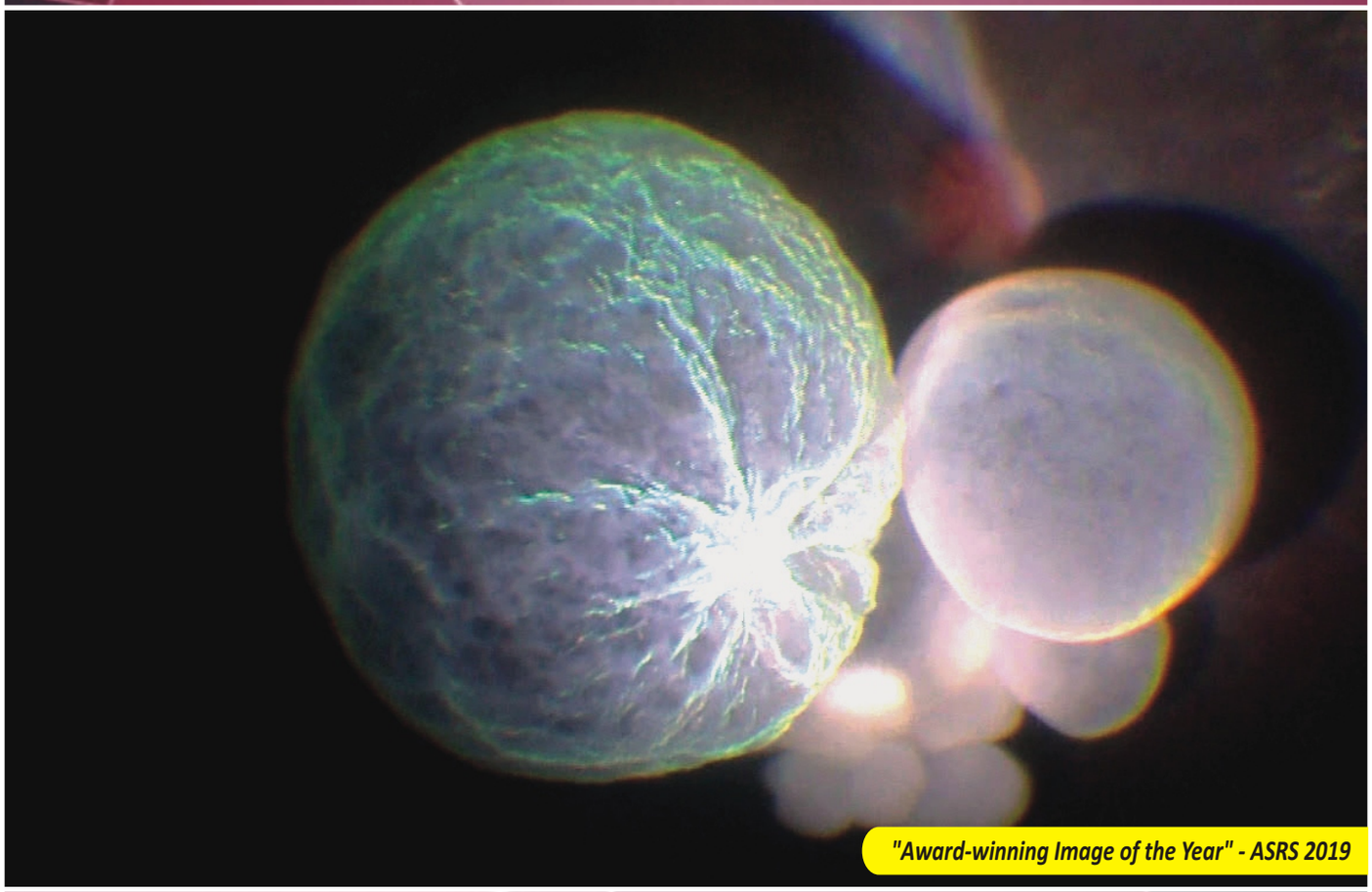
DECEMBER 2019

The Official Newsletter of the

VITREO RETINAL SOCIETY-INDIA



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Wet AMD, DME, RVO, PM: •Treatment is initiated with one injection per month until maximum visual acuity is achieved and/or there are no signs of disease activity. •Thereafter, monitoring and treatment intervals should be determined by the physician and should be based on disease activity as assessed by visual acuity and/or anatomic parameters. •Monitoring for disease activity may include clinical examination, functional testing or imaging techniques (e.g. optical coherence tomography or fluorescein angiography). •While applying the treat-and-extend regimen, the treatment interval should be extended by two weeks at a time for wet AMD and central RVO, or by one month at a time for DME and branch RVO. •Accentrix and laser photocoagulation in DME or in branch RVO: Accentrix has been used concomitantly with laser photocoagulation in clinical studies. When given on the same day, Accentrix should be administered at least 30 minutes after laser photocoagulation. Accentrix can be administered in patients who have received previous laser photocoagulation. •Accentrix must be administered by a qualified ophthalmologist using aseptic techniques. Broad-spectrum topical microbicide and anesthetic should be administered prior to the injection. •Not recommended in children and adolescents. Contraindications: Hypersensitivity to ranibizumab or to any of the excipients, patients with active or suspected ocular or periocular infections, patients with active intraocular inflammation. Warnings and precautions: •Intravitreal injections have been associated with endophthalmitis, intraocular inflammation, rhegmatogenous retinal detachment, retinal tear and iatrogenic traumatic cataract. Therefore proper aseptic injection techniques must be used. Patients should be monitored during the week following the injection to permit early treatment if an infection occurs. •Transient increases in intraocular pressure (IOP) have been seen within 60 minutes of injection of Accentrix. Sustained IOP increases have also been reported. Intraocular pressure and the perfusion of the optic nerve head must be monitored and managed appropriately. •There is a potential risk of arterial thromboembolic events following intravitreal use of VEGF inhibitors. A numerically higher stroke rate was observed in patients treated with ranibizumab 0.5 mg compared to ranibizumab 0.3 mg or control; however, the differences were not statistically significant. Patients with known risk factors for stroke, including history of prior stroke or transient ischemic attack should be carefully evaluated by their physicians as to whether Accentrix treatment is appropriate and the benefit outweighs the potential risk. •Available data do not suggest an increased risk of systemic adverse events with bilateral treatment. •As with all therapeutic proteins, there is a potential for immunogenicity with Accentrix. •Accentrix has not been studied in patients with active systemic infections or in patients with concurrent eye conditions such as retinal detachment or macular hole. •There is limited experience with treatment of patients with prior episodes of RVO and of patients with ischemic branch RVO (BRVO) and central RVO (CRVO). In patients with RVO presenting with clinical signs of irreversible ischemic visual function loss, treatment is not recommended. •Should not be used during pregnancy unless the expected benefit outweighs the potential risk to the fetus. For women who wish to become pregnant and have been treated with ranibizumab, it is recommended to wait at least 3 months after the last dose of ranibizumab before conceiving a child. use of effective contraception is recommended for women of child-bearing potential; breast-feeding is not recommended. •Following treatment patients may develop transient visual disturbances that may interfere with their ability to drive or use machines. Patients should not drive or use machines as long as these symptoms persist. Interactions: No formal interaction studies have been performed. Adverse drug reactions: •Very common (≥10%): intraocular inflammation, uveitis, vitreous detachment, retinal hemorrhage, visual disturbance, eye pain, vitreous floaters, conjunctival hemorrhage, eye irritation, foreign body sensation in eyes, lacrimation increased, blepharitis, dry eye, ocular hyperemia, eye pruritus, intraocular pressure increased, nasopharyngitis, headache, arthralgia. •Common (1 to 10%): retinal degeneration, retinal disorder, retinal detachment, retinal tear, detachment of the retinal pigment epithelium, retinal pigment epithelium tear, visual acuity reduced, vitreous hemorrhage, vitreous disorder, uveitis, iritis, iridocyclitis, cataract, cataract subcapsular, posterior capsule opacification, punctuate keratitis, corneal abrasion, anterior chamber flare, vision blurred, injection site hemorrhage, eye hemorrhage, conjunctivitis, conjunctivitis allergic, eye discharge, photopsia, photophobia, ocular discomfort, eyelid edema, eyelid pain, conjunctival hyperemia, stroke, influenza, urinary tract infection*, anemia, anxiety, cough, nausea, allergic reactions (rash, pruritus, urticaria, erythema). •Uncommon: (0.1 to 1%) : blindness, endophthalmitis, hypopyon, hyphema, keratopathy, iris adhesions, corneal deposits, corneal edema, corneal striae, injection site pain, injection site irritation, abnormal sensation in eye, eyelid irritation. •Serious adverse events related to intravitreal injections include endophthalmitis, rhegmatogenous retinal detachment, retinal tear and iatrogenic traumatic cataract.
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Contents

From the President's Desk

Dr. Shobhit Chawla
Medical Director and Chief - Vitreo Retinal Services
Prakash Netra Kendr
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Dear Friends and colleagues

Best wishes for the festive season and the new year

The last VRSI Newsletter of the year 2019 is here by the efforts of Dr.Anand Rajendran , the Scientific Convenor. Let us all contribute with enthusiasm and think of the best possible ways for keeping the pace with which our society has grown . We are a group of 1000 plus members today. As our focus remains on the core issues of Diabetic retinopathy and it's relevance to our population , We find increase in detection rates and diagnosis of newer disorders like the Pachychoroid group Some of us who have been doing ICG angiography for long find features of this group of diseases in a fairly large number of our patients of macular pathology. The focus of this issue is on these disorders by Dr Muna Bhende and the SN group.

The issue also has views and guidelines for the new AntiVEGF Brolicizumab. Thanks to Dr Anand for bringing out avery relevant newsletter with international participation.

Look forward to personally meeting you all at our much awaited VRSI 2019 Annual meeting at Lucknow.

Warm regards
Shobhit Chawla
President VRSI

From the Honorary Secretary's Desk

Dr. Raja Narayanan
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Dear Friends:

Greetings from VRSI! The excitement of the VRSI annual meeting is building up. I hope that you have booked your travel and accommodation for the Meeting, with enough time for leisure. The Scientific Program has been uploaded on the website, which has been brilliantly compiled by Dr. Anand Rajendran. The local organizing committee lead by Dr. Mohit Khemchandani is working tirelessly to ensure a perfect Meeting for all of us. I am delighted to know that the last issue of VRSI newsletter in 2019 is being published. I am sure that you will find the panel discussion and articles extremely valuable for your daily practice, and to provide the best care to your patients. I take this opportunity to request you all to submit your interesting cases, articles and innovations to the VRSI newsletter, which will help improve the scientific knowledge base of our members. Wishing you all a warm Season's Greetings.

Regards
Raja Narayanan
Hon. Secretary, VRSI

From the Convenor, Scientific Committee's Desk

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Dear Friends and Colleagues

It has been such a pleasure bringing out the December edition of the VRSI Newsletter, and we have strived to place it in your hands ahead of time. As we stand on the cusp of the VRSI 2019 Annual Conference to be held at the historic city of Lucknow from Dec 5th-8th, the VRSI Executive and the Local Organising Committee welcome your presence and participation at what promises to be a scientific and cultural fest. Dr. Shobhit Chawla, our President and Chair, LOC and Dr. Mohit Khemchandani, Organising Secretary, LOC have done a stellar job in laying out plans for the Meet at the majestic Taj Mahal hotel – an extraordinary cultural, gastronomic and artistic experience awaits us.

The current issue has its theme on an area retina specialists have turned their attention to in recent times - Choroidal pathology. We have Dr. Glenn Jaffe, a world renowned retina specialist from the Duke Eye Centre, and one of the key investigators of the HAWK and HARRIER trials, giving us his insights on the much anticipated Anti-VEGF agent - Brolucizumab in the'StalwartSpeak'section. The Spotlight article of the issue, steered by Dr. Muna Bhende, brings together in a Roundtable discussion, an eminent panel of international and national experts and is focused on "The Pachychoroid Disease Spectrum" highlighting the many aspects of the pathology. The Retina Tech corner has Dr. Vinod Kumar offering us a fine account on Ultrawide field Imaging and its applications in retinal practice. The Avastin ban had the entire retina and ophthalmic community in doldrums not a long while ago. Dr. Ajay Aurora, in his article provides an insider's account of the tumultuous events that led to the historic overturning of the ban. In the Innovator's Isle section, Dr. Sangeet Mittal describes his ingenious and novel surgical technique of draining suprachoroidal hemorrhages. Dr. Sabyasachi Sengupta, in the Writer's C(r)amp section demystifies the enigmatic P value. We have a couple oforiginal articles by Dr. Darius Shroff and Dr. Raja Narayanan, who profile PEHCR and Fellow eyes of PCV, respectively, and a Case Report to square off the issue on choroidal disease.

We look forward to contributions from all members to future issues. We are delighted that this year has seen a massive and enthusiastic response from our members with the highest number of submissions recorded to date for the VRSI 2019 Meet. We look forward to seeing as many of our members at VRSI Lucknow.

Dr. Anand Rajendran Convenor
Scientific Committee
Vitreo-Retina Society India

Guidelines - Manuscript Submission for VRSI Newsletter

Original articles:

These include randomized controlled trials, intervention 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 words (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 of up to 1000 words (excluding references and abstract) and could be supported with up to 10 references. Case Reports could be authored by up to four authors.

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The Cover Image was contributed by Dr. Vishal Agrawal, Jaipur
Winner of the ASRS 2019 Retina Image Bank –"Image of the Year"
- *"Multiple Intraocular Cysticercosis"*

- (ASRS RIB Image 28626)

Legend
Dr. Vishal Agrawal *receiving the award from*
Dr. Suber Huang, ASRS

STALWART SPEAK

Brolucizumab: A New Antivascular Endothelial Growth Factor (VEGF) Agent to Treat Neovascular Age-Related Macular Degeneration (AMD)

Dr. Glenn J. Jaffe, M.D.
Robert Machemer Professor of Ophthalmology
Chief, Vitreoretinal Division
Director, Duke Reading Center
Duke Eye Center, USA
Durham, NC, USA

Three anti-VEGF agents are currently used commonly to treat neovascular AMD. These drugs include bevacizumab (Avastin), ranibizumab (Lucentis), and aflibercept (Eylea). The former is given off-label, while the latter two are approved by the US Food and Drug Administration (FDA) and European regulatory agencies. A fourth drug, brolucizumab, was recently approved by the FDA to treat neovascular AMD. In this article, I will review the rationale for development of this drug, the data that led to its approval, and how this agent might fit into our current neovascular AMD treatment paradigms.

The current methods to treat neovascular AMD require relatively frequent dosing to maintain favorable visual acuity and anatomic outcomes. The dosing frequency, which is often at 1-2 month intervals, is a significant burden on the patient, his or her caregiver, eye care provider, and the healthcare system. Brolucizumab was developed to address an unmet need to treat less frequently with the goal to give less frequent dosing of an agent with a prolonged duration of action that will still maintain visual acuity comparable to other currently available drugs. To achieve this goal, brolucizumab was designed as a single-chain antibody fragment that is significantly smaller than that of other anti-VEGF agents. Brolucizumab's molecular weight is 26 kDa whereas that of ranibizumab, aflibercept, and bevacizumab is 48 kDa, 97-15 kDa and 149 kDa, respectively. This smaller molecular weight results is a 22 times greater molar concentration than ranibizumab used as a reference comparator, whereas aflibercept has 1.7-2 times the molar concentration and bevacizumab has 0.8 times the molar concentration of ranibizumab, respectively. The drug is designed with a proprietary human single chain antibody fragment (scFv), which is the smallest functional unit of an antibody that serves as a scaffold for complementarity-determining regions of a novel anti-VEGF-A that is grafted to it. It was hypothesized that the small size would allow delivery of a greater molar dose and more effective tissue penetration, which could increase drug duration, when compared to larger molecules. Furthermore, it has been proposed that the small molecular size with a high molar concentration could provide faster systemic clearance, which might limit systemic side effects. With these features in mind, initial animal pharmacokinetic studies were undertaken, which showed minimal systemic concentrations relative to much higher ocular concentrations and increased primate retinal exposure when compared to that in the vitreous.

Based on the above-mentioned theoretical considerations, and the preclinical pharmacokinetic data, clinical trials were undertaken to test the efficacy and safety of this drug in humans. These trials included the Phase I/II SEE Study, the Phase II Osprey Study, and the Phase III Hawk and Harrier Studies. The SEE study demonstrated a favorable safety profile with suggestions of drug efficacy. Accordingly, the Osprey trial was undertaken that included patients with neovascular AMD and active lesions with leakage that affected the foveal center, and which were associated with subretinal, intraretinal, or sub-RPE fluid. The Osprey study design included matched every 8 week aflibercept or brolucizumab treatment through week 32, and, in addition, brolucizumab was given at 12 week intervals starting at week 32 through week 56, whereas aflibercept was given at 8 week intervals during this time frame. The key primary and secondary study endpoints were met. Brolucizumab, which was compared to aflibercept, was noninferior for mean change in best corrected visual acuity at week 12 (the primary study end point)

through week 28, and there were similar best corrected visual acuity gains through week 56. The visual acuity gains were associated with rapid and sustained reductions in central subfield thickness that were greater at all time points in the brolucizumab group when compared to the aflibercept group. Furthermore, there were fewer rescue treatments that were required during the matched every 8 week treatment phase. There were no serious ocular adverse events in either of the treatment groups and no notable differences in systemic treatment emergent adverse events. Results from the 12 week dosing regimen after week 32 suggested that a group of patients might be treated successfully with a 12 week dosing regimen.

