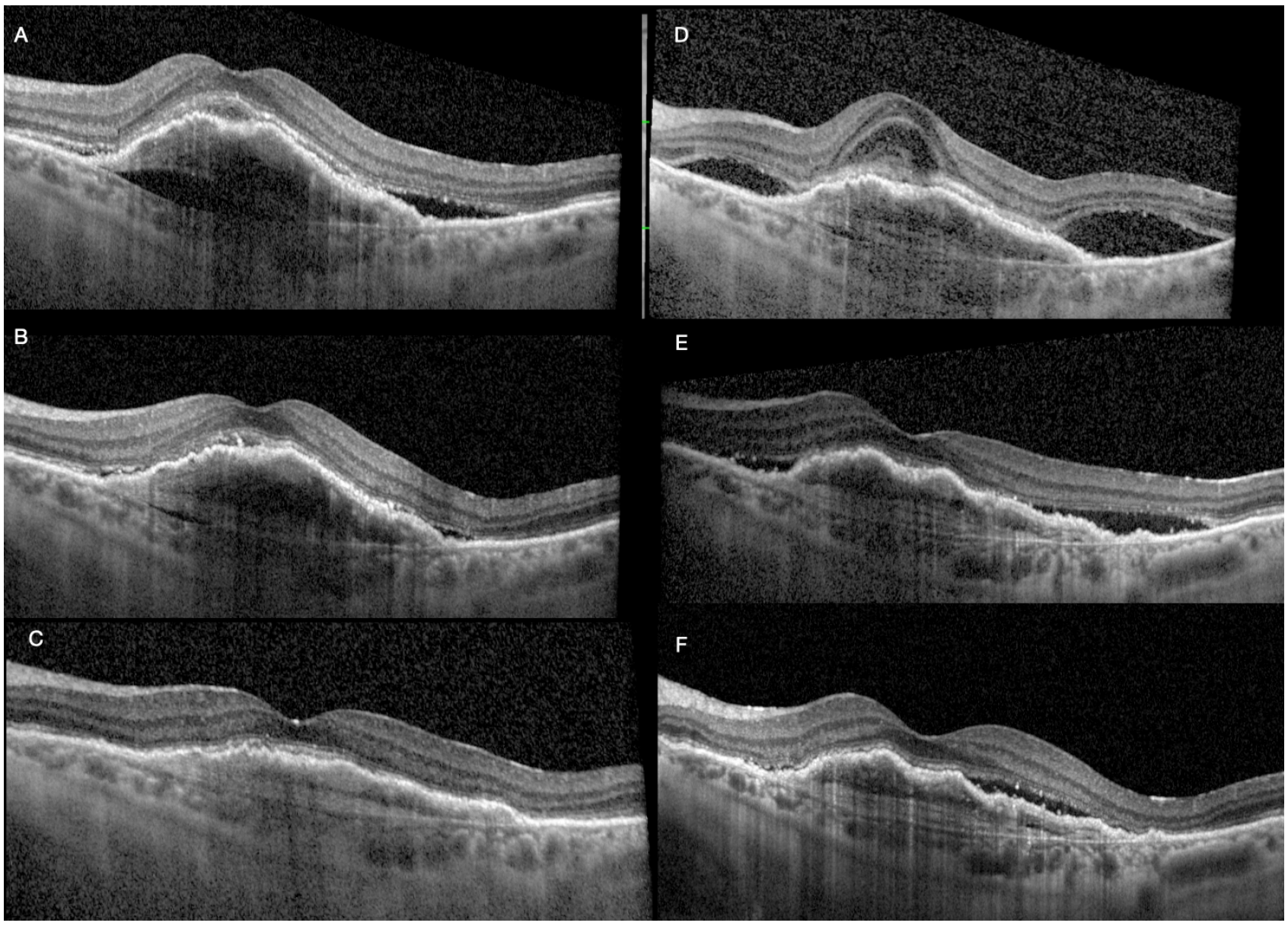

Figure 9 – Continued course of the same patient as in figure 8

A- Recurrence due to missing of one injection (gap of one month)- Para macular SRF increased, sub foveal SHRM recurred with re-appearance of the pre- choroidal cleft.

B- Missed injections for 2 months- recurrence with foveal IRF, para macular SRF and SHRM

C- Monthly injections re-instated an d resolution achieved after more monthly-injections.

D- Two injections of Brolucizumab given (8 weeks apart), on extension to 10- week interval, recurrence of SRF, dome- shaped IRF and increase in PED height.

E- Reduction in SRF and SFCT.

F- Patient tolerating SRF at vision 6/18, N8 on Brolucizumab 8- weekly injections. SRF not being treated to resolution.

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OPTICAL COHERENCE TOMOGRAPHY ANGIOGRAPHY IN NEOVASCULAR AGE-RELATED MACULAR DEGENERATION

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Introduction

Age-related macular degeneration (AMD) is the leading cause of central visual loss above the age of 65 years. Studies suggest that the prevalence of AMD is on the rise due to an increasing number of people living beyond 65 years of age. The exudative or neovascular form of AMD is characterized by choroidal neovascular membrane (CNV) growth and/or serous retinal pigment epithelial (RPE) detachments. Various manifestations in patients with neovascular AMD such as subretinal hemorrhage, vitreous hemorrhage, fibrosis, and scarring are responsible for poor visual outcomes and legal blindness. The goal of therapy has been to salvage vision in this subset of patients with neovascular form of disease.

Optical Coherence Tomography Angiography

Optical coherence tomography angiography (OCTA) is a recent advancement that detects motion, allowing accurate visualization of retinal and choroidal vascular flow. OCTA can provide distinct vascular network patterns that may be otherwise obscured by subretinal hemorrhage on conventional fluorescein angiography (FA). OCTA uses laser light

reflectance from the surface of moving red blood cells to accurately depict vessels through different segmented areas of the eye, thus eliminating the need for intravascular dyes. OCTA may allow calculation of flow indices that may help in judging treatment response in neovascular AMD.