The Osprey study results informed the phase III brolucizumab trial design which included two parallel pivotal phase III studies. The first of these, the Hawk Study, was conducted in the United States, Canada, Latin America, Japan, Australia, New Zealand, Israel, and the Philippines, while the Harrier Study was conducted in Europe, Asia, and Russia. In Hawk, two different doses of brolucizumab, 3 and 6 mg, were compared to aflibercept 2 mg, and in Harrier brolucizumab 6 mg was compared to aflibercept 2 mg, in 2-year randomized, double-masked trials. The study trial design was novel, and was designed to focus on clinically relevant endpoints. After randomization, patients were given three injections at monthly intervals beginning at baseline, during a matched treatment regimen and eyes were then assessed at week 16. After week 16, participants entered the maintenance phase whereby individuals randomized to brolucizumab were treated on an every 12 week regimen as a default, whereas those given aflibercept were maintained on an 8-week dosing regimen throughout the study duration through week 96. Disease activity was then assessed beginning at week 16 at 12 week intervals for Hawk and 8 and 12 week intervals for Harrier. If the disease was active based on visual acuity and/or anatomic factors, the brolucizumab dosing frequency was increased to every 8 week treatments. The primary study endpoint was at week 48 which was the noninferiority of brolucizumab to aflibercept in mean best corrected visual acuity change from baseline to week 48. Key secondary endpoints included the average change in best corrected visual acuity from baseline for the period weeks 36-48, the proportion of patients who could be maintained exclusively on an every 12 week dosing interval through week 48, the predictive value of the first q12 week interval to determine whether patients could successfully stay on an every 12 week interval at week 48, disease activity status at week 16, change in central subfield thickness from baseline at week 16 and 48, and presence of intraretinal and/or subretinal fluid from baseline at week 16 and week 48. Importantly, patients were well balanced across the treatment arms for key characteristics including best corrected visual acuity. The primary noninferiority endpoint was met in both Hawk and Harrier, i.e., the best corrected visual acuity gain for brolucizumab was not inferior to that of aflibercept. The overall ETDRS letter change from baseline was approximately 6-7 in each of the groups. Importantly, 52% of eyes treated with brolucizumab 6 mg could be maintained on a 12 week dosing regimen until week 48 and if patients successfully made it past the first 12 week dosing regimen, more than 80% could stay on this treatment regimen through week 48. The proportion of eyes with intraretinal fluid and/or subretinal fluid or sub-RPE fluid was less in the brolucizumab treated groups and fewer eyes had disease activity at week 16. Patients were followed through week 96 and, overall, the visual acuity gains achieved by week 48 were maintained at week 96; 75% of patients who successfully completed the first 12 week dosing interval could continue at every 12 week dosing through week 96. The better fluid drying effect was also observed through week 96. Overall safety was similar in the brolucizumab and aflibercept groups.

Recently, an analysis was performed to determine the efficacy and safety of brolucizumab in a Hawk prospective substudy. In this substudy, Japanese patients with polypoidal choroidal vasculopathy were treated with brolucizumab or aflibercept with the identical treatment protocol described above for the overall study group. Notably, the main study results were replicated in this substudy group: brolucizumab was not inferior to aflibercept, more than 50% were maintained on a q12 week dosing regimen, and if subjects successfully made it past the first 12 week dosing interval, then there was a more than 90% probability that they could stay on this every 12 week dosing regimen through 96 weeks.

Based on the favorable phase III study results, and supporting data from early-phase studies, brolucizumab 6 mg was approved as Beovu, by the FDA in October 2019, to treat neovascular AMD. Now that we have this additional agent, how will this drug fit into our current treatment regimen? Data from the trials mentioned above are helpful in this regard. If you choose to use brolucizumab, you can tell your patient that expected visual acuity is similar for brolucizumab and aflibercept, at least through the first two years of treatment, and that a significant proportion will be able to achieve this visual acuity level at every 12 week dosing intervals. Furthermore, you can tell the patient that if they make it past the first 12 week interval, after three initial loading doses, then there is a very high probability that they will be able to stay on this every 12 week regimen. In addition, the drug works well as primary therapy for eyes with typical AMD and those with polypoidal vasculopathy. Similarly, in the recently reported Planet study, aflibercept monotherapy

was also effective to treat eyes with polypoidal choroidal vasculopathy, and could be used as an alternative to brolucizumabin this population.

There are several remaining open questions regarding the use of brolucizumab relative to the other agents. Trials are currently underway to answer some of these questions. For example, the proportion of eyes that can be maintained on every 12 week brolucizumab injections relative to those treated with aflibercept or ranibizumab has yet to be definitively determined. In addition, the relative efficacy of brolucizumab compared to ranibizumab and aflibercept when given at monthly intervals or every 8 week treatment intervals over an extended time has not been reported. Brolucizumab pricing will be similar to that of aflibercept, and both are more expensive than ranibizumab, and all three of these agents are significantly more expensive than bevacizumab. Whether to start with brolucizumab or one of the other three agents in a given patient will be determined by a variety of factors that include insurance coverage and patient preference. I believe that the results of ongoing studies to address relative efficacy of the different agents in head-head trials will further inform these treatment decisions. In addition, the landscape will be further complicated by results from other ongoing trials of other agents or drug delivery methods. For example, the port delivery system is a ranibizumab sustained drug delivery reservoir that shows promise, as reported in the Ladder study to provide ranibizumab drug delivery over a 6-9 month period with efficacy similar to that of standard ranibizumab therapy. In addition, combination treatment with ranibizumab and angiopoietin inhibitor may provide longer drug delivery than that afforded by ranibizumab alone. Additional agents such as conbercept, a recombinant anti-VEGF fusion protein has shown benefit to treat eyes with every 12 week dosing. Currently, phase III trials with this agent are underway. These studies are meant to be representative examples of additional treatments but are not all inclusive, as several other agents to treat neovascular AMD are under development. It is truly an exciting time to be a treating retina physician. We now have a new agent, brolucizumab, to offer our patients. We will likely have several other alternatives in the not too distant future. Treatment paradigms will continue to evolve, but the net result will be better options to preserve our patients' sight, while at the same time reducing treatment burden.

SPOTLIGHT

The Pachychoroid Disease Spectrum

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The first PubMed indexed reference to the term Pachychoroid is dated 2013. With increasing access to better imaging systems especially autofluorescence imaging, Indocyanine green angiography (ICGA), Enhanced depth and swept source OCT and OCTA, there is a new role of choroidal evaluation as a biomarker . From a simple diagnosis of an abnormally thick choroid, we are now faced with an entire spectrum ranging from CSCR to CNV where there are morphological alterations in the layers of the choroid that have implications on function and treatment response. However, as with any new definition, there is always confusion as to where in the disease spectrum to place the patient, how to interpret the findings on imaging and eventually debate on the need to change the practice pattern.

We raised a few controversial questions to 5 retina specialists with experience in imaging and managing these complex and often confusing cases, with the aim of providing some clarity to our readers. The situations have been prepared and responses compiled by Dr MunaBhende and Dr Amit Palkar

Q1 - MPB: The terms pachychoroid (thick choroid) and pachychoroid disease are used interchangeably. How would you distinguish between them and which investigation would you choose to differentiate?

AG: The term pachychoroid and pachychoroid disease are quite different. Pachychoroid refers to an increase in choroidal thickness whereas pachychoroid disease refers to an increase in the thickness of the choroid along with certain morphological changes evident on detailed spectrum domain OCT (SD-OCT) examination. This includes the presence of pachy vessels which is a dilatation of the outer choroidal vessels (Haller's layer) along with compression of the inner choroid with overlying changes in the retinal pigment epithelium and outer retina. This includes irregularity in the retinal pigment epithelium and sometimes subtle changes in the ellipsoid and external limiting membrane. In view of the wide range of the choroidal thickness and the variation in the choroidal thickness with age, the general consensus of defining thick choroid is choroidal thickness greater

than 300 microns and it is necessary to scan and segment the choroid both in the sub-foveal area and also in the surrounding extra-foveal area. If the extra-fovealchoroidal thickness is 50 micron more than the sub-foveal choroidal thickness this is also considered significant.

SS: The most specific feature to identify the pachychoroid phenotype or disease is the presence of choroidal hyperpermeability on ICGA. The next most helpful sign is a large choroidal vessel that compresses the overlying choriocapillaris. A thick choroid, while consistent with the pachychoroid phenotype, is not required to make the diagnosis.

RN: The term "pachychoroid" denotes increased choroidal thickness, which may or may not be associated with any pathological retinal disease. The term "pachychoroid disease" denotes dilation of choroidal vesselsassociated with a secondary compression of the overlying choriocapillaris. Pachychoroid disease may not necessarily be associated with overall increased choroidal thickness.

I would perform Enhanced Depth Imaging (EDI) Optical Coherence Tomography (OCT) or Swept Source OCT (SS-OCT) to detect compression of choriocapillaris or Sattler layer vessels. This is the most important feature that I look for in choroidal disease. Enface OCTis a non-invasive and commonly available tool to image the entire length of pachyvessels.

GM: Pachychoroid is a frequently bilateral and possibly inherited condition characterisedby structural and functional choroidal alteration, as the key pathophysiologic mechanism essential to diagnose pachychoroid diseases. These alterations include: A) Pachyvessels dilated choroidal vessels in Haller's layer onEDI OCT and enface OCT, B) Attenuation of inner choroid focal or diffuse attenuation of the choriocapillaries and intermediate calibre vessels within Sattler's layer on SS-OCT and EDI OCT, C) Choroidal vascular hyper permeability on Indocyanine green angiography (ICGA), D) Focal or diffuse increase in choroidal thickness using EDI or SS-OCT.

The pachychoroiddisease spectrum includes clinical entities associated with pachychoroid, including Central serous chorioretinopathy (CSCR), Pachychoroid pigment epitheliopathy (PPE), Pachychoroid neovasculopathy (PNV), Polypoidal choroidal vasculopathy (PCV), Focal choroidal excavation (FCE) and Peripapillary pachychoroid syndrome (PPS). Choroidal thickness per se is not the most important criterion for defining the pachychoroid disease phenotype.

JC: Term “pachychoroid” is just not “thick choroid”. One needs to be very careful before using the term “pachychoroid”. Presence of pachyvessels (preferably on en-face structural OCT) along with inner choroidal thinning is necessary to diagnose “pachychoroid”. Pachychoroid disease primarily means the spectrum of diseases such as pachychoroid pigment epitheliopathy, CSCR, pachychoroidal neovasculopathy, and PCV in presence of pachychoroid features. ICG, structural en-face OCT, cross-sectional OCT, autofluorescence are useful to establish the diagnosis of pachychoroid diseases.

Message : Pachychoroid refers to an increase in choroidal thickness, whereas pachychoroid disease refers to the presence of pachyvessels (dilated Haller's layer), compression of overlying inner choroidal vessels (Sattler's layer and choriocapillaris) that gives rise to a spectrum of clinical entities including Pachychoroid pigment epitheliopathy (PPE), Central serous chorioretinopathy (CSCR),Pachychoroid neovasculopathy (PNV), and Polypoidal choroidal vasculopathy (PCV). Pachychoroid disease may not necessarily be associated with overall increased choroidal thickness, but the presence of pachyvessels is essential. EDI OCT or SS-OCT, Enface OCT and ICGA are useful to differentiate and establish the diagnosis of pachychoroid disease.

Q2 - MPB: How would you measure the diameter of a choroidal vessel and determine if it is dilated or not? Do you segment the various layers of the choroid? What are your guidelines?

AG: In our Institute we are using the enhanced depth imaging software in the Heidelberg Spectralis system to image the choroid. We are not using any other automated software based on binarized OCT or ICGA images in routine day-to-day patient practice. We measure the thickness of the choroid from the Bruch's to the choroid scleral interface using the callipers to get an idea as to the thickness of the choroid. Earlier we were focussing primarily on the sub-foveal thickness but now we are looking at the para-foveal area also. Morphological changes in the choroid like dilatation of the vessels in the Haller's layer is estimated using the EDI images.

SS: There is too much variability in my opinion for a measurement of an individual choroidal vessel to be meaningful. If the main goal is to use this as a quantitative metric to identify pachychoroid, I think it is better to assess subjectively to see if there are any vessels that are “significantly” (meaning >50%) larger that surrounding vessels within the same deep choroidal layer. In a way, this is using an internal control to determine if a “pachyvessel” might be present. I do not bother segmenting choroidal layers, unless I am doing OCT-Angiography (OCTA) to study the choriocapillaris.

RN: I do not measure the choroidal vessel diameter, and there is no universally accepted cut-off for labelling pachyvessel. Choroidal vessels can even be in a plexus-like configuration in the Haller layer, with no overlying retinal pathology. I look at the segments of choriocapillaris, Sattler layer and Haller layer. I find steroid antagonists useful in cases of pachychoroid disease with dilation of vessels in both Haller and Sattler layer.

GM: For measuring diameter of a choroidal vessel,an EDI OCT image with spectral domain OCT (Spectralis®; Heidelberg Engineering, Germany)is used. Seven sections, each comprising 100 averaged scans, are obtained in a 5° x 30° rectangle centred on the macula, and the horizontal section going directly through the centre of the fovea is selected. Measurement is done with Heidelberg Caliper software. Within the choroid, in the outer layer ofHaller and in the intermediate layer of Sattler, hypo-reflective lumen in the OCT image with reflectivity similar to that of sub-retinal fluid,a re taken as surrogates for choroidal vessels. All discernible hypo-reflective lumens within a zone with a width

of 4500µm centred on the fovea are assessed and largest lumen is localized, the diameter of this largest lumen is measured. The diameter of each hypo-reflective lumen is assessed perpendicular to Bruch's membrane always in the region of the widest diameter of the lumen. Though, in histological sections with PCV, dilated choroidal vessels with diameter up to 300µm have been observed, generally pachyvessel diameter is < 250µm.

To facilitate detailed evaluation of the morphology of choroid, software based on binarized OCT or ICGA images have been developed to quantify the ratio between choroidal vascular luminal areas to total choroidal area. However, in clinical practice we do not segment various layers of choroid and there is no defined cut-off each layer or vessel lumen diameter as far as pachy-disease is concerned.

JC: It is a challenging question, as we know choroidal vessel do not follow a particular pattern and the cross-sectional OCT may not be the best way to measure the exact diameter. However, in our previous studies, we measured the large choroidal vessel diameter on a swept source OCT scan passing through fovea. It is very challenging to segment the layers of the choroid; however, we have tried Haller's layer volumetric analysis as well. I believe there is no specific measurement available yet to define the "normal" diameter of the vessel. A 3-dimensional modelling may help with this complex vascular structure.

Message: The diameter of a choroidal vessel can be measured using the OCT software callipers or binarization. However, there is no consensus regarding the method to measure a choroidal vessel. The individual variability of choroidal vessel anatomy may influence any measurement and definition of any cut offs. However, relative comparison of a large choroidal vessel with the adjacent choroidal vessels at the same choroidal layer may be helpful.

Q3 - MPB: How would you differentiate a case of "typical" acute CSCR from the first episode of CSCR in a patient with pachychoroid disease? Or, are both part of the same spectrum?.

AG: The first episode of CSCR on OCT shows a classic serous macular detachment with presence of a serous pigment epithelial detachment. The serous macular detachment is echolucent justifying the first attack of CSCR. We also do the fundus autofluorescence (FAF) and this is useful to tell us whether this is the first attack in a patient. The absence of patches of decrease autofluorescence which are signs of previous episodes is very useful in such cases. The typical acute CSCR and the first episode of CSCR are both parts of the same spectrum. The typical acute CSCR on OCT also may show similar changes of serous macular detachment with or without the presence of pigment epithelial detachment. Careful examination of the roof of the PED may show a microrip which corresponds to the area or the RPE leak in fluorescein angiogram. Multimodal imaging using the fundus autofluorescence may show a patch of increased autofluorescence corresponding to the area of fluid and surrounding areas of patches of decrease autofluorescence which gives important information to the clinician that this recent episode probably is not the first episode of CSCR. To me both are parts of the same spectrum but in a patient, who is coming to me with what possibly could be the first episode of CSCR with a short history I may not go further than doing the OCT and fundus autofluorescence. However, in a patient who comes to me with acute typical CSCR, but where the OCT and FAF gives me an inclination that although this an acute attack, this is not the first, I may go ahead with other modalities of multimodal imaging like ICGA or FFA depending on the clinical situation.

SS: I do not distinguish these entities and think they are part of the same spectrum. More important is to distinguish idiopathic CSCR from a secondary CSCS-like syndrome from a choroidal infiltrative process.

RN: I do not differentiate between the two in my clinical practice at present.

GM: Both "typical" acute CSCR and first episode of CSCR in a patient with pachychoroid disease are part of the same spectrum. Many reports have demonstrated a pathologically thickened choroid in CSCR eyes. In addition, the mean subfoveal choroidal thickness in symptomatic eyes is usually greater than that in asymptomatic fellow eyes. Dilated choroidal vessels in Haller's layer accounts for thickened choroid in CSCR. Using binarization method to determine the sizes of the hypo-reflective lumen and hyper-reflective stroma, larger hyper reflective stroma in the inner choroid has been found and is thought to be related to the inflammation and oedema occurring during the acute stage of CSC, in addition to dilation of larger vessels in the outer choroid.

JC: "Typical" acute CSCR will not have any other signs of previous disease. "First episode of CSCR" in a pachychoroid disease will have signs of pachychoroid pigment epitheliopathy along with typical features of pachychoroid.

Message: "Typical" acute CSCR and first episode of CSCR in a patient with pachychoroid disease are both possibly part of the same spectrum. The first episode of CSCR in an older patient however should suggest that it is part of the pachychoroid disease spectrum. Fundus autofluorescence helps to differentiate acute on chronic CSCR from the first episode of CSCR. In conjunction with OCT, tell-tale signs of pachychoroid pigment epitheliopathy should be noted. In addition, the possibility of a secondary "CSCR-like" appearance due to a choroidal infiltrative process cannot be ignored.

Q4 MPB: We often see patients with a few scattered drusen like deposits at the posterior pole, not necessarily in the macula. Would you call this pachychoroid pigment epitheliopathy or AMD? Is it possible, and more importantly necessary to differentiate? What would you advise a patient in whom you have diagnosed pachychoroid pigment epitheliopathy?

AG: I would call this pachychoroid pigment epithiliopathy and not dry age related macular degeneration. It is possible to differentiate these two conditions based on both clinical

examination and on basic multimodal imaging. Clinically patients with PPE are much younger and it need not necessarily be bilateral to start with. These are faint and discrete changes at the level of the retinal pigment epithelium (RPE) and they are less seen close to the fovea and it is distributed more in the parafoveal area in the posterior pole. On OCT corresponding to these areas that we clinically see in PPE, you can beautifully demonstrate irregularities in the RPE. Corresponding to these areas in the RPE the overlying ellipsoid layer also shows discontinuity. The infrared images are very diagnostic and in the infrared picture you see characteristically discrete patchy areas of the increased autofluorescence. This, I feel, is a very beautiful imaging feature in PPE. It is important to differentiate these two conditions because the behaviour is definitely far different. I would definitely like to follow up patients with PPE on a regular basis and at the first examination itself I may do an OCTA because I have seen nascent neovascular network in some of these patients but are near asymptomatic and have near normal visual acuity. So,if I have ruled out a pachychoroid neovasculopathy I will probably request these patients to come for regular check-up once in six months to one year or earlier if they develop symptoms of metamorphopsia. I would not scare such patients with PPE because still we do not have much literature on the natural course of such patients and their progress to symptomatic disease.

SS: This may very well be pachychoroid pigment epitheliopathy. But the key is to look for these so-called “pachydrusen”, which are well-demarcated, but tend to form irregular rather than round shapes. As these patients are prone to CSCR or PCV they are important to differentiate and identify. Patients with these findings should be advised to monitor their vision and to have regular eye examinations (at least every 4-6 months, or sooner if there are new symptoms).

RN: Patients with ARMD would be in the 5th to 7th decade of life with thinning of the choroid evident on OCT. In contrast, patients with pachychoroid pigment epitheliopathy are in 3rd to 4th decade and have "pachy" vessels evident on OCT. I would follow up the patient regularly at 6 months interval with OCTA and FAF.

GM: The clinical appearance of PPE includes mottling of the RPE, irregular areas of RPE elevation termed “drusenoid RPE lesions” and an absence of soft drusen seen in eyes with AMD. Thesedrusen associated with thickened choroid were called “Pachydrusen”, generally larger than 125µm, round or ovoid shape with irregular outer contour and distributed singly or in small bunches throughout the posterior pole. The choroid seems featureless and has a redder hue than does thinner choroids in AMD. Soft drusen of AMD often aggregate in the central macula and over time focal hyperpigmentation can be seen over thedrusen. Choroidal hyperpermeability with ICGA in PPE, as well as Pachyvessels helps to differentiate from AMD.

Since the eyes do not manifest neurosensory detachment, PPE was considered a formefruste of CSCR. Moreover, it was subsequently observed that patients with PPE could go on to develop type 1 neovascularization, with or without aneurysmal (polypoidal) lesions, without necessarily developing CSCR. So, patients of PPE require routine follow-ups to look for development of CSCR or PNV.

JC: Few drusen-like deposits in pachychoroid disease can be seen, however, making the diagnosis of pachydrusen and ruling out typical dry AMD drusen is important by evaluating the OCT. In regard to pachychoroid pigment epitheliopathy, there is no treatment so far. Such cases can be observed, however, following-up the patient twice in a year with imaging, may be beneficial to understand the progression.

Message: A few scattered drusen at the posterior pole in a patient can be differentiated based on age of the patient, size and morphology on clinical examination and OCT and the presence of pachyvessels, in which case, they may be termed as pachydrusen. The presence of RPE irregularity with altered autofluorescence along with pachydrusen and pachyvessel characterizes Pachychoroid pigment epitheliopathy and differentiates it from AMD. PPE can be a harbinger of CSCR, pachychoroid neovasculopathy, Type 1 choroidal neovascularization (CNVM) or PCV. Periodic follow-up atleast once in 6 months is warranted in such patients with monitoring using OCT, OCTA and FAF.

Q5 - MPB: How would you differentiate pachychoroid neovasculopathy from typical AMD? Do you follow a different treatment protocol?

AG: Pachychoroid neovasculopathy is diagnosed based on multimodal imaging features. Clinically patients with PNV have a serous macular detachment (SMD) and on SD OCT apart from the SMD you see the diagnostic flat irregular pigment epithelial detachment or otherwise described as a double layer sign (DLS) showing the separation of the RPE from the Bruch's membrane. This particular feature if you do video ICGA with OCT will demonstrate the neovascular network growing between the Bruch's membrane and the retinal pigment epithelium throughout this area of DLS or Fibrovascular pigment epithelial detachment (FVPED). OCTA probably is more sensitive in identifying the neovascular network when compared to the ICG Angiogram. In a case of typical wet AMD there are very classic features which are quite different from what we see in PNV. Most important, I think, is the presence of intra retinal fluid in the very early stage apart from the presence of serous macular detachment. The other features like FVPED and the presence of a beautiful pre-RPE hyperreflective well delineated area corresponding to the neovascular membrane with overlying intraretinal fluid and possibly some subretinal fluid is again very diagnostic (wet AMD). FFA will confirm the diagnosis with a corresponding lacy network of increasing hyperfluorescence in size and intensity resulting a fuzzy large area in the late phase. Therefore, summarising on clinical examination, the PNV has primarily a serous macular detachment but the area underlying the SMD shows a double layer sign whereas typical wet AMD shows classic drusenoid changes along with greyish membrane with a speck of deep haemorrhage and overlying fluid.

SS: The key here is identifying the pachychoroid phenotype. Although choroidal hyperpermeability on ICG-A is most specific, but pachyvessels on OCT, and pachydrusen on exam can help make the diagnosis. With this pachychoroid phenotype, when CNV appears it can be considered pachychoroid neovasculopathy. In contrast with typical AMD, they key findings is the presence of regular, soft (and at times, confluent) drusen.

RN: ARMD

a. Elderly
b. Thin choroid
c. Both type 1 and 2 CNVM
d. Hemorrhage and hard exudates are commonly associated
e. Presence of drusens
f. Other eye having drusen, active CNVM or a disciform / geographic scar.

Pachychoroid neovasculopathy

a. Middle aged
b. "Pachy" vessels in OCT
c. Typically have type 1 CNVM
d. Hemorrhage and hard exudates are not commonly seen unless PCV is associated with it.
e. Absence of drusen
f. Other eye having "pachychoroid disease"

I would advise PDT for PNV,whereas for AMD CNVM, I would perform monotherapy with anti-VEGF.

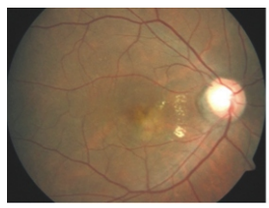
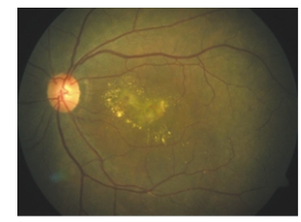
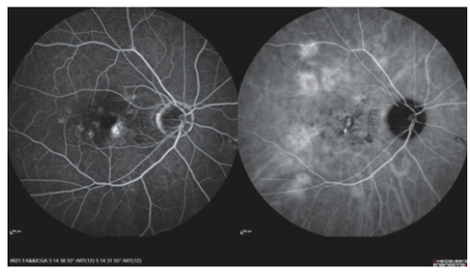
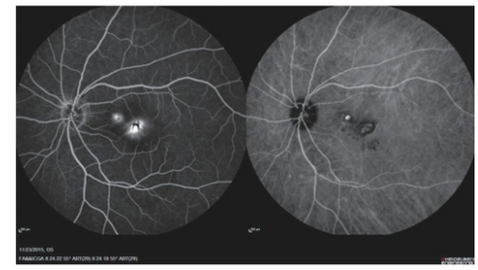
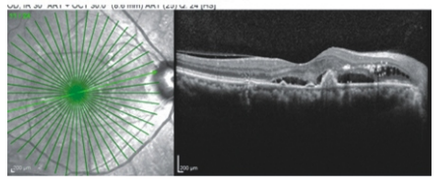
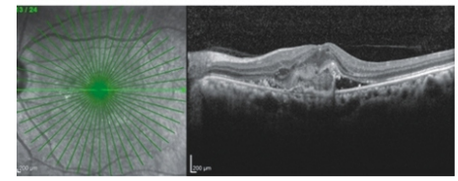
GM: Eyes with PNV display background features common to the pachychoroid disease spectrum including reduced fundus tessellation indicative of thickened choroid in the area of type 1 neovascularisation, absence of soft drusens and also younger age group of patients, unlike neovascular AMD. EDI or SS-OCT helps in further differentiating the two, with Pachychoroid features in PNV compared to thinchoroid in AMD. OCT angiography is particularly useful in picking up these fine sub-RPE neovascularisations, in the setting of Chronic CSCR.

Generally, eyes with PNV respond favourably to intravitreal anti-VEGF therapy with a significantly longer retreatment-free interval than those seen in more typical neovascular AMD, following the initial loading injections .The apparent lower dependence on repeated injections in these cases may relate to lower intraocular VEGF concentrations in PNV eyes compared to eyes with more typical neovascular AMD. However, some eyes with PNV appear refractory to intravitreal anti-VEGF monotherapy. Anti-VEGF therapy in combination with PDT is useful in such cases.

JC: This is a very important question. PNV shows the presence of pachychoroid features in presence of type 1 neovascularization, contrary to wet AMD, which would show absence of pachychoroid features and thin choroid. There are no guidelines to treat PNV differently from wet AMD. However, I suspect poor response to anti-VEGF monotherapy, and may need combination therapy more often in PNV than wet AMD, however, we need more data on this.

Message: The presence of Pachychoroid (pachyvessels +/- pachydrusens) or CSCR, an irregular RPE or PPE, absence of tall peaked or notched PED, with no subretinal or intraretinal exudation, hemorrhages or leakage in ICGA; and the detection of a vascular network on OCTA identified at the RPE fit or Outer retina Choriocapillaris (ORCC) slab, is referred to as Pachychoroid neovasculopathy. PNV may berefractory to anti VEGF therapy possibly due to a relatively lower intraocular concentration of VEGF. Anti VEGF therapy should be initiated once appearance or increase in subretinal or intraretinal fluid or haemorrhage is noted. The role of observation of PNV and aggressive intervention with PDT is debatable.

Q6 - MPB: Choroidal hyperper meability on ICG is noted to be present in >90% of eyes with PPE and CSC and in 10-50% of eyes with PCV. Does demonstration of choroidal hyperpermeability on ICGA change your line of management? The cases of two patients below could be examples:

AG: Demonstration of significant choroidal hypermeability in ICGA is more suggestive of a CSC spectrum of disease and definitely the management is different. In my practice, PDT is not the first line of management in all patients with CSCR at this moment of time. I reserve it for specific clinical situations which I have elaborated later. Two cases that have been shown if you look at the ICG image of the right eye it shows nodular hypercyanescence with surrounding halo and this corresponds to the area of exudation sign on clinical examination. This could be diagnosed as juxtafoveal PCV. Choroidal hypermeability in both these cases are not very significant. The left eye also shows a nodular hypercyanescence with surrounding halo and along with that, I feel, there is a network with surrounding hypocyanescence. The OCT image of the left eye has not gone through the area of nodular hypercyanescence but it shows the irregularity in the retinal pigment epithelium corresponding to the network seen in ICGA. Whereas, in the right eye the OCT has gone through the area of nodular hypercyanescence and you can see the elevated pigment epithelial detachment (PED).

SS: The lack of choroidal hyperpermeability does not change my management per se, but it will make me question the diagnosis of pachychoroid disease in the first place. However, I am still willing to make the diagnosis if other findings are consistent.

RN: If ICGA shows choroidal vascular hyper-permeability (CVH), I would look for "pachy" vessels on OCT to differentiate pachychoroid neovasculopathy and polypoidal choroidal vasculopathy from other causes of CNVM. I would also re-evaluate ICGA to identify BVN, polyps and presence of feeder vessels. I prefer to do combination with PDT (or micropulse laser) in eyes with CVH, and monotherapy with anti-VEGF without CVH. Extrafoveal polyps can be treated with thermal laser in eyes without CVH. Eyes without CVH would behave similar to AMD CNVM.

GM: PCV with associated choroidal vascular hyper permeability (CVH) is reported to have better visual outcome and lower injection number in combination therapy with PDT. Thus, CVH can be potential biomarker for selecting patients for combination therapy. Therefore, PDT can be considered as either initial therapy or additional treatment in patients with PCV and CVH. Choroidal vascular hyperpermeability and increased choroidal thickness represent different functional disturbances and anatomical changes within the choroidal vasculatureand ICGA still remains an important imaging modality to prognosticate treatment outcome.

JC: Presence of choroidal hyperpermeability (CVH) definitely points towards the CSCR related CNV or pachychoroid spectrum. CVH may suggest an early combination therapy. In my opinion, PDT becomes an important treatment option for pachychoroid disease spectrum.

Message: Any hot spot or plaque in the background of choroidal vascular hyperpermeability with pachyvesselson ICGA indicates the disease in pachychoroid spectrum. Unlike neovascular AMD, the response to anti VEGF therapy may be less effective in these patients. Combination of PDT may demonstrate a synergistic action; use as first line treatment is still however dependant on other logistics.

Q7 - MPB: What is the current role for PDT in your practice? Which part of the spectrum and your parameters? Using the same example above, if you were to do a PDT which lesions in case 1 will you treat and why?

AG: Current role of PDT in my practice is for the following clinical situations:

a) Subfoveal and juxtafoveal PCV
b) Chronic CSCR esp. with ICGA shows choroidalhy permeability and FFA fails to identify any definite RPE leak.
c) Recurrent CSCR patients presenting with periodic exacerbation and ……
d) Persistent CSCR in an eye with subfoveal leak.
e) Selected cases of PNV.

I use half fluence PDT. I cover entire lesion including the network as far as PCV is concerned. Therefore in this particular case which you have shown in the right eye it would be juxtafoveal treatment where the edge of treatment burn may just abut on to the fovea, whereas in the left eye it will be a subfoveal treatment which will also cover the network that you can see apart from the nodular hypercyanescence.

SS:I use low fluence PDT regularly to treat CSCR (chronic or persistent acute) and I use full fluence PDT to treat PCV. For the first treatment session with PCV, I will treat the BVN and the polypoidal lesions. If additional PDT is necessary for persistent activity I will only treat the leaking polypoidal lesions/aneurysms.

RN: I perform PDT in foveal leaks in acute CSCR, and chronic CSCR that have persistent SRF/ IRF and progressive visual impairment. I use reduced-fluence PDT in CSCR. For PNV and PCV with CVH, I use standard fluence PDT. In case 1, I would do PDT to the lesion containing BVN. Isolated extrafoveal CVH without BVN is not an indication for PDT in my cases.

GM: PDT is the current first line management for Chronic CSC with subfoveal and juxtafoveal leaks including DRPE or PEDs. Reduced Fluence(RF) PDT is the norm (25 J/cm2 for 83s and 300 mW/cm2after 6mg/m2 verteporfin injection) and treatment spot covers the areas of choroidalhyperpermeability in the mid-phase ICGA. Multi spot treatment may be needed in many cases. Subfoveal PCV is managed with Standard fluencePDT(50 J/cm2 for 83 s and 600 mW/cm2) in combination with anti VEGF injection 48 hours later and the treatment spot greatest linear diameter (GLD) includes leaking polyps and BVN. RF PDT may be used with similar results in patients especially with good vision(>20/40), large serosanguinous PEDs or very large lesion size to minimize complications like RPE rips, subretinalhemorrage and choroidal ischemia.

For patient 1 with subfoveal PCV, if the vision is better than 20/40, I would prefer to do RF PDT in combination with anti-VEGF andwould cover the areas of extra foveal choroidal hyperpermeability on ICGA as well.

JC: PDT is an important component in treatment strategy. I

usually offer PDT very early in the treatment plan if I see PCV features (as in case 1) along with anti-VEGF therapy. I prefer to use standard fluence PDT (full dose, full time) covering the whole BVN on ICG. I repeat ICG in 2 months after PDT to understand the polyp activity and late geographic hyperfluorescence extent and evaluate the probability of recurrence.

Message: The current role and indication of PDT are reduced fluence in chronic CSCR with subfoveal or juxtafoveal leaks and standard fluencein subfoveal or juxtafoveal PCV. Reduced fluence PDT can be used to treat areas of choroidal hyperpermeability with multispot treatment. The BVN and polypoidal lesions in PCV should be covered entirely in a treatment session.

Q8 - MPB: Peripapillary pachychoroid is a new entity sometimes included as part of the spectrum. What are your guidelines to diagnose it? How do you differentiate it from uveal effusion syndrome?

AG: Peripapillary pachychoroid I feel is not a new entity. It has been described and identified recently, but I have been seeing such cases for the last at least 15 years. Unfortunately, we did not report it or publish it. These are very characteristic cases where you see more often the bilateral disease with peripapillary serous macular detachment and very often they show a chronicity in the form of cystoid change in the peripapillary area and now using OCT we are able to identify the pachy vessels underneath the area of fluid that is seen in OCT. Usually you would see that the pachy vessels are reasonably large, sometimes occupying the whole of the choroid and the overlying RPE is thinned out. Uveal effusion syndrome is very different. Most importantly they may show serous choroidal detachment, change in the IOP and acute drop in visual acuity whereas peripapillary pachychoroid is a slow progressive disease. FFA in uveal effusion syndrome may show a hot optic disc unlike in peripapillary pachychoroid disease.