Recently, an international panel of experts formed the Consensus on Neovascular AMD Nomenclature (CONAN) group and published a new consensus nomenclature to standardize definitions in AMD. In this updated classification, OCT is used to detect the anatomical location of neovascularization and then classify the vascular component of the pathological process. Macular neovascularization (MNV) is the term adopted for this classification to underline that neovascularization does not exclusively originate from the choroid. According to this new classification, subtypes are defined as: (1) Type 1 MNV: an ingrowth of vessels from the choriocapillaris into the sub-RPE space; (2) Type 2 MNV: the proliferation of new vessels arising from the choroid into the subretinal space; (3) Type 3 MNV: a down growth of vessels from the retinal circulation toward the outer retina.

Lesions of Neovascular AMD on OCTA

Based on the OCTA appearance of pathological alterations in AMD, the lesions include:

Branching vessels: This term is applied to the numerous tiny capillaries with small branching vessels forming thin tangled capillaries. They generate from a main trunk that appears straighter (Figure 1).

Vascular loops: These are small inner anastomoses between the newly formed vessels. Loops are curved and densely packed vessels related to an uncontrolled proliferation.

Peripheral anastomotic arcades: These are defined as small anastomotic and looping vessels in neovascularization vessel termini. Anastomosis in OCTA appears with marked hyperreflectivity.

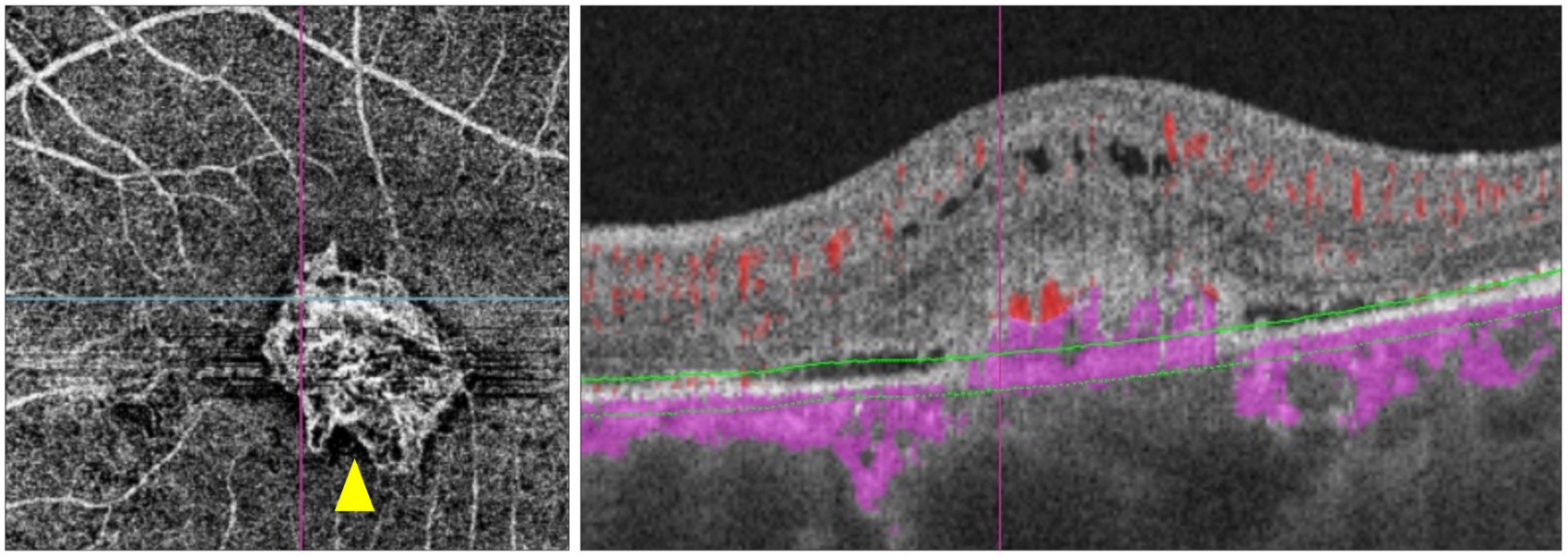
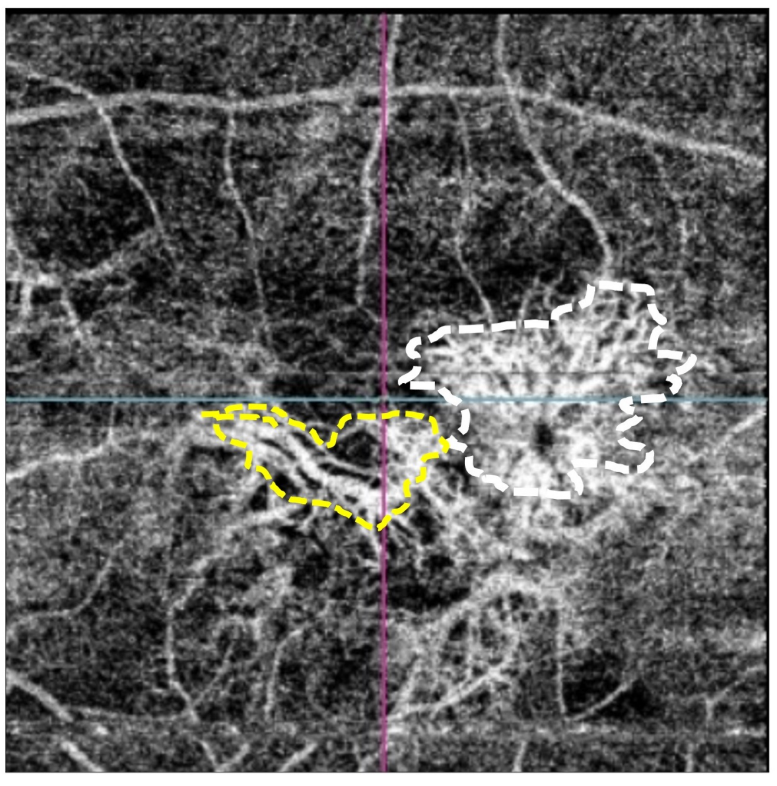


Figure 1: shows optical coherence tomography angiography (OCTA) of a patient with an active macular neovascularization (MNV) with age-related macular degeneration (AMD). The OCTA shows a well demarcated network of new vessels surrounded by a halo of flow deficit area round the neovascularization (yellow arrowhead).