SS: Peripapillary pachychoroid is localized and diagnosed by a thicker choroid and pachyvessels nasal to the macula. Whereas the choroid generally thins as one approaches the optic nerve, the opposite happens in peripapillary pachychoroid. In uveal effusion syndrome, the choroid is usually thick throughout the retina, often with choroidal folds and characteristic FAF changes.

RN: Peri-papillary pachychoroid syndrome (PPS) patients are elderly males with nasal macular choroidal thickness more than temporal macular thickness. They have associated peripapillary intra-retinal and/or sub-retinal fluid over pachy vessels. They may also have serous PED and gravitational tracts, along with optic disc edema. Choroidal folds, short axial length and hyperopia may be associated with PPS.

Uveal effusion syndrome patients are typically young males, with choroidal detachment. Choroidal thickness is the same throughout the nasal and temporal half of macula. They may have exudative retinal detachment and leopard skin appearance of the retina.

ICGA shows diffuse CVH in both the conditions. Episcleral veins may be dilated in uveal effusion syndrome.

GM: PPS is characterized by a relatively thickened nasal macular choroid with associated intraretinal and subretinal fluids extending from the disc margin, even nasal to the optic disc. Peripapillary RPE and ELM atrophy at the disc margin with choroidalhy pertransmission is usually seen. FAF and FFA may show peripapillary RPE mottling with late staining and ICGA shows pachyvessels and multifocal hyperpermeability in the peripapillary region. The optic nerve head is usually crowded with mild late leakage with FFA and Choroidal folds, hyperopia and short axial lengths are common in these relatively older patients than typical CSC.

This entity may be differentiated from a rare Posterior variant of uveal effusion syndrome by the presence of preferential nasal macular involvement, PEDs, RPE tracts, pachyvessels with multifocal choroidalhy perpermeability in the mid-phase ICGA and the absence of early diffuse granular ICG hyperfluorescence with late diffuse intense leakage reported for uveal effusion syndrome.

JC: Thickened nasal choroid and hyperpermeability / pachychoroid features, predominantly around the optic disc makes the diagnosis of peripapillary pachychoroid. Absence of peripheral choroidal detachment and predominant peripapillary findings differentiate this entity from Uveal Effusion Syndrome.

Message: Uveal effusion syndrome is an important differential diagnosis for peripapillarypachychoroid.

Features	Peripapillary-Pachychoroid	Uveal Effusion syndrome
Location of thickened choroid	Peripapillary (nasal macularchoroid, choroidnasal to optic disc)	Entire choroidal tissue
Pachyvessels & Pachy choroid features	Present	Absent
Choroidal folds and etachment	Absent	Present
RPE changes, PED	Present	May be present (leopard skin appearance)
Serous exudation	Both subretinal and intraretinal	Predominantly subretinal
ICGA features	Pachyvessels with multifocal choroidalhy-perpermeability in the mid-phase	Early diffuse granular hyper-fluorecence with late diffuse intense leakage
Hyperopia, Nanophthalmos, Thick sclera	Rare	Common

Q9 - MPB: What is your opinion on combination therapy with steroids in pachychoroid neovasculopathy or PCV given that CSCR is at one end of the spectrum?

AG: An interesting question. To answer this question, we have to first define where does CSCR come in the pachychoroid spectrum. A patient with pachychoroid pigment epitheliopathy may directly progress to a pachychoroid neovasculopathy subsequently aneurysmal dilatation what is described as PCV. So, we have a sequence of events which is possible. Therefore, the question I ask myself is where CSCR comes in the spectrum. Therefore, we need to really go in depth to our understanding of CSCR esp. CSCR presenting in the elderly population above the age of 50 years. I would say that CSCR is probably a separate entity in this spectrum and whether certain chronic cases of CSCR progress to PNV is something which we need to look into. So, in this context I will not question the use of combination therapy with steroids in pachychoroid neovasculopathy or PCV and I use this combination quite often in my practice because a small dose of triamcinolone of 1 mg intravitreal or for that matter dexamethasone takes care of the immediate post inflammatory effect of PDT.

SS: I would not advise using steroids in this setting.

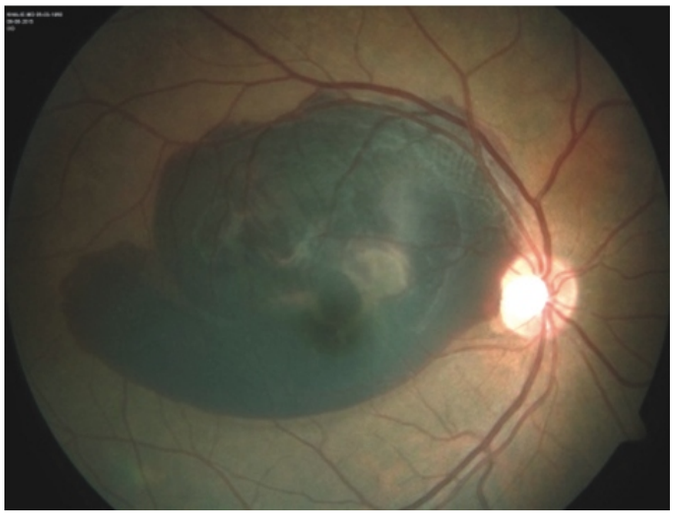
RN: In my experience, large sero-sanguinous PEDs/ hemorrhagic PEDs respond well to local or systemic steroids in PCV. I usually give intravitreal steroids in such cases.

GM: We have limited experience with the use of intraocular steroids in pachychoroid diseases and for a case of PNV or PCV resistant to antiVEGF, my take will be combination therapy with PDT. Steroids in any form, inhalational, topical or systemic, is a well-known risk factor for CSCR. Though rarely, aggravation of CSCR has been noted with intravitreal triamcinolone and dexamethasone injections as well.

JC: Interesting. In past, I have used intravitreal steroids in cases with extra-large PEDs, in combination with PDT+anti-VEGF therapy and in very exudative PCVs. CSCR and its exacerbation to steroids remains a mystery. I think such cases of CSCR are of different spectrum, more of an acute insult rather than a chronic process as we see in PNV or PCV. The recent concept of both mineralocorticoid and glucocorticoid pathways involvement may explain such situation, however, that needs further evidence.

Message: We have limited knowledge regarding the sequence of events in pachychoroid spectrum and as to where do the CSCR, PNV or PCV lie on the spectrum, as yet. Intraocular steroids may be helpful to mitigate inflammation secondary to PDT, theoretically. However, steroids in any form being a risk factor for CSCR, it use in the pachychoroid diseases is debatable.

Q10 - MPB: You are faced with a 65 year-old hypertensive who presents with a drop in vision of 3 days duration and a fundus picture as below. What would be your treatment options and why?



AG: The colour photograph shows a medium sized sub-macular haemorrhage with variable thickness and probably looking at the colour predominantly sub RPE. It is recent based on history and examination. Based on these findings I would go ahead with intravitreal TPA with gas and position the patient so that he looks down at an angle of about 60 degrees in a sitting position. The reason why I choose this particular treatment is considering the size, location, configuration and thickness of the haemorrhage. We still do not have evidence to say which treatment is better and choice of procedure very often is based on the surgeon's experience and comfort.

SS: While it is tempting to say this is due to PCV, there may other causes such as a ruptured microaneurysm. I would obtain an ICG to better confirm the diagnosis. If it is CNV/PCV, given the thick subfovealheme, I might consider PPV/tPA/displacement if there is largely sub-retinal and not sub-RPE heme. I would also treat with anti-VEGF therapy.

RN: I would obtain OCT to know the location of blood. Subretinal blood would be more easily displaced than sub-RPE blood. I would perform Intra-vitreal t-PA (50 microgram in 0.05 ml) + intra-vitreal injection of 0.3ml of pure expansile C3F8 gas. This blood is likely to migrate not just sub-retinallyinferiorly, but also into the vitreous cavity. This patient may need PPV if significant blood accumulates in the pre-macular space. This blood de-hemoglobinizes rapidly. If the blood comes in the vitreous cavity, I would perform Pars planavitrectomy + intravitreal t-PA (20 microgram in 0.05 ml) + Gas. Sub-retinal surgery is generally not required in such cases. Patients on anti-platelets are at high risk of bleeding in the fellow eye, as well as recurrent bleeding in the same eye. Once the blood clears, I would perform ICG to look for polyps/ CNVM. I would treat it accordingly.

GM: If SD-OCT in this patient with > 5 disc diameters of sub macularhaemorrhage, shows thick subfovealhaem(>500µ), a non-vitrectomizing approach of intravitreal injection of recombinant tissue plasminogen activator (rtPA) at dose

25µg/0.1mL, intravitreal anti-VEGF along with pneumatic displacement with expansile gas (0.3 cc C3F8) may clear the sub macular haemorrhage. rtPA has demonstrable effect on the liquefaction of sub macular clots but there are remaining uncertainties with regards to the dose, safety and the timing of initial and repeat treatments. In cases presenting early, pneumatic displacement alone with anti-VEGF may also be sufficient. At 1 month followup, if sufficient clearing of haemorrhage permits ICGA, then based on the activity of polyps, may consider combination treatment with PDT or Focal laser depending on the location.

JC: As the history of vision loss is only three days, pneumatic displacement of the blood should be possible. After 3-4 days of face-down positioning, if pneumatic displacement fails, I may consider subretinal TPA along with fluid-gas exchange and post-op face-down positioning. After knowing the primary pathology, anti-VEGF can be added at end of the surgery. In my experience, intravitreal TPA has limited role, and time is the key in such cases.

Message: The location (predominantly submacular or sub RPE), thickness and duration of the haemorrhage is important while planning treatment of the patient. Spectral domain or Swept source OCT confirms the location and thickness. In presence of thin hemorrhage and absence of a history of blunt trauma, ICGA may identify the source of haemorrhage (Polyp/CNVM/ Retinal Artery Macroaneurysm).

Pneumatic displacement of the subretinal haemorrhage with pure expansile gas followed by face down or 60 degrees in sitting position, can clear the visual axis, anywhere before 7-10 days from the onset of the event. Once the blood clots and de-hemoglobinizes, vitrectomy needs to be considered.

The use of rtPA facilitates liquefaction of the blood. Injectingi ntravitreally or subretinally remains a choice at discretion and expertise of the treating surgeon. However, cumulative cost can be a concern.

Anti VEGF injection reduces the exudation secondary to either the polyp, CNVM or RAM, and is useful when combined in the treatment plan. This is despite a preoperative deferred or a non-yielding ICGA. Addition of focal laser or PDT can be planned after sufficient clearing and identification of lesions clinically and angiographically.

The risk of break through haemorrhage is high in eyes treated with massive subretinal and sub RPE hemorrhages and needs vitrecto my if non clearing.

Welcome to

Vitreo-Retinal Society of India

28th ANNUAL CONFERENCE OF
VITREO RETINAL SOCIETY - INDIA

VRSI LUCKNOW 2019

DIWAAN-E-AWADH

5th Dec - 8th Dec 2019

HIGHLIGHTS OF SCIENTIFIC SESSIONS

- First Time in VRSI
  - Webcast
  - Dr. Steve Charles - Innovations in VR Surgery
  - Dr. Neil Bressler - DME : Lessons learnt from the DRCR trials
- Symposium by the American Macula Society
- Symposium by the Euretina Society
- Symposium by the Egyptian VR Society
- Symposium on Myopia by Experts from the East
- Symposium by the ASRS-VRSI : Complicated Surgical Scenarios
- The Buckle Symposium
- The Trauma Symposium
- OCT Angiography Symposium
- First Time in VRSI
  - Breakfast with Experts Session
  - EurekaZone – Innovations of the Year
- Hyper-Imaging : OC(T)ean's Twelve Session
  - Twelve OCT Diagnoses/terms You Must Know
- Workshop on EyeSi Surgical Simulator
- Workshop on Heads up 3D Vitrectomy
- Multiple Advanced VR Surgery Sessions
- Challenging cases "ICOTY -Indian Case of the Year" Session by RetNet
- Uveitis and Oncology Sessions
- Debates and Duels on Hot Topics
- Practice Management Symposium

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Charles Retina Institute
USA

Dr. Phil Rosenfeld
Bascom Palmer Eye Institute
USA

Dr. Hassan Mortada
Cairo University
Egypt

Dr. Neil Bressler
Wilmer Eye Institute
USA

Dr. Glenn Jaffe
Duke Eye Centre
USA

Dr. Adnan Tufail
Moorfields Eye Hospital
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RETINA TECH CORNER

Ultra-wide-field Imaging in Retinal Disease - Clinical Utility

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The gold standard of posterior segment examination has been binocular indirect ophthalmoscopy along with scleral indentation, which provides comfortable view upto the ora serrata. Drawing colour charts has been used since long for documenting the fundus findings including those in the periphery. However colour charts tend to be subjective as it varies with the expertise of the examiner as well as with his/her drawing skills. Moreover one unconsciously ignores or fails to document other subtle findings like foveal reflex, disc details and chorio-retinal degenerations etc. The need for documentation of these minute details brought into the picture the first commercially available fundus camera by the Carl Zeiss, which provided a 30 degrees field of view of the retina.[1] Then ETDRS came with the idea of 7 standard fields prepared by montage of traditional fundus camera images in 7 standard fields giving a total of 75 degrees view.[2]However mid and far periphery could not be documented and it was impossible to obtain the 7 pictures in the same time frame especially in case of fluorescein angiography. Pomerantzeff used a contact lens system which he called the "Equator plus camera" with trans-pupillary or scleral illumination to view 148 degrees of retina with nodal point of eye as reference point.[3] Staurenghi developed a contact lens which enabled visualization of 150 degrees of retina.[4] The Retcam provides 130 degree field of view but is constrained by its inability to image retina in cases of mild media opacities, though is excellent and still investigation of choice for children and preterm babies due to better ergonomics.[5] But when it comes to visualize far periphery, retinal imaging has taken a giant leap with coming up of ultra-wide field (UWF, Optos, Optos Inc) imaging systems. Optos uses a confocal scanning laser ophthalmoscope technology with an ellipsoid mirror which contains 2 focal points.[6] The laser is passed through the first focal point and the second focal point is virtually placed on the iris plane giving us a 200 degree view of retina (Figure 1). Optos uses 2 lasers- green laser light (532nm) and red laser light (633nm). The green being the lesser wavelength and thus lesser tissue penetrance is used to image anterior retinal structures and red being the greater wavelength penetrates into the deeper retinal and choroidal layers. The two can be individually imaged as well. Autofluorescence is available with excitation wavelength of 532nm and emission wavelength of 570-580nm.[7]Two variant of Optos imaging systems are available: Optos TX 200 and Optos California. The latter is able to capture Indocyanine green (ICG) angiography images as well. Superiority of Optos over other wide filed imaging systems have been previously documented as by Witmer et al, who documented the imaging span of Optos to be 151,362 pixels as compared to Heidelberg Spectralis to be 101,786 pixels. Also Optos was able to screen nasal and temporal periphery farther as compared to the latter.[8]The utility of UWF imaging and angiography has been documented in various retinal disorders.

DIABETIC RETINOPATHY:

Standard and even montage fundus photographsmay miss lesions in mid and far periphery of the retina[9] where significant non-perfusion or neovascular lesions may be present. UWF has been documented to screen 3.2 times more retinal area on fundus photograph and 3.9 times more retinal area on angiography as compared to standard 7 filed photographs.[10] UWF imaging thus better detects areas of peripheral non-perfusion and leakage, which may be associated with neovascularization, macular ischemia and macular oedema. [11,12] Oliver and Schwartz showed direct association between peripheral non-perfusion and peripheral vascular leakage on UWF-FFA with neovascularization and macular ischemia.[11]

An upcoming approach in the management of diabetic retinopathy and other vascular disorders is that instead of panretinal photocoagulation, laser photocoagulation is applied onlyto the non-perfused areas. Reddy et al showed regression of neovascularization with targeted photocoagulation to ischemic

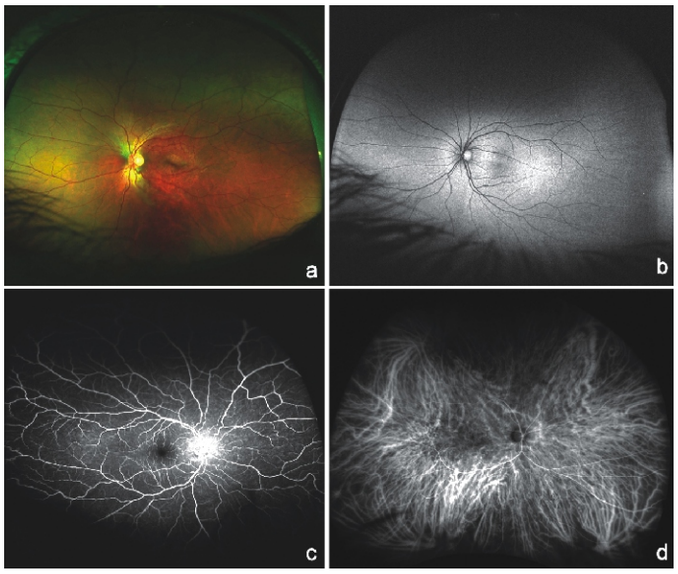

Fig.1: Normal UWF pseudo-colour(a), autofluorescence(b), fluorescein(c) and ICG angiogram (d)

areas on UWF-FFA in 2 cases of diabetic retinopathy.[12]The peripheral non-perfused areas can be well picked up by UWF imaging and this approach will prevent macular oedema, field loss and other complications associated with panretinal photocoagulation (PRP).

Case example 1 (Figure2):

A 50-year-old diabetic male presented with proliferative diabetic retinopathy and absolute neovascular glaucoma (NVG) in the left eye. The patient had undergone PRP as well as anterior retinal cryotherapy (the cryo spots are visible in superior periphery). In spite of all measures, the eye progressed to absolute stages of NVG. UWF-FFA shows large areas of capillary non-perfusion anterior to the previous laser scars.