Choriocapillaris dark halo: Presence of a choriocapillaris hypointense halo circumscribed to MNV is considered as regions of choriocapillaris flow impairment or localized atrophy. This area may be impactful in assessing the activity of the MNV lesion (Figure 2).

Figure 2: OCTA of a patient with MNV with AMD shows two components – inactive (yellow dashed lines) with a large trunk, minimum branching, no collaterals, and minimal anastomosis. There is an active (white dashed lines) component which shows numerous branching, collaterals and significantly more anastomosis.



Based on the OCTA appearance, the lesions of neovascular AMD can be classified as:

1. Non-exudative neovascular AMD: evidence of MNV network on OCTA or the presence of a hot spot on indocyanine green angiography (ICGA), but no leakage on FA or presence of intra-/subretinal fluid on OCT. This term can be applied to lesions which are treatment naïve.

2. Exudative neovascular AMD: evidence of network on OCTA or the presence of a hot spot on ICGA with leakage on FA and presence of intra-/subretinal fluid on OCT. These are generally active MNV lesions that are visible on OCT. Various OCTA appearances have been described for these lesions including 'medusa head' or 'pruned tree' based on the morphology.

Conclusions

In the last decade, there have been numerous advances and breakthroughs in the imaging of neovascular AMD including techniques such as OCTA. With a comprehensive and rehabilitative approach, the management of AMD continues to advance.

NON EXUDATIVE NEOVASCULAR AMD

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Age related macular degeneration (AMD) is a condition described in patients typically beyond 50 years of age, in which the structure and function of macula deteriorates. CONAN study group[1] reached a consensus on the nomenclature of various clinical features seen in neovascular AMD. The group recognized non exudative macular neovascularisation (MNV) and this form of neovascularization could be identified more commonly with advances in imaging technology. The group could not come to a consensus that the designation '*quiescent'* was a needed term.

Sarks reported histopathologic evidence of choroidal new vessels under the retinal pigment epithelium in eyes with no clinical signs of neovascularization in 1973.[2] Neovascular plaques with no signs of exudation could be discovered in fellow eyes harbouring soft drusen with the development of indocyanine green angiography. These eyes with non exudative neovascular plaques had a much higher risk of progression to exudative AMD. In 2012, Amissah-Arthur et al found OCT evidence of neovascularization in 88% of eyes before the development of exudation, with conversion occurring up to 35.5 months after initial entry in the study.[3] In 2013, Querques et al. defined the term

'quiescent neovascularization' to describe the cases of neovascularization without exudation in separate examinations separated by 6 months or more.[4] In 2018, de Oliveira Dias et al[5] described that eyes with non exudative MNV identified on OCTA had a higher risk of progression to exudative MNV. They concluded that, eyes with non exudative MNV, needs more frequent follow-up and home monitoring and intravitreal therapy is not recommended.

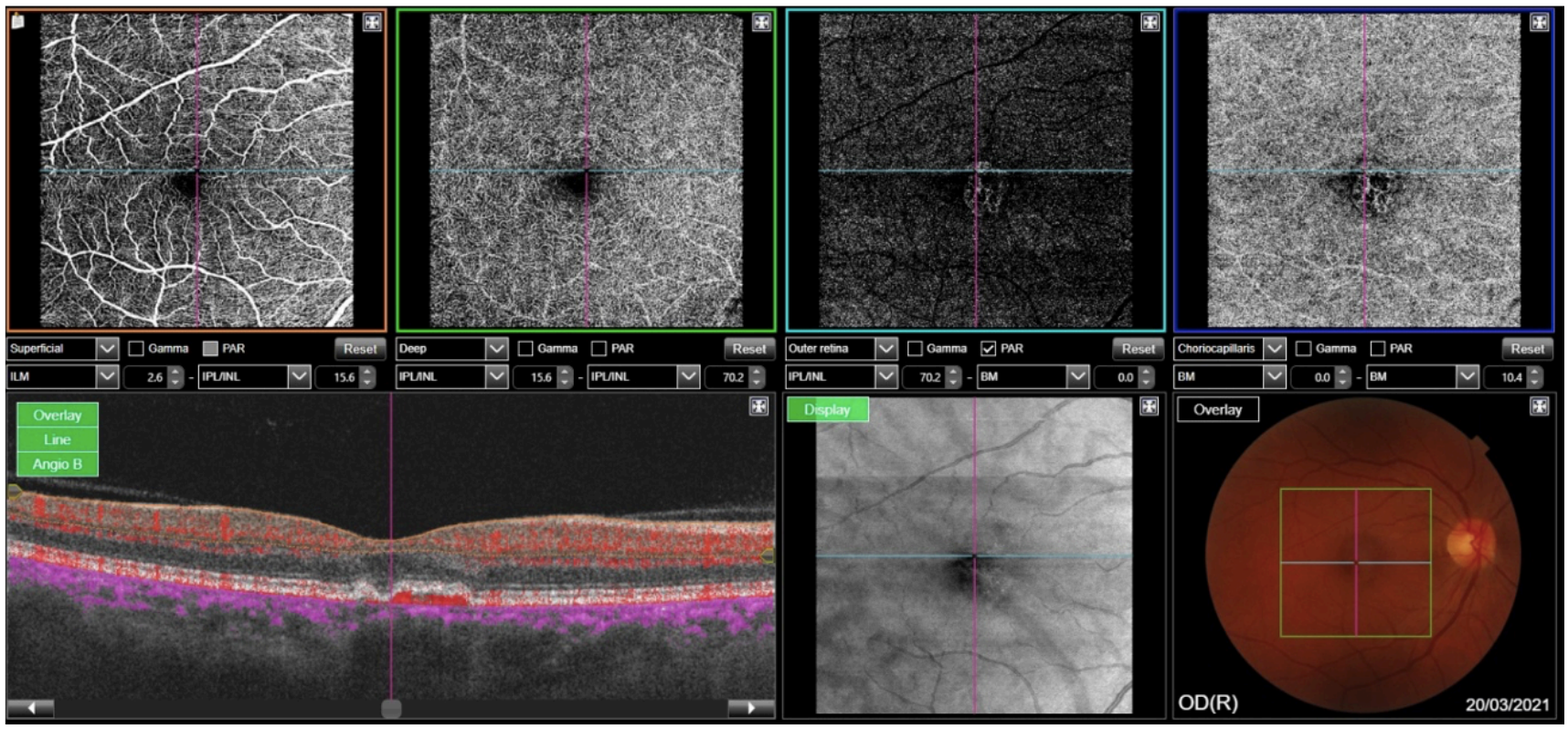
Adriano Carneveli et al[6] demonstrated biological activity of quiescent CNV by showing lesion growth over 12 months. They found the lesions to be subclinical in 15 eyes of 14 patients among an overall pool of 950 neovascular AMD patients. Fourteen of 15 CNVs remained quiescent, and the rate of clinical activation was 6.6%. CNV growth was displayed in 3 of 14 eyes at 6 months and in 10 of 14 eyes at 12 months compared with baseline images. They suggested that these lesions may remain quiescent even when showing anatomic growth over time.