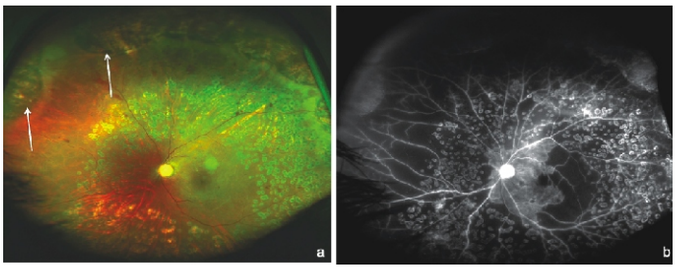

Fig.2: (a) UWF images shows lasered PDR along with cryotherapy scars in periphery (arrows,a). (b) UWF-FFA shows large non-perfusion area between the laser and cryotherapy scars. (b).

Case example 2 (Figure 3):

A 46 years old female with diabetic retinopathy underwent conventional FFA that failed to reveal any neovascularization (a). Steered images on UWF-FFA revealed neovascularization elsewhere (NVE) in the inferior periphery that may be an indication of early PRP (arrow, b).

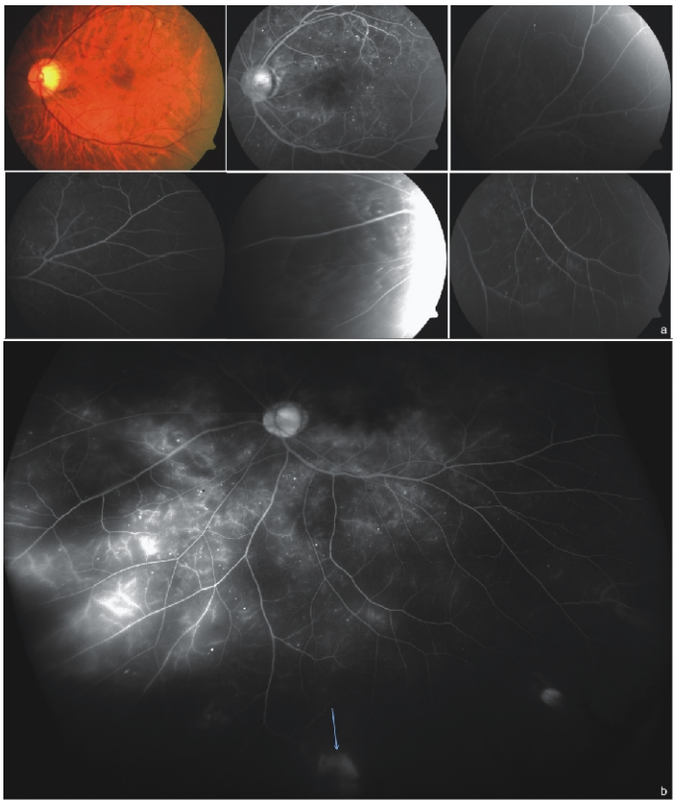

Fig.3: Retinopathy appears to be non proliferative when seen on conventional imagings (a) but turns out to be proliferative type as NVE is picked upon UWF FFA (b).

Case example 3 (Figure 4):

Traditionally diabetic retinopathy is considered to be a disorder of posterior pole. UWF-FFA has demonstrated that the disease may be more peripheral in some cases while it could be localized to posterior pole in others.

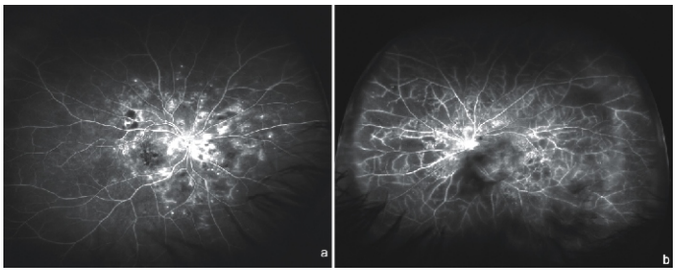

Fig.4: Central (a) and peripheral (panretinal, b) involvement in diabetic retinopathy

VASCULAR OCCLUSIONS:

For vascular occlusions as well, neovascular complications and macular oedema have been correlated with areas of peripheral non-perfusion, which are better picked up by UWF imaging. UWFFA-guided targeted retinal photocoagulation has been shown to reduce the number of injections of Ranibizumab in patients having BRVO with macular oedema, while maintaining similar benefits in the improvement of BCVA, central subfoveal thickness without deleterious effect on the visual field, and contrast sensitivity.[13]

Case example 1 (Figure 5):

A 56-year-old male was referred with diagnosis of moderate NPDR. UWF-FFA shows the obvious presence of inferior hemi-retinal vein coclusion in addition to NPDR.

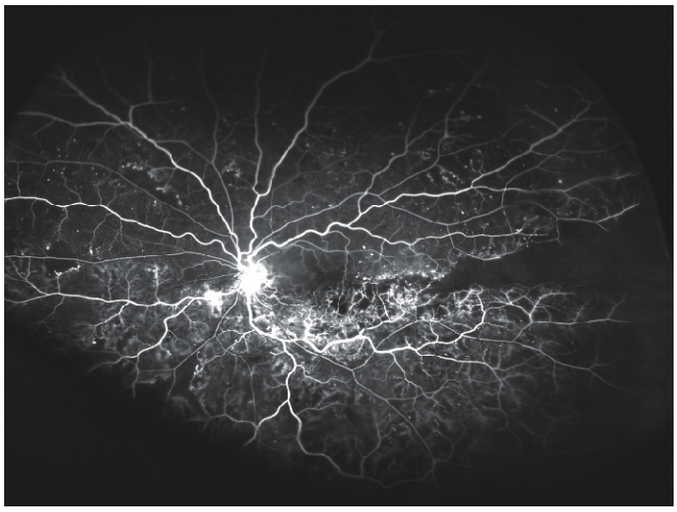

Fig.5: UWF-FFA of left eye shows inferior hemi-retinal vein occlusion in addition to NPDR.

Case example 2 (Figure 6):

The amount of non-perfusion detected on UWF-FFA is much higher as compared to conventional imaging. In this case of BRVO, approximately 60 disc diameters (DD) of ischemia is there. Hence classic definitions of 5 disc diameters in a case of BRVO (Branch vein occlusion study) may not be valid in todays scenrio. Presently 60 DDs of non-perfusion in the setting of CRVO is considered high risk for neovascularisation. There are no set guidelines for BRVO however.

RETINAL VASCULITIS:

UWF-FFA is useful in the documentation of various retinal vasculitis. Kumar et al in their study showed that UWF angiography was useful in the better documentation, exact quantification, and location of CNP areas and better determination of disease activity. [14]Sheemar et al in their

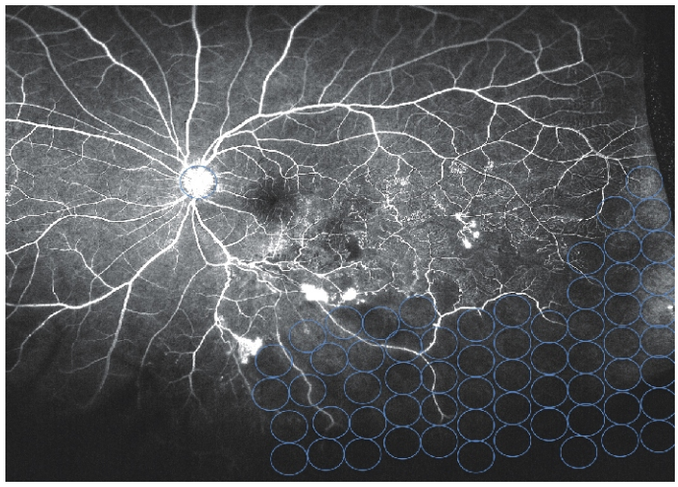

Fig.6: Measurement of non-perfusion in terms of disc diameters in BRVO. Approximately 60 DDs of non-perfusion is there.

study of 200 eyes with retinal vasculitis concluded that UWF imaging was useful in detecting retinal vasculitis, which was otherwise obscure to clinical examination and assessing risk factors for retinal neovascularization.[15]. It has been found useful in other vasculitis such as Behcet's disease as well. [16]

Case example 1 (Figure 7):

A patient with Eales disease underwent photocoagulation, however neovascularization at optic disc persisted. UWF-FFA revealed large non-perfusion area peripheral to the existing laser marks (a). Peripheral laser augmentation resulted in prompt resolution of neovascularization (b).

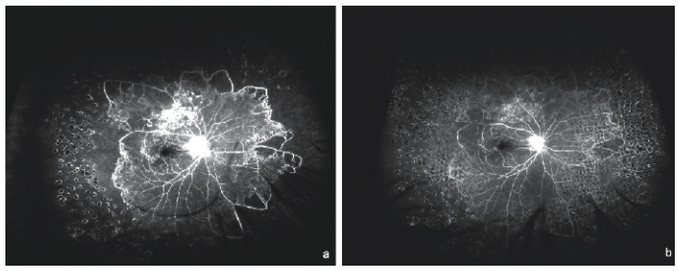

Fig.7: UWF FFA of patient with Eales disease before and after completion of laser photocoagulation.

Case example 2 (Figure 8):

It can provide exact extent of activity as well as non-perfusion.

OTHER VASCULAR DISORDERS:

In retinal disorders where poor patient cooperation create barriers for successful conventional imaging, UWF imaging serves as a boon andis useful in the management of congenital vascular disorders like Coat's disease and Familial exudative

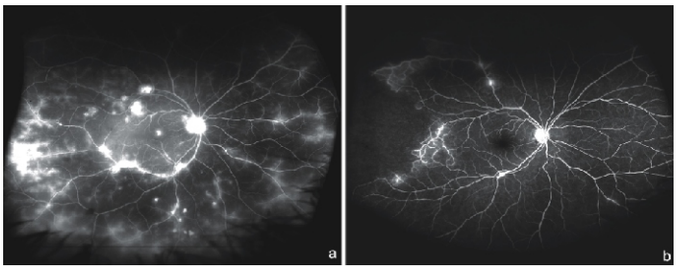

Fig.8: UWF-FFA depicting active vasculitis (a) and healed vasculitis with NVE (b).

vitreoretinopathy (FEVR).It is also useful in the management of retinal vascular tumours like retinal hemangioblastomas. Tsui et al studied the role of UWF-FFA in childrenfor diseases like uveitis, coat's disease, retinopathy of prematurity, toxoplasmosis and concluded that the macula and periphery were adequately imaged, obtaining important information for documentation, diagnosis, and management.[17]Kumar et al have shown that peripheral non-perfusion area could be picked up in the periphery of eyes with adult onset Coats disease. [18]Kang et al in their study of paediatric patients with Coats disease and FEVR concluded that UWF imaging can be used successfully as an outpatient procedure without the necessity of examination under anaesthesia and can aid the physician in the documentation and evaluation of peripheral retinal pathology. [19]

Case example 1 (Figure 9):

UWF colour imaging (a) and FFA in the setting of FEVR showing temporal multiple NVEs.

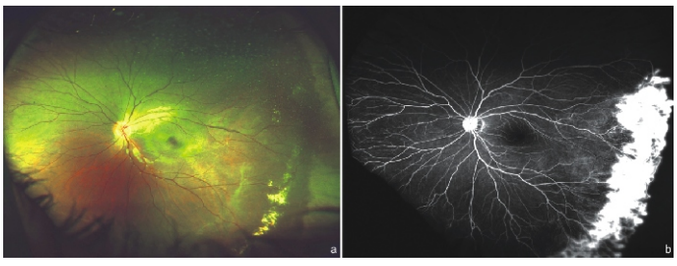

Fig.9: UWF photograph shows temporal drag, exudation and avascular retina in FEVR (a). FFA shows multiple temporal NVEs (b).

Case example 2 (Figure 10):

UWF FFA in Coats disease showing multiple bulb like aneurysms, non-perfusion areas and vascular abnormalities.

Case example 3 (Figure 11):

UWF FFA is able to pick small hemangiblastomas in the periphery, which may be missed on conventional imaging. It is imperative to find these early and treat as it is very difficult to treat the lesions once they enlarge in size.

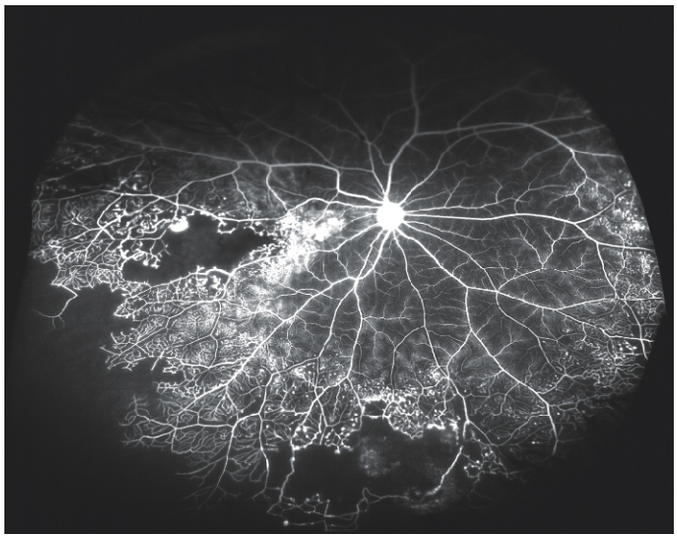

Fig.10: UWF FFA shows features typical of Coats disease in addition to non-perfusion areas.

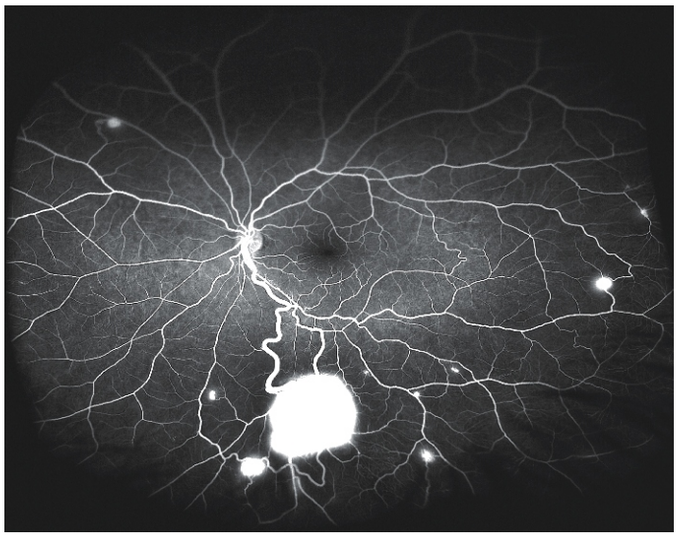

Fig.11: Multiple retinal hemangioblastomas in a case with VHL disease.

UVEITIS:

UWF imaging is also helpful in cases of intermediate and posterior uveitis where it can be used to document disease extent upto far periphery of retina, disease progression and response to medications. Tsui et al showed role of UWF imaging in documenting periphlebitis and macular edema in patients of sarcoidosis and pars planitis. They described vascular staining patterns in 6 of such eyes.[20] Kaines et al documented role of UWFA in revealing lesions in CMV retinitis, lupus vasculitis, idiopathic intermediate uveitis. Ultra wide field angiography was found to have advantages compared to traditional angiography. It allowed clear identification of peripheral signs and accurate documentation of disease progression.[21]Wider field of

imaging can explore newer areas which might need our attention and accordingly modify our plan of action. 40 percent more area of CMV retinitis lesions have been documented to be visualized by UWF as compared to standard imaging.[22]

Case example 1 (Figure 12):

UWF imaging of CMV retinitis shows progression of disease over time in the setting of acute lymphoblastic leukaemia.

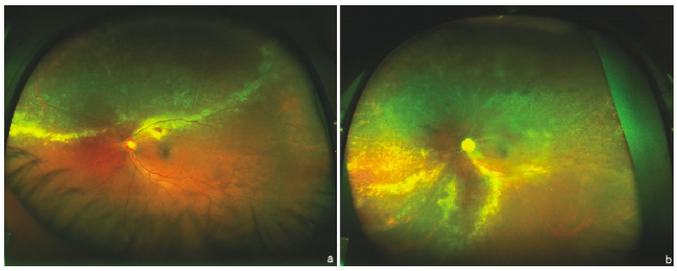

Fig.12: Progression of CMV retinitis in a patient with leukemia.

Case example 2 (Figure 13):

UWF-FFA can be used to monitor exact extent of disease in posterior uveitis (Multifocal choroditis in this case).

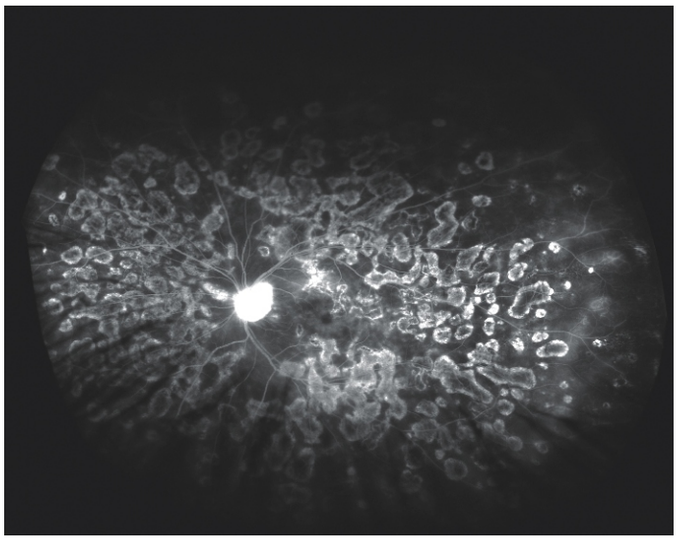

Fig.13: Extent of multifocal choroditis as seen on UWF-FFA.