Forte R et al[7] evaluated the long-term progression of quiescent CNV associated with AMD and pachychoroid disease. A total of 67 eyes of 65 patients, with quiescent CNV and a follow-up of 12–112 months were included. Among them, 39 eyes did not show any signs of activity at 24 months follow up.

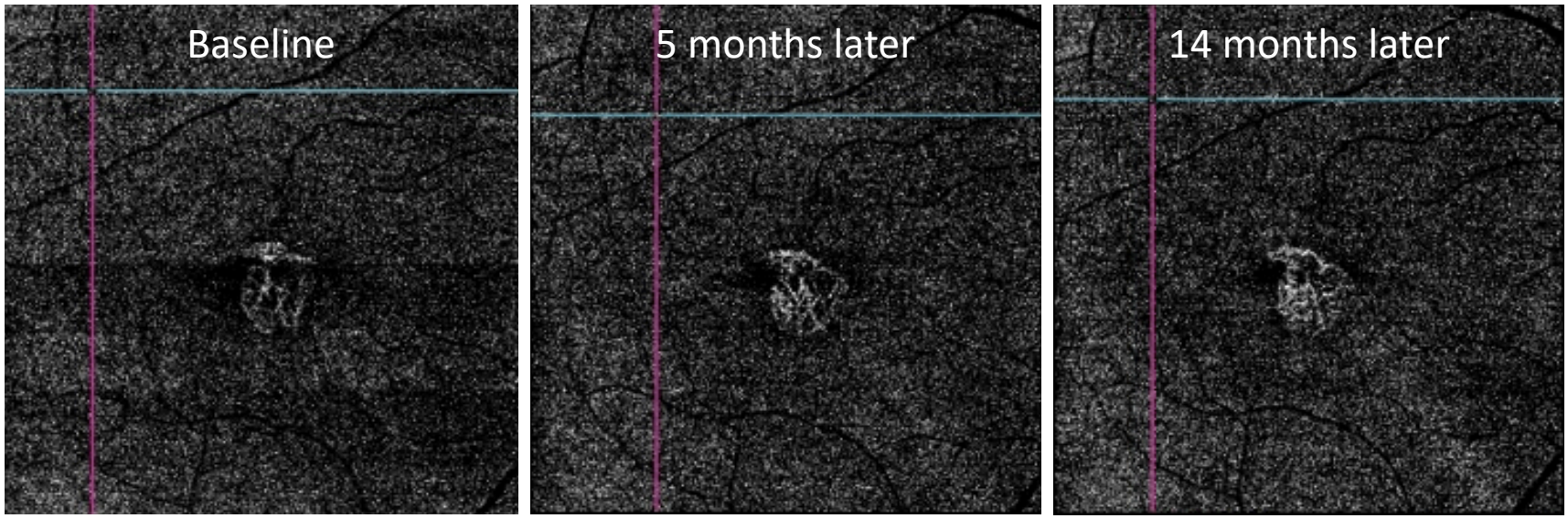
Querques G[8] reported two different patterns for subclinical MNVs: subclinical MNVs characterized by short-term activation which could represent simply a pre-exudative stage in the development of an ordinary type 1 MNV, and quiescent MNVs characterized by low rate of growth and possible long-term activation. Analysis of OCT-A features may predict short-term activation for subclinical MNV but no features could predict the long-term activation.

Burden of repeated treatments with anti VEGF injections cautions against the idea of treating these lesions before they reach clinical stages. There is no need to hurry to treat

non exudative AMD till the time we understand the natural history better.



A 54-year-old female came for a routine check-up. Best corrected visual acuity was 6/6 in both the eyes. On examination there was pigment epithelial detachment (PED) at fovea in right eye that prompted OCT and OCTA. A neovascular network was seen in outer retinal slab on en face OCTA and flow signal was seen within the PED on cross sectional OCTA. There was no evidence of intraretinal or subretinal fluid, hemorrhage or hyper-reflective material suggestive of non exudative CNV



She was followed up for over 14 months at regular intervals with serial OCT and OCTA. There were no signs of activity till the last follow up.

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OPINIONS ON CURRENT TRENDS IN MANAGEMENT OF AMD

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1A. Would you consider dye based angiography for the diagnosis of MNV in AMD at baseline routinely ?

Dr. Anand Rajendran: No, I would not and have not been so for a while. Historically, the value of Fluorescein Angiography (FFA) for MNV in AMD has been to delineate the angiographic subtype of the MNV – essentially to detect a classic or occult component. This was essential to plan / decide on the utility of Photodynamic therapy (PDT). As of the last one and a half decades or thereabouts, post the ANCHOR trial, once anti-VEGF

therapy has taken over as primary treatment for Neovascular AMD (NVAMD) MNVs, the role of FFA has largely diminished as efficacy of antiVEGF did not hinge on the MNV subtype.

Dr. Jay Chhablani: I would not consider dye based angiography for MNV in AMD, if I am not suspecting PCV. Though I routinely do OCTA to document and assess the MNV network. Now we understand the OCT signs of PCV, and helps to suspect or diagnose PCV using structural en-face OCT, so the need for dye-based angiography has come down significantly. Another indication for baseline dye-based angiography if there is suspicion of RAP (Type 3) or any pathology other AMD.

1B. If not, when would you consider fundus fluorescein angiography and indocyanine green angiography?

Dr. Anand Rajendran: There still remains a role, albeit reduced, of fundus fluorescein angiography (FFA) and indocyanine green angiography (ICG) in Neovascular Macular Degeneration. These are

A. To distinguish NVAMD from Polypoidal Choroidal Vasculopathy (PCV), a close differential. Since approximately 30-40% of Neovascular Macular Degeneration in our subcontinent is potentially PCV, FFA-ICG retains value in differentiating the two.
B. This assumes greater value especially when NVAMD is refractory to antiVEGF therapy so as to detect a polypoidal component.
C. In case, there is disproportionate retinal hemorrhages, and a RAP (retinal angiomatous proliferans) lesion is suspected, FFA-ICG is essential in highlighting the

retinovascular origin of the MNV. Identifying RAP lesions early, in turn, helps, as RAP invariably has a more aggressive natural course with rapid visual debilitation than the other MNV subtypes, and thus warrants greater proactive antiVEGF therapy.

Dr. Jay Chhablani: I perform FA/ICG in following conditions

A. If there is inadequate response or resistant to anti-VEGF therapy

B. In established cases of PCV before and after PDT

C. Suspicious RPE breach or early signs of type 2.

2. What are your indications for antioxidants and vitamin supplements (AREDS formulation) ?

Dr. Anand Rajendran: I usually offer AREDS formulation vitamin-antioxidant supplements strongly for

A. Patients with Intermediate AMD unilateral or bilateral

B. Dry AMD with Hard/Soft Drusen and Geographic atrophy in the same or fellow eye

C. Dry AMD with Hard/Soft Drusen and CNVM in the same or fellow eye

D. Dry AMD with Hard/Soft Drusen and Disciform Scar in the same or fellow eye.

Dr. Jay Chhablani: We follow AREDS guidelines for AREDS formulation.

3A. What is your initial choice of anti VEGF in neovascular AMD?

Dr. Anand Rajendran: My initial choice of anti-VEGF agent is Aflibercept.

Dr. Jay Chhablani: We start with Avastin@ unless I am suspecting PCV, then my choice could be Eylea@ if insurance approves.

3B. Would you consider Brolucizumab as first line anti VEGF in management of neovascular AMD?

Dr. Anand Rajendran: I do not use Brolucizumab as first line anti VEGF therapy for any indication.

Dr. Jay Chhablani: No, we are no more using Brolucizumab

3C. When would you consider switching of anti VEGF agent ?

Dr. Anand Rajendran: I would consider switching anti-VEGF agent if I do not observe optimal anatomical improvement (≥100µm reduction in IRF/SRF) with concomitant visual improvement.

Dr. Jay Chhablani: Poor response after three monthly injections using same drug, resistant cases and unaffordability

4A. What regime would you prefer in neovascular AMD- Treat and extend or Pro re nata

4B. What are your criteria to choose treatment regime

Dr. Anand Rajendran: In Neovascular AMD, I prefer a PRN regimen in the first 6-9 months (depending on lesion presenting features – extent of subretinal hemorrhage/ height/ fluid/exudates/ pigments etc) and then may consider a Treat & Extend regimen if the lesion shows repeated episodes of recurrence after a quiescent period. Another

situation in which I may prefer a T&E is if patient is unable to follow up at the requisite time point – I may inject and extend the follow up.

Dr. Jay Chhablani: For most of the patients I perform "Treat & extend", however, I would say "personalized treat & extend", as I learn about individual patient and their recurrence pattern, I modify their treatment free interval and modify drugs.

5A. Would you consider treating cases with Predominantly scarred MNV with poor vision at presentation ?

Dr. Anand Rajendran: I rarely treat a predominantly scarred CNVM.

Dr. Jay Chhablani: Having poor vision and predominantly scarred CNV shouldn't preclude treatment. Anti-VEGF therapy can be used for preventing further loss, prevent massive subretinal hemorrhage, and stopping the treatment could be risky in monocular patients, especially if they are anti-coagulants.

5B. What are your criteria to consider treatment in Predominantly scarred MNV with poor vision?

Dr. Anand Rajendran: I would consider doing so if

A: The patient has intraretinal fluid (IRF) and the retinal structure appears to be reasonably intact with potential to improve vision

B: The scar is predominantly juxta/extrafoveal

C: Patient is one-eyed and is eager to try and improve vision in the only seeing eye

D: Above all, patient consents and clearly understands that there is a low possibility of visual improvement.

Dr. Jay Chhablani: Depending upon signs of activity, areas of extrafoveal fixations, extent of the scarred area, fellow eye status and risk factors for subretinal haemorrhage.

PEGCETACOPLAN IN THE MANAGEMENT OF GEOGRAPHIC ATROPHY

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Pegcetacoplan (Syfovre) was approved by the FDA on February 17, 2023. Pegcetacoplan targets C3 and C3b in the complement cascade, which is part of the body's immune system. C3 plays a role in driving the downstream effects of complement over activation in the progression of geographic atrophy (GA) secondary to age related macular degeneration, including uncontrolled inflammation, opsonization, and retinal cell death.

The approval was based on the OAKS (n = 621) and DERBY (n = 637) Phase 3 double-masked, sham-controlled trials. The trials evaluated the efficacy of monthly and every-other-month (EOM) Pegcetacoplan compared to sham assessed by change in the total area of GA lesions from baseline as measured by fundus autofluorescence (FAF). Both monthly and EOM dosing showed a reduction in GA lesion growth from baseline compared to sham in the 24-month data:

- DERBY: 19% reduction in monthly and 16% reduction in EOM group
- OAKS: 22% reduction in monthly and 18% reduction in EOM group

The effects of Pegcetacoplan were cumulative over time with DERBY/OAKS showing that the longer a patient was treated, the greater the impact of the medicine. Between months 18-24, the Pegcetacoplan treatment effect accelerated, with reductions of GA

lesion growth during this period being

- DERBY: 36% reduction in monthly and 29% reduction in EOM group
- OAKS: 24% reduction in monthly and 25% reduction in EOM group

Visual function, as expected was similar between Pegcetacoplan and sham at 24 months. Post hoc analysis using junctional zone microperimetry analysis and automated OCT segmentation have shown that Pegcetacoplan slows photoreceptor and RPE cell loss. A 3-year clinical extension study will continue to monitor patients for side effects, efficacy, and outcomes.