RETINAL DETACHMENT AND ALLIED DISORDERS:

Anderson et al published a case report highlighting the utility of Optos in documenting retinal detachment, monitoring and follow up of the case after surgical treatment.[23]UWF imaging proves helpful indocumenting the peripherallesions predisposing to retinal detachmentsas well. Intraretinal macrocysts in case of old retinal detachment [24], and bilateral idiopathic retinal dialysis[25] have been documented on UWF imaging.

Case example 1 (Figure 14):

UWF imaging is useful in documenting peripheral lesions such as retinal macrocyst (a) and retinal dialysis (9).

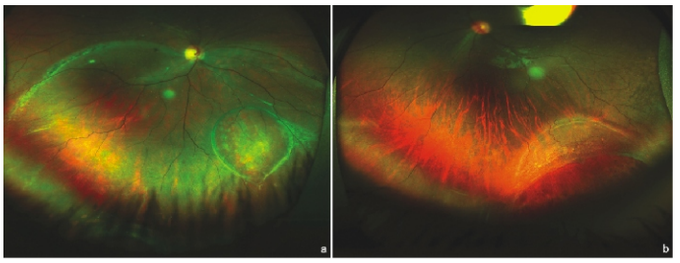

Fig.14: Intraretinal macrocyst in retinal detachment (a) and infero-temporal retinal dialysis (b).

Case example 2 (Figure 15):

Retinal detachment due to superior giant retinal tear (a). Post-operative picture shows attached retina with gas bubble in situ (b).

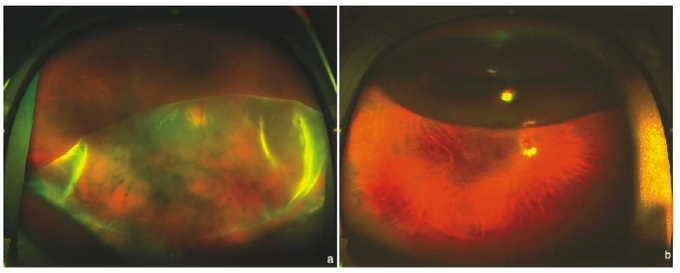

Fig.15: Retinal detachment with giant retinal before (a) and after vitrectomy with gas (b).

RETINAL AND CHOROIDAL DYSTROPHIES:

UWF imaging is very useful in the setting of retinal and choroidal dystrophies. Poor central vision, nystagmus and poor fixation make conventional imaging difficult in these situations. UWF imaging has documented widespread retinochoroidal abnormalities in cases of pigmented para-venous retinochoroidal atrophy- a disease considered by manyto be an early form of retinitis pigmentosa.[26]UWF imaging holds its grounds by providing better documentation of progression especially in disorders of choroid which start from periphery.[27]In fact UWF imaging has shown its role even in dystrophies which have traditionally been considered to involve macula only. Kumar et al showed that extent of background hyperfluorescence in Stargardt disease corresponds to the outer most boundaries of retinal flecks. [28] UWF can provide good

quality images even in conditions like Leber's congenital amaurosis.[29]

Case example 1 (Figure 16):

UWF pseudo colour and autofluorescence images of pigmented paravenous retinochoroidal dystrophy.

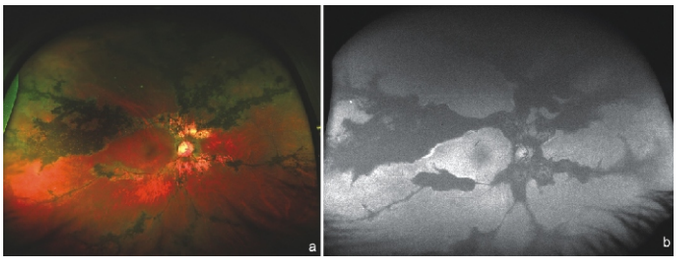

Fig.16: UWF pseudo-colour and autofluorescence of pigmented paravenous retinochoroidal atrophy.

Case example 2 (Figure 17):

UWF-FFA of choroideremia (a) and gyrate dystrophy of choroid (b)

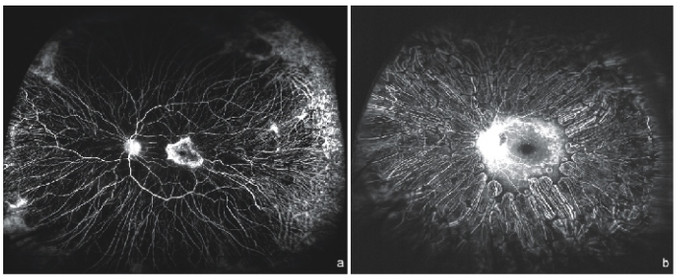

Fig.17: UWF FFA of choroideremia (a) and gyrate atrophy (b).

Case example 3 (Figure 18):

UWF autofluorescence of Stargardt disease

There are certain limitations as well to the use of this machine. Firstly it gives a pseudo-colour image instead of a true colour one because of absence of blue wavelength in scanning lasers. Secondly it still doesn't provide ora to ora coverage, whichwould be desirable.Optos lags behind Heidelberg Spectralis in imaging of superior and inferior retina. Eyelashes and other structures anterior to equator like natural lens, IOL, anterior chamber pigmentation frequently caught in the image produce artefacts. An effort to project a 3 dimensional retina onto a 2 dimensional image screen leads to unavoidable peripheral distortions and poor correlations of the measurement in image to actual dimensions inside the eye.Last but not the least is the cost factor and availability of equipment.

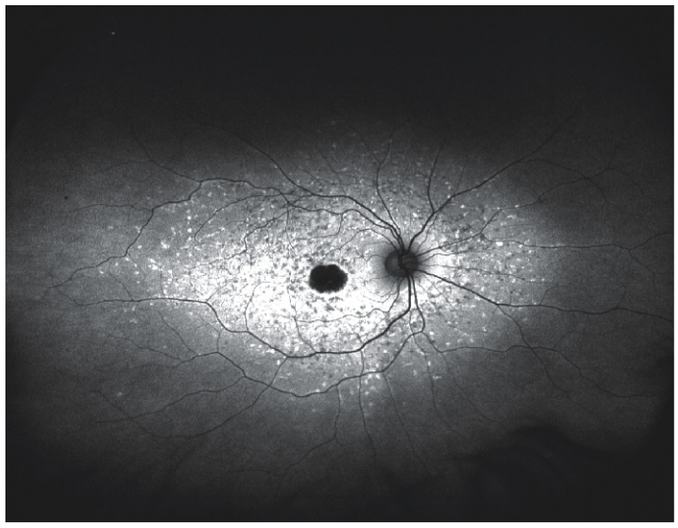

Fig.18: UWF autofluorescence of Stargardt disease.

To conclude, Optos imagingis fast, non-contact method to record high-resolution images of up to 200 degrees of retina in a single click. It is useful teaching tool, helpful in documenting and monitoring of various retinochoroidal pathologies and has provided newer insight into various retinal disorders.

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LEGALESE

Avastin Alert: The Untold Story

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"There is no greater agony than bearing an untold story within you"
wrote Maya Angelou. On 21st January 2016, Directorate General of Health Services, Central Drugs Standard Control Organization, India's federal drug regulator,"banned " Intravitreal use of Avastin. It was a bolt from the blue for Indian ophthalmologistsand our patients. The saga that unfolded in next 18 days shows the impact of such decisions and the vision and collective grit of our leaders of AIOS, VRSI, Chief Rajendra Prasad Centre for Ophthalmic Sciences, New Delhi and numerous members, who came forward voluntarily to help. Never ever before the ban on a drugblack listed by Drugs Controller General of India (DCGI) had been revoked, that too,in a matter of few weeks. Team Ophthalmology, India achieved this amazing feat against all odds. This is the narrativeof Avastin Saga of which I was part of the coreteam,and am fortunate for an opportunity to share the story with you.

On 21st January 2016, DCGI issued an alert, which read as follows:

"Reports had appeared in media that the drug Avastin (Bevacizumab injection)100mg/4ml,400mg/16ml vials manufactured and marketed by M/S Roche Product (India) Ltd., have been used in the treatment of eye ailments through intra-vitreal route and this has lead to loss of vision in certain patients at C H Nagri Eye Hospital, Ahmedabad, Gujrat. The drug is not approved in the country for Intravitreal use for ophthalmology purposes.

In view to safe guard the public health and as a precautionary measure, all concerned are hereby directed that the drug is not used in ophthalmology and the State/UT Regulatory Authorities may alert their inspectorate staff to monitor the movement of the said drug and its use in ophthalmology"

The news of the alert spread rapidly like wildfire throughout the country, thanks to an active social media. Everyone, all over the country, wanted to know the next steps. Unfortunately, no one had a clue. There was chaos. Patient's appointments were being cancelled. Many patients who would travel from far and wide to get their injections were returning disappointed and with a spectre of worsening vision. Avastin injection, in our country, was being charged differentially in various places. Someinstitutions were injecting Avastin virtually free of cost, thanks to their funding, while others were charging an affordable fee. Ranibizumab (Lucentis), the FDA approved Intravitreal antiVEGF injection, and the alternative to Avastin, was too expensive for this group of patients. With the ban, social media was abuzz with numerous questions and opinions but very few had clarity of the immediate and next steps. The chaos was worsening with each passing day.

Prior to 21stJanuary, 3000 Intravitreal Avastin injections(a rough

estimate) were being given in India daily. Physicians tend to be altruistic; doing good is their second nature. Hence, many wanted to overlook the alert and continue injecting Avastin, despite knowing that it was fraught with danger. No one could protect them in the event of an adverse reaction to Avastin. And it happened again...! On 28th January, unfortunately, five additional cases surfaced at the Institute of Medical Science, Banaras Hindu University, following Intravitreal injection of the same batch of Avastin. Tests on the vial revealed the presence of gram-negative bacilli. Media was waiting for such an opportunity! Doctors were being blamed for not heeding the alert.No one cared of our altruism and why should they this act amounted to hara-kiri.

Through this conundrum, leaders of AIOS, VRSI and many of its members started meeting to find ways to fight the alert. I remember, on 22nd January, I got a call from our President, Dr. Debashish Bhattacharya to join the core group and fight the AvastinBan. For me, to be able to do something for the country that would benefit lacs was a very powerful call and I believe it became the driving force of the group. On 24th January, Dr. Debashish Bhattacharya, formally constituted a steering committee consisting of Dr. D Ramamurthy (President Elect) Dr. Lalit Verma (Chairman, Scientific Committee, AIOS), Dr. Ajit Babu Majii (President, VRSI), Dr. Vishali Gupta (Chair Scientific Committee, VRSI), Dr. Mahesh Shanmugham, Dr. Ajay Aurora (Member Scientific Committee& Treasurer VRSI) and Ex Officio members included the President AIOS, Honorary General Secretary AIOS and Honorary Treasurer, AIOS. I was given the arduous task of coming up with a document on Avastin that could convince the Health Minister and the corridors of power in the Ministry of Health, that it was safe to continue using Avastin and it was the need of the hour for Indian masses. Simultaneously we started the process of getting a date with the DCGI for a meeting with the (AIOS-VRSI) Avastin Ban Committee (ABC) to present our story. Dr. Lalit Verma was able to get us an appointment with the Secretary, Health and the meeting was scheduled on 29th January. The Avastin document was to be ready by then and submitted to Shri J P Nadda, the then Health Minister,Government of India. I had just four days and nights to come up with the Avastin document. Now, when I look back, I wonder how we achieved it!

Whatsapp helped us a lot. Multiple groups were created and ideas exchanged. Innumerable people helped in this onerous task and it will be difficult to name all. However, I must mention the help provided by Dr.Abhishek Kothari, Dr.Hemant Trehan, Dr.Queresh Maskati and Dr. Kim and all members of the ABC. We poured through tons of data and relevant papers. On the night of 26th January I managed to connect with the office of Dr. Geoffrey G Emerson who was the then chair and advisor to FDA on behalf of ASRS (American Society of Retina Specialist). Considering the cause, he agreed to talk to me in the middle of his OPD. I was able to convince him to help us. Dr. Geoff, who was also Chair ASRS to the Research & Safety in Therapeutics Committee, was appalled at the decision by the DCGI and agreed to write to them and help us with the status of Bevacizumab with the FDA. I reproduce part of my communication with him:

RE: Test: Avastin Ban in India
Ajay Aurora
Wed 1/27/2016 11:37 PM

To: *Geoff Emerson <geoffrey.g.emerson@gmail.com>*
2 attachments (207 KB)
Strategy Avastin Ban. docx; Ban on use of AvastinDGCI.jpg;

Dear Dr. Geoffrey,

It was indeed my pleasure to talk to you, and thank you very much for your time in the middle of a busy clinic.

Attached please find the ban that has been put on ophthalmic use of Avastin in India by the Drug Controller General of India (DCGI). This is fallout due to the occurrence of Endophthalmitis in 15 eyes in Ahmedabad, a city located in Western part of India. We believe, it was due to the use of counterfeit Avastin. The event is being investigated.

Everyday, more than 4000 Avastin Injections are given in India. This has stopped! Our patients, particularly the poor, are suffering.

All India Ophthalmological Society (AIOS) and the VRSI (Vitreo Retinal Society of India) has made a committee to look into this and formulate strategy and meet appropriate people in the Ministry for needful action. As a member of this committee, I am approaching you for guidance. I have attached my plan. I have few key questions at present:

1. *Who allowed ophthalmologists in the US to use Avastin as an off label drug Intravitrealy? (Can you share the document)?*

2. *The Drug Insert of Avastin worldwide mentions that it is not approved for Intravitreal use. And, if used can lead to loss of sight. With these words in the drug insert how do physicians in the US justify off label use of Avastin in the law courts?*

3. *How do you ensure in the US that the Avastin that is being aliquoted by the compounding pharmacy is not counterfeit? Other than the packaging details, do you use the Kessler Coding or other methods to confirm the authenticity of Avastin.*

4. *We in India do not have the concept of compounding pharmacy for Avastin. I would need guidance from you, on this regard.*

Looking forwards to an early reply.
Best Regards

Ajay

Dr. Ajay Aurora MS (Gold Medal),
FRF Fellow Retina, Vitreous and Uveitis (UC, SanDiego)
Tel: +91 9810253256
Email auroraajay@hotmail.com; auroraeye@gmail.com

Dr. Geoff replied:

Fri, Jan 29, 2016 at 9:40 AM

Geoff Emerson *<geoffrey.g.emerson@gmail.com>*
To: Ajay Aurora <auroraeye@gmail.com>

Hello Dr. Ajay,

Thank you for your hard work on this noble effort.

In the US, it is permissible to use an FDA-approved medication for a non-FDA-approved indication (even when there are FDA-approved alternatives).

For example, we use Kenalog for cystoid macular edema or for diabetic macular edema, even though those conditions are not listed as FDA-approved indications. As another example, prednisone is used in temporal arteritis, sarcoidosis, and other non-FDA-approved indications. Off-label use of medications is permitted because getting FDA-approval for a specific condition is a lengthy, expensive process and many times a manufacturer will decide it is not worth their while. However, the manufacturer cannot advertise a product for an off-label use. I think Allergan got in trouble for advertising Botox in the treatment of wrinkles, another off-label use.

The FDA has not yet finalized its guidance on compounding or repackaging of biologics. However, there is draft guidance from 2015 (see link below) and in the draft guidance the FDA specifically gives Avastin as an example of a medication that can be repackaged into multiple syringes even though the label says "Single use vial ...discard unused portion" (see footnote 15). Also, line 111 - 114 of the document explains that repackaging is sometimes done for pediatric or ophthalmic use because the doses are smaller than the manufactured quantity.
http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm434176.pdf

Sincerely,
Geoff

Subsequently he sent us a letter (Annexure1) supporting the use of Avastin and how it was being used in the US. This was submitted with the Avastin document both to Shri J P Nadaji and to the DCGI.

On the request of Dr. Raja Narayan, LV Prasad Eye Institute, we also had Dr. Michael Stewart write on the matter to the Ministry of Health (Annexure 2)

During my pursuit to collect more evidence to support our cause, I accidentally got connected to one of my seniors from JIPMER, Pondicherry, who was the pharmacologist from India involved in preparing the WHO essential medicines list. And what came out of this discussion was revealing. Ranibizumab (Lucentis) was not included in the WHO Essentials medicine list, Bevacizumab (Avastin) was!This was on recommendation of the International Council of Ophthalmology. This too became an important part of the Avastin document that eventually influenced DCGI and the Health Ministry.

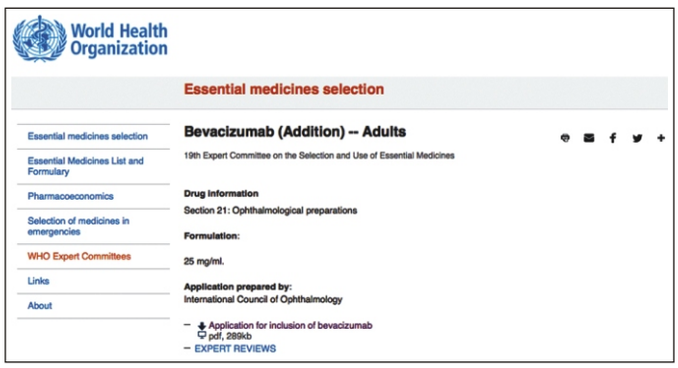

Fig1: From 19th Expert Committee WHO on the Selection and use of Essential Medicines (April 2015)[1]

At this time we were also able to procure the press release revealing the Italian Competition Authority fining Roche and Novartis over 180 million Euros for cartelizing the sales of two major ophthalmic drugs, Avastin and Lucentis. This coming from the drug authority was compelling evidence supporting our cause. In addition, the Avastin document submitted included all the relevant studies on Avastin and Lucentis over the years including the Cochrane review of the safety of Avastin. The document, when submitted finally was of 243 pages! All this, with multiple copies, had been prepared in four days and nights!!

At the meeting with the Secretary Health, Govt. of India we were able to impress the need for an early meeting with the DCGI and an intervention by the Health Minister Shri J. P. Nadda. We were all extremely impressed with the quick response and grasp of Shri J.P. Nadajiwhen he wrote on the Avastin document " ***Is Avastin causing blindness or there is more blindness because of its absence?"*** With his intervention, and help by Prof. Atul

Kumar (Chief RP CENTRE for Ophthalmic Sciences) and Dr. Lalit Verma, we finally managed to fix a date of meeting with the DCGI on 8thFebruary 2019 (exactly 18 days after the ban!)

The Expert Committee meeting was held on 8thFeb under the Chairmanship of Mr. V Somani, Joint DCGI at the FDA bhawan. This meeting was attended by the following:

1. Dr. V Somani
2. Panel of Experts from all over India including Prof. Atul Kumar, Chief RPC and Advisor to the Govt of India.
3. Representatives of the All India Ophthalmological Society (AIOS) and the Vitreo Retinal Society of India (VRSI)
4. Representatives of ROCHE. India.

This meeting had presentations from Prof. Atul Kumar, Dr. Ajay Aurora and ROCHE representative. It lasted over 5 hours with healthy discussions. During the meeting we requested ROCHE to reintroduce the Kezzler code that was available with all Avastin vials till 2013 and helps in tracking and tracing the vial in the supply chain.

Fig 2 Avastin Vial with it's carton as available in the Indian market in 2015-16

The Kezzler code is a unique 16 digit alphanumeric code developed by the Norwegian company, and printed on each vial of the drug. The validity and genuineness of the drug can be confirmed from the manufacturer directly by messaging the code using the short message service (SMS). This was introduced in India in 2008 and remained effective for all vials of Avastin supplied in India till 2013. India did not have any problem with Avastinduring this period. In 2011, there were blinding episodes of endophtha lmit is following Intravitreal injection of compounded Avastin in USA. This was traced to a spurious vial of Avastin that had originated outside USA. Interestingly, Kezzler code was not in use in the US. The group also looked at the non-Kezzler options being followed by ROCHE to prevent spurious Avastin entering the Indian market in 2016; but it appeared that the methods were not as foolproof as the Kezzler code. Hence we requested, ROCHE to re-introduce the Kezzler code. We also discussed the printed warning on the vial regarding availability of the vial on the prescription of oncologists to be removed.

Fig 3 Spurious vials of Avastin

At the end of the meeting it was agreed that after further internal discussions within the ministry of health, DCGI would lift the alert on Avastin. ROCHE would look at reintroducing the Kezzler code and ensure a secure supply chain. Also ROCHE would provide a list of its approved distributors for Avastin in India. AIOS-VRSI will come up with Avastin usage guidelines.

Immediately after the expert committee meeting, everyone thought that it will be days within which the ban would be lifted. It took some time and a lot of communication within the corridors of power before DCGI finally issued the reversal to the alert.

On 11thMarch2016, DCGI officially communicated the lifting of Ban on Avastin. An unprecedented result had been achieved. It was such a relief to all the ophthalmologists in India and to all our patients. We could now start using Avastin, legally, once gain as an off-label drug.

Though the Avastin alert had been lifted, we realized that to make safe Avastin available to all, a lot more needed to be done. AIOS-VRSI and RP Centre for Ophthalmic Sciences under the guidance of Prof. Atul Kumar came up with Avastin Injection guidelines[2, 3] for the country that was circulated to all ophthalmologists in India. The AIOS VRSI core group made a consent form for Intravitreal injection of antiVEGF with Dr. Mahesh Shanmugham and this was circulated amongst all AIOS members. The official list of ROCHE authorized Avastin distributors in India were also shared with AIOS members.

President AIOS and the leaders of AIOS and VRSI communicated with all ophthalmologists in India regarding the status of off-label use of Avastin and its use after the reversal of DCGI alert notice. I reproduce a letter written by Dr. D Ramamurthy, the then AIOS President to all members of the AIOS, summing up the then situation and the obstacles in front of us.

Dear Fellow member,

Though DCGI reversed the ban on the intravitreal use of AVASTIN by a notification dated 11/3/2016, many of the authorised distributors of ROCHE in different parts of the country were refusing to sell the drug to ophthalmologists claiming they had not received instructions to that effect from the parent company. We had constantly been in touch with them in various ways & initially managed to get the list of authorised distributors.

Yesterday by e-mail & by a telephone call, it was confirmed that ROCHE will instruct its distributors to consider selling it to ophthalmologists across the country. Still there maybe some issues in procuring this drug due to restrictions placed by the state FDA. In such a case the DCGI notification revoking the ban maybe shown to the local regulators.

Please remember that use of AVASTIN in ophthalmology continues to be OFF LABEL & it has to be used with extreme caution & responsibility. Please go through each of the following links carefully.

- ***DCGI notification revoking the ban on use of AVASTIN***
- MOST RECENT EXCHANGE OF E-MAILS WITH ROCHE MEDICAL DIRECTOR
- ***List of ROCHE authoriseddistributors.Always procure the drug from them***
- ***Caveats & caution issued by ROCHE in the use of AVASTIN in ophthalmology***
- ***AIOS - VRSI guidelines for use of AVASTIN***
- ***AIOS - VRSI consent form to be taken before the injection***

This was possible only because of the AIOS - VRSI core team on AVASTIN :
Dr.DEBASHISH, Dr.VISHALI GUPTA, Dr.MAHESH SHANMUGAM, Dr.QURESH MASKATI, Dr.LALIT VERMA, Dr.AJAY AURORA & Dr.AJIT BABU.
The support & guidance offered by Dr.ATUL KUMAR, Dr.ROHIT SAXENA, Dr.KIM & Dr.SANGWAN was immense.

I sincerely hope this issue will resolve now. We will closely follow up to enforce the KEZZLER code.

Best regards,
Dr.D.Ramamurthy
President - All India Ophthalmological Society
Email : president@aios.org

The links mentioned in the above letter of Dr. Ramamurthy may no longer be active, but the information is available. The events that unfolded till reversal of the alert demonstrate the power of Indian ophthalmologists, when united!

A lot has happened since 2016 on many fronts. ROCHE has not brought back the Kezzler code. A biosimilar of Lucentis, Razumab has been launched in India and Lucentis is now available as Accentrix in India at a lower cost! There have been episodes of reaction to Intravitreal injection of Razumab, but it has also shown its efficacy and its usage has increased as the confidence grows over its safety.T hough a lot more needs to be done to increase its acceptance. A biosimilar of Avastin has also been launched in India. Aravind Eye Hospital and RP Centre for Ophthalmic Sciences, package Avastin in smaller aliquots for internal use. This is not available for rest of the country. India does not have the concept of compounding pharmacies like the west. Avastin still remains a popular antiVEGF for Intravitreal injections in most parts of the world and is safely available to them through these compounding pharmacies. We certainly need safe single use antiVEGF in India and compounded Avastin, if available can fill this gap. We have to keep pursuing doggedly the dream of safe Avastin that is legal. The cause is noble, the goal clear and achievable, but a lot has to be done collectively. If and when this happens, it will be a dream cometrue!!

Acknowledgements: *I would like to thank Prof. Atul Kumar, Dr. Debashish Bhattacharya, Dr. D Ramamurthy, Dr. Lalit Verma and Dr. Anand Rajendran for their guidance in preparing this manuscript. I would also like to thank Dr. Geoffrey G. Emerson and Dr. Michael W. Stewart, Dr. Ajit Babu, Dr. Vishali Gupta,Dr. Mahesh Shanmugham, Dr. A Giridhar, all the members of the Avastin Ban Committee and everyone who pitched in to make the Avastin Ban reversal a reality.*

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Annexure - 1

RETINA CENTER

Department of Health
Government of India

January 30, 2016

To Whom It May Concern:

I am sorry to hear of the recent decision in India to prohibit the use of bevacizumab (Avastin) for intravitreal injection. Although bevacizumab was originally FDA-approved in the treatment of colon cancer, it has since become a common treatment for several serious ocular conditions, including macular degeneration, diabetic retinopathy, retinal vein occlusion, neovascular glaucoma, and others. According to the American Society of Retina Specialists (ASRS) Preferences and Trends survey of 2015, most US retina specialists use bevacizumab as their first-line treatment in these conditions, rather than commercially available alternatives such as ranibizimab (Lucentis) or aflibercept (Eylea). The decision to use bevacizumab is commonly based on cost (as bevacizumab is significantly less expensive than the others) and also based on the proved track record of bevacizumab, which has been in use for longer than the others.

The recent series of endophthalmitis in 16 patients in India due to a contaminated or counterfeit vial of bevacizumab is disheartening and reminds us that patient safety is always paramount. In the US, we have also had outbreaks of endophthalmitis due to contaminated bevacizumab. These unfortunate instances prompted us to re-examine the safety of bevacizumab and to focus on keeping the medication sterile from beginning to end, with a secure supply chain, careful repackaging into sterile syringes for individual use, and required sterility testing. VanderBeek and colleagues reviewed 530,382 intravitreal injections administered between 2005 and 2012, using the medical claims data from a national US health insurer.[1] They report a post-injection endophthalmitis rate of 0.017% for patients who received bevacizumabintravitreal injection, as compared to 0.025% for patients who received ranibizumab, demonstrating a high degree of safety for both the medications and no increased risk of infection forbevacizumab. A similar report by Hsu and colleagues reviewed 503,890 intravitreal injections from across the US and similarly found no significant risk of infection after bevacizumab as compared to ranibizumab or aflibercept.[2] These reports concluded that while contamination of bevacizumab can rarely occur, the concern for increased risk of endophthalmitis is likely unfounded.

It is also important to note that patients who have macular degeneration, diabetic retinopathy, etc., loose vision progressively and permanently if they go without treatment. These patients desperately need treatment that is both safe and available, and I thank you for your efforts to reinstate bevacizumab for intravitreal use, as it is a very important treatment option in the US, and India, and throughout the world.

Sincerely,

Geoffrey G. Emerson, M.D., PhD

[1]VanderBeek BL, et al.Association of compounded bevacizumab with postinjectionendopthalmitis.*JAMA Ophthalmology* (2015).
[2]Hsu J. Post-injection endophthalmitis rates and characteristics following intravitrealbevacizumab, ranibizumab, and aflibercept.*American Journal of Ophthalmology* (in press).

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RETINA CENTER of MINNESOTA

Annexure - 2

MAYO CLINIC

4500 San Pablo Road
Jacksonville, Florida 32224
904-953-2000
mayoclinic.org

Department of Health
Government of India

January 27, 2016

Dear Sirs:

I am writing regarding the recent decision to prohibit the intravitreal use of bevacizumab (Avastin®) for the treatment of eye diseases in India. I realize that this decision was not reached without considerable deliberation but, unfortunately this puts intraocular pharmacotherapy out of the reach of much of the populace and will increase the incidence of blindness due to diseases such as macular degeneration, diabetes mellitus and retinal vein occlusion.

Retinal physicians in India will now diagnose many patients that should receive regular intravitreal injections of an anti-vascular endothelial growth factor drug to stop blood vessel growth and decrease edema. Since Avastin is no longer available, they will have to recommend Lucentis® to their patients. Lucentis is an excellent drug but its cost will be excessive for much of the population and thousands of people will be unable to receive any treatment. Patients will develop irreversible blindness because of this.

I realize that the Health Ministry has questions and concerns about the off-label use of Avastin in ophthalmology. Multi-center, masked, randomized international trials have shown that it is as effective as Lucentis for patients with macular degeneration and most patients with diabetic retinopathy. Safety analyses show no differences in side effects between the two drugs.

Most physicians in the United States, including myself and my colleagues at Mayo Clinic, use Avastin as our first-line therapy. It has proven time and again to be effective and economical. Our treatment of patients would be significantly limited if we did not have access to Avastin.

I realize that there are unique problems with the use of Avastin, particularly the reliability of the supply chain. Counterfeit drug can be ineffective at best and dangerous at worst. But I hope that you are able to work closely with the Indian ophthalmology societies, a group of high-quality compounding pharmacies, and industry to secure the supply chain and allow for the rapid reinstatement of Avastin for ophthalmic use. A rapid and successful resolution of this problem with access to quality Avastin will be in the best interest of Indian patients.

Thank you for your attention. I would be happy to communicate further there are any questions.

Yours truly,

Michael W. Stewart, M.D.

Michael W. Stewart, MD
Professor and Chairman, Department of Ophthalmology
Mayo Clinic Florida

MAYO CLINIC 150 Years SERVING HUMANITY

INNOVATOR'S ISLE

Controlled Cannula Drainage: A novel way to drain supra-choroidal & subretinal fluid using 26-gauge intravenous catheter

Dr. Sangeet Mittal, M.S.
Thind Eye Hospital Ltd.
Jalandhar, Punjab, India

Dr. Abdulelah Al-Abdullah, M.D.
King Khaled Eye Specialist Hospital
Riyadh, Saudi Arabia

To present the applications of a novel technique of draining subretinal or supra-choroidal fluid using 26 Gauge (26G) intravenous catheter. 26G intravenous catheter is inserted 6-10 mm from limbus trans-conjunctivally. Once the cannula is in proper place, the metallic stylet is removed and Teflon cannula is left behind. The cannula is connected to the extrusion pump of vitrectomy machine.Drainage of fluid was observed in all cases with no complications using the active suction from vitrectomy machine. 26G intravenous catheter provides a simple and safe option for draining subretinal and supra-choroidal fluid in various situations in a controlled manner.

Introduction:

Choroidal detachments could be serous or haemorrhagic. While most choroidal effusions resolve spontaneously, surgical drainage may be necessary in some cases to restore normal anatomy and visual function. Drainage of choroidal detachment may be necessary while performing vitrectomy to create space and maximise results. We describe a novel technique to drain suprachoroidal and subretinal fluid using a 26 gauge (26G) intravenous catheter attached to the active extrusion pump of vitrectomy machine.

Methods:

Infusion cannula was placed either in the anterior chamber or 3.5 mm behind the limbus in the vitreous cavity through pars plana. The proper placement of infusion cannula is verified by direct observation of the tip in the vitreous cavity after scleral depression before starting the infusion. Endo-illumination port is made 3.5 mm posterior to limbus in supero-temporal or supero-nasal quadrant. The site of maximum elevation of the choroidal/retinal detachment is visualised and the quadrant for drainage is identified. 26G intravenous catheter consists of 2 parts a metallic stylet and a Teflon cannula (Fig1). 26G intravenous catheter is inserted trans conjunctival in the desired supra-choroidal or sub-retinal space 6-10 mm away from limbus with bevel down. A change of pressure is felt at the finger tips as soon as the cannula pierces the coats of the eye and enters the potential space. The tip of the catheter is visualised through the wide field fundus viewing system attached to the operating microscope. Once the correct placement of the catheter tip is ensured, the metallic stylet is removed leaving the plastic cannula behind (Fig 2A). The fluid is drained through the plastic cannula either through passive drainage or the cannula can be connected to the extrusion pump of the vitrectomy machine and the fluid can be drained in a more controlled manner using the active suction (Fig 2B). After the fluid is drained, the cannula is removed. As the incision is small, it is self-sealing and left without sutures. This technique was used for draining supra-choroidal fluid in cases of Rhegmatogenous Retinal Detachment associated with Choroidal Detachment (11 eyes), Post traumatic supra-choroidal haemorrhage (1 eye), Post Cataract surgery supra-choroidal haemorrhage (1 eye), Post trabeculectomy Choroidal Detachment (2 eyes). This method was also used to drain subretinal fluid in bullous Rhegmatogenous Retinal Detachment (8 eyes), bullous Combined Retinal Detachment (2 eyes), Uveal effusion syndrome (1 eye) and Coats disease (1 eye). In cases of supra-choroidal haemorrhage, surgery was delayed for 20 days to allow liquefaction of blood clots.

Discussion:

Controlled Cannula Drainage is a simple technique that offers many advantages over the traditional methods.