There remain several questions that we need to elucidate answers to, including what is the real world compliance with this treatment as the treatment burden and lack of visual improvement is different from what is seen with anti-VEGF therapies for exudative diseases and may impact patient motivation. The treatment in its current form would likely need to be continued in perpetuity. Clinical treatment protocols for GA may also need to be rethought – for example patients may be on a treatment plan of monthly or every other monthly injection for 6 months with FAF imaging obtained every 6 months while OCT is performed at every injection to evaluate for macular neovascularization (MNV) development which remains a concern. There is a potential value of performing OCT Angiography prior to initiating treatment to detect non-exudative MNV which is a risk factor for conversion to exudative MNV. The volume of Pegcetacoplan injected (0.1mL) is double of what is typically injected with anti-VEGF therapy (0.05mL) and patients with glaucoma will need to be carefully monitored. There is an increased risk of MNV development that is also frequency and duration dependent and concurrent treatment with both anti-VEGF and Pegcetacoplan may also impose additional burden on the patient and long-term outcomes in such patients still need to be evaluated. There

is also interest in evaluating whether Pegcetacoplan helps in slowing progression of macular atrophy secondary to exudative AMD.

The discussion about initiating therapy needs to be individualized to each patient's situation and expectations from the therapy. Some might embrace early therapy to slow down progression of GA towards foveal center point and attempt to preserve central vision over a longer term, while other patients may decide to wait until they become symptomatic before starting treatment. In the US, pegcetacoplan is approved for all patients with GA secondary to AMD. This includes both subfoveal and non-subfoveal lesions. The label approved by the FDA offers flexible dosing every 25 to 60 days, giving physicians options in treatment intervals based on individual patient needs although it is conceivable that patients would prefer the 60 day interval albeit with a slightly lower therapeutic effect. It would be rational to prioritize pegcetacoplan treatment for patients who have impending foveal involvement with GA, especially if the fellow eye has experienced vision loss from either wet AMD or GA. With more clinical experience, the indications may be broadened.

There needs to be a balance between discussing the need for repeated treatments, potentially in perpetuity, the strength of the efficacy, and the safety signal with risk of MNV with patients, so they can make individual decisions about what is appropriate for them. It would also be helpful to collect data on each patient's "run in" GA lesion growth rate in the years leading up to initiating therapy to determine individualized levels of effectiveness in slowing GA lesion growth on therapy.

Overall, for retina and patients with GA the approval of Pegcetacoplan is a significant positive milestone demonstrating the viability of complement inhibition strategies in slowing the progression of disease without alternative treatment options. Validation of

FAF based endpoints, rather than visual acuity, which is typically used in ophthalmology clinical trials also provides the framework for other compliment inhibitors in development with a path forward in the regulatory evaluation process. Addressing the dosing frequency challenge is a key next step with several approaches including AAV based gene therapy delivery of compliment inhibitors being investigated. Ultimately, the decision about treatment will be based on the discussion between the physician and each patient regarding the frequency of injections and whether the anticipated benefit will be appreciated as preserved quality of life by the patient considering the treatment burden and the cost of treatment.

ROLE OF RPE CELL THERAPY IN AGE-RELATED MACULAR DEGENERATION

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Introduction:

The Retinal Pigment Epithelium (RPE) is a continuous monolayer of hexanocuboidal post-mitotic epithelial cells situated between the photoreceptors and Bruch's membrane. The daily phagocytosis of photoreceptor outer segments (POS) and secretion of neurotrophic factors required to stabilize the neural retina are some of the important roles of RPE. RPE is an integral part of the visual cycle; it supports the isomerization of 11 cis-retinal to all-trans-retinal during the phototransduction cascade and recycling of all-trans retinal to 11 cis-retinal. It is also highly metabolically active since each RPE cell interacts with several photoreceptors.[1]

Age-related changes in RPE[2]

RPE is the fulcrum of AMD pathogenesis. Although AMD is a multifactorial disease, the late stage of non-neovascular AMD includes atrophy of the RPE. With increasing age, the human RPE undergoes changes such as loss of melanin, lipofuscin accumulation, reduced antioxidant capacity, and progressive accumulation of drusen deposits in the space between the basal lamina of the RPE and Bruch's membrane. In addition to oxidative stress and chemical alteration of extracellular matrix proteins, ultra-structural pathology studies show that necrosis and pyroptosis are potential mechanisms of RPE cell death in AMD. RPE dysfunction with a mutation in retinoid cycle-related genes such as RPE65, LRAT, BEST1, or phagocytosis-related genes such as MERTK leads to visual impairment and various forms of inherited retinal diseases.

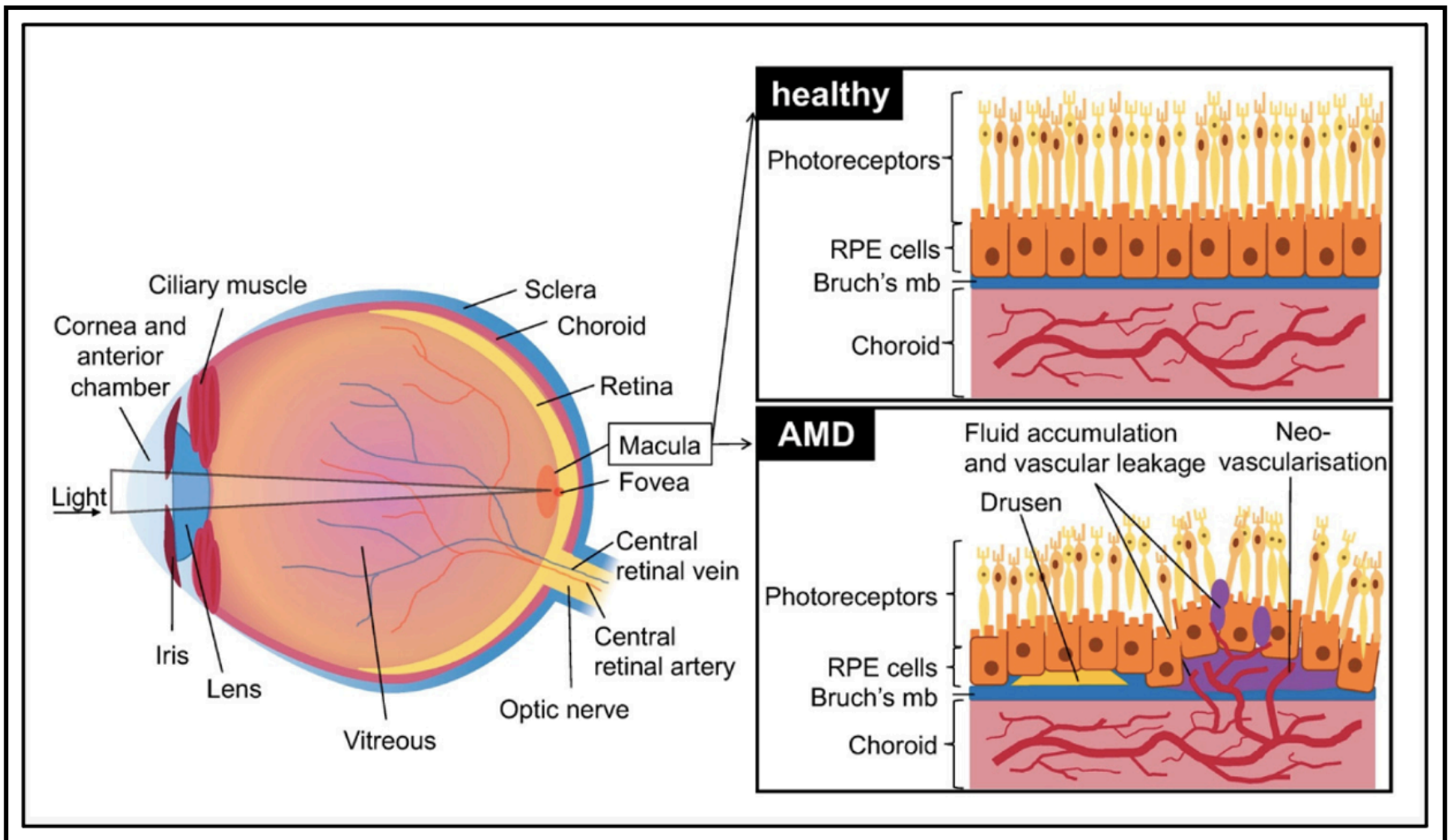

Fig 1. Schematic of the eye showing healthy RPE and changes in AMD. Adapted from Rastoin et al.[3]

Cell therapy and AMD:

In contrast to neovascular AMD, treatment of dry AMD and geographic atrophy has been elusive. Recently, intravitreal Pegcetacoplan, a complement-C3 inhibitor has been approved by the USFDA for arresting the progression of geographic atrophy.[4]

A promising cell replacement strategy for treating AMD involves using human embryonic stem cells (hESCs) or human induced pluripotent stem cells (hiPSCs). Both types of stem cells are infinite in supply and hiPSCs in particular hold promise as a patient-specific pluripotent cell source derived from adult tissue. The RPE cells derived from hESCs or hiPSCs are similar to human fetal RPE in terms of expression of key markers, and RPE functionality, as demonstrated by phagocytosis assay and ion transport, and have the ability to rescue visual function.

Protocol for generation and characterization of RPE:

The pluripotent cells are differentiated into RPE by embryoid body (EBs) aggregation. These EBs are then coaxed into neuroectodermal fate by inhibition of pluripotency markers like FGF2 and BMP2/4 using Dual-SMAD inhibition. This is achieved by using small molecules like SB431542 and LDN. LDN acts as a BPM inhibitor and SB431542 inhibits Activin/TGF-β pathways. iPSCs differentiate to form the anterior neural plate (ANP) and eye field specification to the formation of the bilayered optic cup. Upon the formation of the neuroectoderm, the non-rosette population gives rise to RPE. Mature RPE exhibit tightly packed cuboidal cells and blackish pigmentation with apical-basal polarity. ZO-1+ RPE cells indicate such tight junction and apical-basal polarity. They also express retinal transcription factors such as RX, CRX, and MITF.

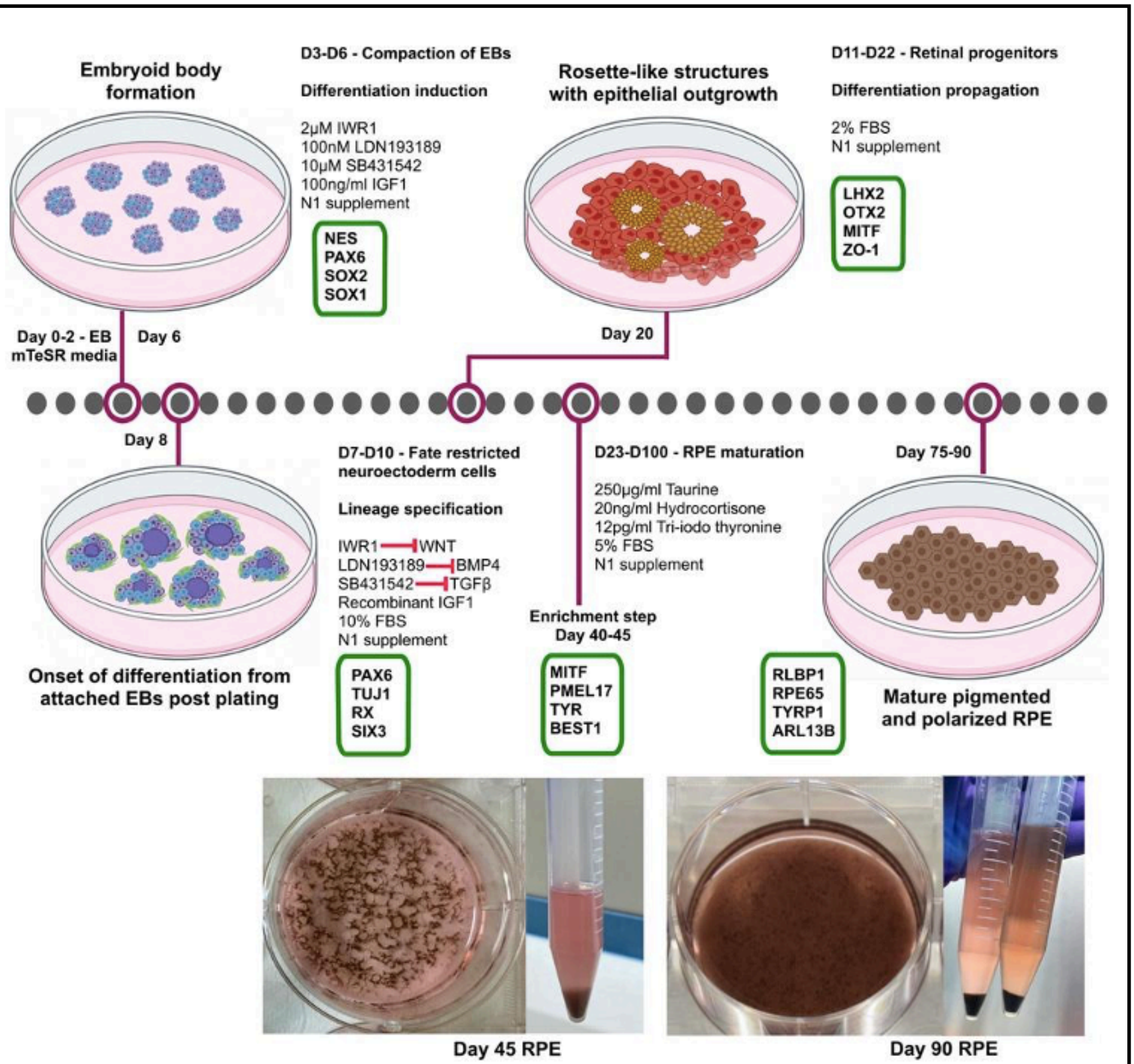

Fig 2. Protocol for generation and characterization of hiPSC-derived RPE. Adapted from Surendran H et al.[5]

RPE transplantation:

Several factors make RPE transplantation an attractive target for cell therapy. The cell structure and function of RPE are fairly well understood, the cells grow readily in laboratory cultures and, unlike other cell types within the retina, RPE cells do not

require synaptic connections for their function. Compared to other organs in the body, the number of cells required for transplantation is relatively small. In addition, the outer retina is easily amenable to imaging via optical coherence tomography and adaptive optics.[6] The rationale for using cell replacement therapy in retinal dystrophies is twofold—one, that the cells integrate with the host retinal tissue and show functional benefits and the second is the benefit of neurotrophic factors associated with the transplantation of these cells.[7,8]

The two major strategies for replacing atrophic RPE cells include an RPE cell suspension and an RPE cell sheet grown on a scaffold. While injecting a cell suspension into the subretinal space is relatively easier compared to injecting a sheet, the latter has the advantage of cells with polarity maintained, and therefore easier to integrate within the host tissue.

Clinical trials:

Currently, there are several clinical trials in phase 1/2 for the transplantation of hESC/iPSC-derived RPE either as suspensions or sheets in patients with dry AMD and Stargardt macular degeneration.[9] Lineage cell therapeutics is using a unique method to deliver their cells subretinally via the suprachoroidal approach through microinjection using the Orbit Subretinal Delivery System developed by Gyroscope Therapeutics (formerly Orbit Biomedical, Ltd.), which avoids the need for retinotomy and associated complications.[10]

Regenerative Patch Technologies has developed a composite subretinal implant, named the California Project to Cure Blindness-Retinal Pigment Epithelium1 (CPCB-RPE1), consisting of a polarized monolayer of human embryonic stem cell-derived RPE (hESC-RPE) on an ultrathin, synthetic parylene substrate designed to mimic Bruch's

membrane. Bharti *et al.* are developing an AMD-patient specific iPSC-derived RPE (iRPE)-patch using a biodegradable scaffold that forms a monolayer of RPE cells in animal models when injected subretinally.[11] The discussion of these clinical trials and results is outside the scope of this paper. Since the majority of these are allogenic RPE transplants, it is necessary to use systemic or local immunosuppression.

Future prospects:

Stem cell science is advancing, and although early, offers unprecedented opportunities for cell replacement strategies. This is an attractive option since it overcomes the limitations of gene therapy and pharmaceutical therapy. Stem cell therapy and subretinal transplantation of RPE cells seem promising new ways to replace the lost cells, with several stem cell therapies on the anvil for hitherto untreatable diseases.

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MANAGEMENT OF AMD IN A SCHEMATIC

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- Age related Macular Degeneration (AMD)
  - Early
    - Yearly follow up with OCT / FAF
    - Home Amsler monitoring
  - Intermediate
    - AREDS2 supplements
    - 6 monthly follow up with OCT/ FAF
    - Home Amsler Monitoring
  - Advanced
    - Neovascular AMD
      - Quiescent MNV
        - AREDS2 Supplements
        - Periodic follow up with OCT/OCTA
      - Active MNV
        - Predominantly Hemorrhage
          - Anti VEGF alone
          - or
          - Anti VEGF + Pneumatic displacement
          - Or
          - Anti VEGF +TPA + Pneumatic displacement
        - Predominantly MNV
          - Subfoveal/ Juxtafoveal
            - Anti-VEGF therapy (continued in next page)
          - Extrafoveal
            - Laser is likely to cause a significant scotoma
              - Yes
                - Anti-VEGF therapy (continued in next page)
              - No
                - Laser photocoagulation
        - Predominantly Scar
          - Treatment can maintain a reasonable stable vision
            - Yes
              - Anti-VEGF therapy (continued in next page)
            - No
              - Low vision aids
      - Disciform scar
        - Low vision aids
    - Geographic atrophy
      - AREDS2 supplements
      - 6 monthly follow up with OCT/ FAF
      - Low vision aids in central GA
      - Monthly/ Every other month intravitreal Pegcetacoplan (15 mg/ 0.1 ml) is US FDA approved for management

MANAGEMENT OF AMD IN A SCHEMATIC