1. In this technique, a blunt, malleable Teflon cannula is used to drain supra-choroidal/subretinal fluid. The cannula

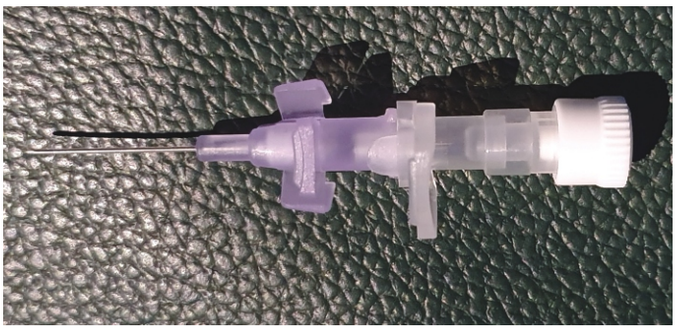

Fig 1: 26G Intravenous Catheter

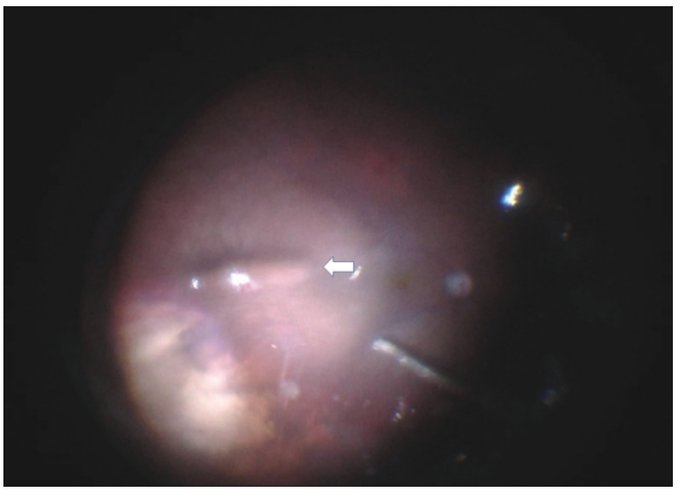

Fig 3: Intra-operative photograph of 26G Cannula tip reaching up to macula (white arrow)

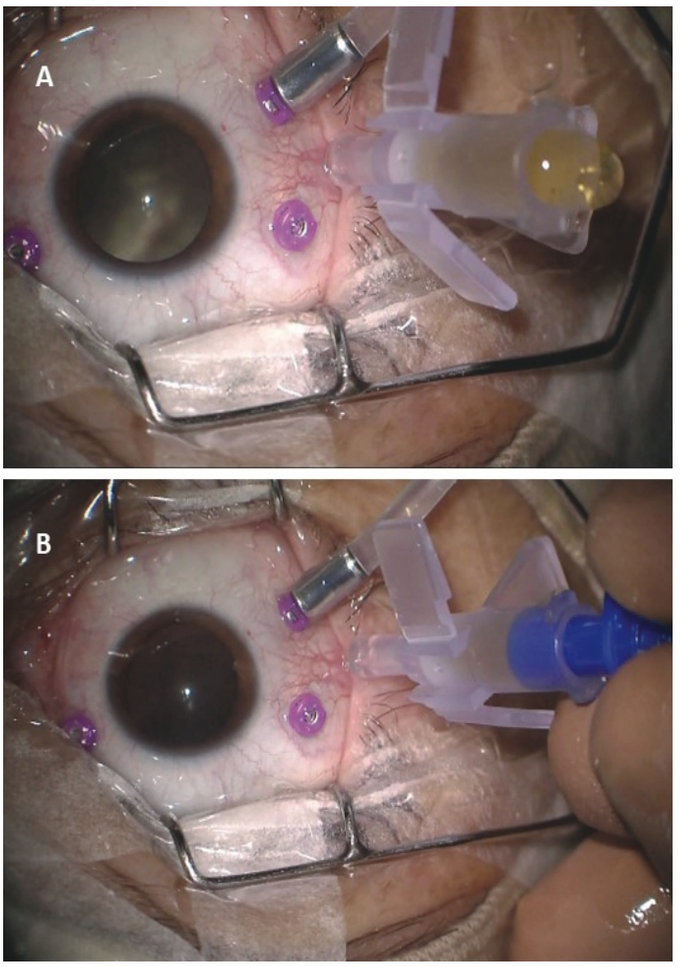

Fig 2: Intra-operative photographs of 26G Cannula in place (Fig 2A) & 26G cannula connected to extrusion pump of Vitrectomy machine (Fig 2B)

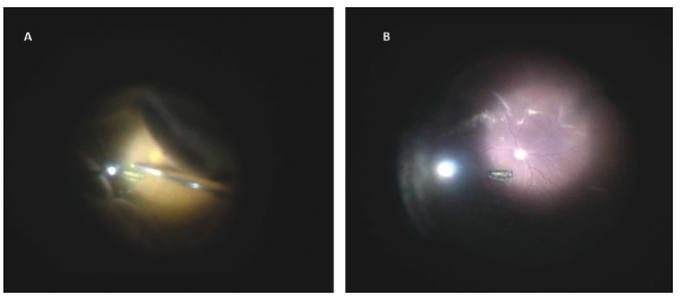

Fig 4: Intra-operative photographs of a case of post traumatic choroidal detachment & haemorrhage. (A) Pre drainage photograph shows massive choroidal detachment (B) Post drainage photograph shows flattening of choroid.

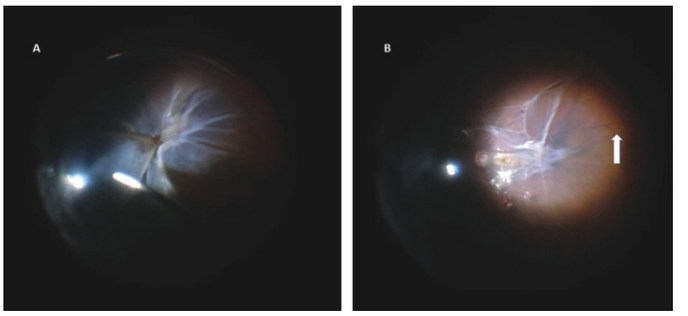

Fig 5: Intra-operative photographs of a case of Combined Retinal Detachment. (A) Pre drainage photograph shows massive bullous retinal detachment. Drainage retinotomy at this stage is undesirable as it will hamper the dissection of pre-retinal membranes (B) Post drainage photograph shows improved visualisation of retina. Also, the tip of cannula is seen in the subretinal space (white arrow)

conforms well in the available space and reduces the risk of iatrogenic retinal or choroidal injury.

2. Because the tip of the cannula is blunt, it is not necessary to withdraw it outside on decrease in fluid, thus maximizing the drainage at a single-entry site.

3. Also due to the trans conjunctival approach of the cannula, it can be easily inserted at multiple sites to attain a complete drainage of fluid. It avoids multiple conjunctival incisions.

4. Due to its length and malleability the cannula can be easily manoeuvred in the subretinal/supra-choroidal space, which helps to reach out to the posterior localised pockets of fluid. The length of the cannula allows it to reach up to the macula (Fig 3).

5. The presence of this cannula in subretinal/supra-choroidal space does not require continuous visualisation hence the cannula can be left in place while performing other steps of the surgery.

6. Theoretically, keeping the cannula in place (without movement) will help tamponade any minor vascular injury around the cannula since there will be appropriate clotting time without disturbing clot formation at the entry site.

7. The cannula also gives an access to the subretinal/supra-choroidal space for the delivery of any drugs at the end of procedure.

8. Attaching the cannula to the extrusion pump of vitrectomy machine provides a controlled suction which can facilitate faster removal of fluid (Fig 4). Also, when the space becomes shallow the suction pressure can be reduced to eliminate the risk of retinal or choroidal tissue getting incarcerated in the wound.

9. In the management of exudative retinal detachments, controlled cannula drainage effectively removes subretinal fluid in exudative retinal detachments and eliminates the need of creating drainage retinotomies. This further reduces the use of tamponade agents in these cases.

10. While doing vitrectomy for bullous rhegmatogenous or combined retinal detachments, controlled cannula drainage at the beginning of surgery helps to flatten the retina thus making the visualisation and dissection of pre-retinal membranes easier. It prevents the creation of unwanted drainage retinotomies at the start of the surgery. Controlled cannula drainage can also be combined with chandelier assisted scleral buckling surgery.

The controlled cannula drainage, however has a theoretical risk of retinal injury or break formation during its insertion. This risk can be minimized by identifying the insertion site either by indirect ophthalmoscope or through operating microscope before inserting the cannula and point of maximum elevation is used for drainage.

Vitreous incarceration of the cannula can block the tip of the cannula if the cannula is placed close to large retinal breaks. One patient undergoing chandelier assisted scleral buckling for bullous rhegmatogenous retinal detachment was found to have multiple star folds after drainage of fluid and had to e converted to vitrectomy.

To conclude, using the 26G intravenous catheter provides a simple and safe option for draining subretinal and supra-choroidal fluid in various situations in a controlled manner.

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WRITER'S C(R)AMP

P Value Decoded –A Clinician's Perspective

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Recently, there have been a lot of discussions on "**P value**" and it's significance. While the concept of p value has been in existence since the 1920's, its interpretation has always generated controversy. You can Google the term "p value" and read the top 3-4 hits. You will realize that most of these write ups including the one on Wikipedia are utterly technical, confusing and difficult to interpret. Considering that scientists use the p value to find significant differences between variables, p values are used to decide fates (acceptance/rejection) of manuscripts by journals and these values decide how we adopt new drugs, devices, technologies and new treatment regimens into our daily patient care, it is imperative that we understand p values. Here I have tried to simplify this concept as much as possible with the help of a simple example and have purposefully tried to keep jargon away.

When there are two groups (for e.g. treatment vs. control group), differences in characteristics between groups (e.g. mean age, height, weight, vision, blood pressure, HbA1c etc.) have to be determined. The p value tells us how significant the differences are between these characteristics.

Lets take an example of a study where two drugs are used to control diabetes. The mean blood sugar level at end of one month with drug A is 103mg and that with drugs B is 117mg, with a p value of 0.10. Stop reading for a minute and reflect on how you will interpret this result. What the p value of 0.10 signifies is that this difference in blood sugar between drug A and drug B at end of one month will happen by chance only 10% of the time. In other words, if you repeat the study 100 times, you will get a similar difference between drugs 90% of the times and a different result 10% of the times. What if the p value was 0.04?. This means you will get a similar result 96% of the times and a different result (by chance) only 4% of the times. What if p was 0.01? That means you will get a similar result 99% of the times and a different result (by chance) only 1% of the times. Most studies use $p<0.05$ as a reasonable cut off to interpret differences as statistically significant. Yet there is a lot of difference when the p is 0.1 vs. 0.5 vs. 0.9. You can understand why if you have followed the above argument.

WHAT INFLUENCES P VALUE?

Having grasped what p value means, you should also understand what factors influence the p value. These are:

1. **Sample size is perhaps the most important factor that influences the p value:**

If the sample size is too small, most differences between drugs A and B will turn out to be not significant. From the above example, if blood sugar at 1 month with drug A is 103mg and with drug B is 155mg, it is obvious that drug A probably works better than drug B. But if you are given a p value of 0.23, you will be surprised isn't it? The p is not significant because the study enrolled only a handful of subjects i.e. sample size is very small. If sample size calculations had been done properly before starting, this would not have happened. Incidentally, this is called a beta error (so please Google for types of errors). If the sample sizes are too large, then even small differences between drug A and drug B will come out to be statistically significant, though they may appear meaningless in clinical terms. Hence it is important to have an optimum sample size. In the future, please look at the sample size and how it has been determined before looking at the p value.

2. **Distribution of data also influences p values:**

If there are too many extreme values (called outliers), regular statistical tests cannot be employed to find the p value. Ensure that appropriate tests are being used to calculate the p values in your own study or papers you read/review. **Remember that standard deviation and 95% confidence intervals influence the p value much much more than the mean value.** Hence, two means which are quite close (blood sugar of 103mg in drug A and 117mg in drug B) may turn out to have a high p value (e.g. 0.60) in one study and low p value in another study (e.g. 0.03). The caveat is to look at the standard deviation more than the mean while interpreting p values.

If you are reading till here, please continue for another minute to make the most of this write up.

What influences P Value?

1. Sample size.
2. Standard deviation and 95% confidence interval.
3. The test used to find the p value.
4. Mean influences the p value the least.

EFFECT SIZE and P value:

Understanding and reporting effect size is critical. Do you think it makes sense reporting p value without means? In the above example, does the sentence " Drug A leads to significantly better control of diabetes than drug B, p=0.03" make sense? Not at all since the means and standard deviations (i.e. measures of treatment effect) of each group are not reported at all.

Treatment effects are best reported using regression analysis. For example, the sentence "Drug A was 3 times better (95% confidence interval=2-4 times) than drug B in controlling blood sugar levels at 1 month, p=0.03" makes a lot more sense than just reporting the mean and standard deviations. **Regression analysis not only helps you quantify differences, it also allows you to adjust for confounders in your study.**

Treatment effect is more important than the P value itself. Treatment effect is shown by:

1. Means with standard deviations
2. Odds ratios
3. Relative risk
4. Beta coefficient etc.

In conclusion, don't rely heavily on p value alone, look at the sample size, test used to derive the p value, and treatment effect. Remember that effect size (means, std deviations, Odds ratios, relative risk, beta coefficient etc.) along with 95% confidence intervals are crucial to report. Without these measures, p values have no meaning.

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Real life evidence comparable to clinical trials[10-15]

INNOVATIVE MODE OF ACTION[16-22]

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ORIGINAL ARTICLE

Peripheral Exudative Haemorrhagic Chorioretinopathy (PEHCR) - A Review

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Introduction

Peripheral exudative haemorrhagic chorioretinopathy (PEHCR) is a bilateral degenerative disease of the retina which is characterized by peripheral subretinal pigment epithelium(sub-RPE)and/or subretinal haemorrhage and exudation in the elderly. The disease remains asymptomatic unless the peripheral lesion extends into the macular area or causes breakthrough vitreous haemorrhage.

History

Historically, PEHCR has been reported mostly in Caucasian patients, but recent reports from Asian countries have narrowed down the racial disparity in the prevalence of PEHCR. On account of its peripheral location and asymptomatic nature, PEHCR principally remained unidentified and unreported as a disease entity until the advent of indirect ophthalmoscope. Since its first description by Reese and Jones in 1961 as peripheral hematomas under the retinal pigment epithelium, PEHCR has been associated with diverse terminology, diagnostic ambiguity, and equivocal treatment strategies.[1] Annesley was the first one to use the term PEHCR in a case series of 32 eyes, published in 1980.[2] He proposed a complex classification system based on the clinical presentation and evolution of PEHCR lesions. After a hiatus of almost three decades, Shields et al. published the largest case series on PEHCR including 173 eyes, all referred for management of possible choroidal melanoma.[3]

Demography

PEHCR is a disease of the elderly. The mean age various from 74-80 years.[3-7]As per the Western literature, upto 69%of those affected are female.[3-7]Goldmann et al. studied a subset of patients with PEHCR who had peripheral polyps and found that the mean age was slightly lower (70 years) in this subset, and majority of patients were men. Most of the earlier studies on PEHCR were conducted on European population and thereby show a high prevalence in Caucasian patients (99-100%).[8]However, later studies include case series and reports from Asian countries, including India as well.[9,10]PEHCR has been associated with systemic anticoagulants in 44-67% cases, and hypertension in upto 83% cases.[3,7]

Differential diagnosis

PEHCR is most commonly misdiagnosed as choroidal melanoma. Shield et al found it to be the second most common cause of pseudomelanoma, and delineated the features differentiating PECHR from choroidal melanoma as presence of retinal exudation, diffuse macular and peripheral RPE atrophic findings, hypofluorescence of the lesion on fluorescein angiography, lack of intrinsic vascular pulsations, presence of a clot retraction cleft on ultrasonography, and lack of sentinel vessels on slit-lamp biomicroscopy.[3]

Pathophysiology

The origin of PEHCR lesions has been hypothetically ascribedeither to peripheral choroidal neovascular membrane

(CNVM)or peripheral polypoidal choroidal vasculopathy(PCV). Although this hypothesis has no histopathological support but we do have the histopathological evidence of presence of peripheral choroidal neovascularization in aging eyes. 32.6% of senileeyes that Sarks studied,had choroidal neovascularization beneaththe peripheral retina.[11]Interestingly, Friedman and colleagues found that essentially everyone above 60 years of age has new vessel formation near oraserrata between Bruch's membrane and theretinal pigment epithelium, especially temporally.[12]Moreover, the highly exudative and haemorrhagic characteristics of PEHCR resembling wet age-related macular degeneration (ARMD), also corroborate the hypothesis that PEHCR develops secondary to peripheral CNVM. Certain features of PEHCR also resembles those of PCV, including haemorrhagic pigment epithelium detachment (PED) and lipid exudation and dome-shaped PED on optical coherence tomography (OCT). The hypothesis is further substantiated by the presence of peripheral choroidal vascular network or peripheral polypoidal lesions on ultrawide-field fundus fluorescein angiography (UWF-FFA), indocyanine green angiography (ICGA) and OCT in eyes with PEHCR, as reported in more recent studies.[6,8,13]

Clinical manifestations and imaging

The lesion is most commonly found in the temporal quadrant (77-100%), usually involving 1-2 quadrants, located between the equator and oraserrata in upto 89% of cases.[3-5,7,13]The components of peripheral lesion can include subretinalhemorrhage (64-78%), subretinal fibrosis (56%), sub-RPE hemorrhage (26-44%), serous RPE detachment(28-83%), lipid exudation (52%), vitreous hemorrhage (24%), RPE tear (10%) and RPE hyperplasiaor atrophy (75%)**(Fig 1a and Fig 2a)**.[3-5,13] In the series by Shields et al. the lesion presented as an elevated tumor-like mass in 77% eyes.[3]

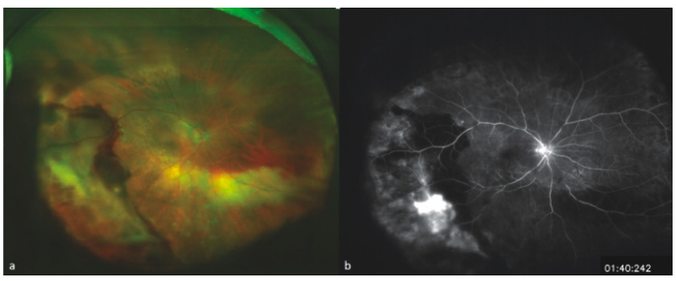

Fig.1: Peripheral CNVM in PEHCR. a) Optoscolor fundus photo of the right eye showing sub-RPE and subretinal haemorrhage with surrounding RPE changes in temporal and inferotemporal mid-periphery. b) FFA showing blocked fluorescence corresponding to subretinal haemorrhage, mottled hyperfluorescence corresponding to the temporal lesion with and area of late hyperfluorescence in inferotemporally suggestive of CNVM.

The condition can be self-limiting and asymptomaticif it is confined to the peripheral retina, but it can alsolead to visual impairment due to causes which are either PEHCR-related (21%) or secondary to concomitant ARMD (upto 69%).[3,6,7]PEHCR-related causes of decreased vision include vitreous haemorrhage (14%), extension of subretinal haemorrhage (5%) or subretinal fluid (2%) into the macular area**(Fig. 2e)**, and rarely macular oedema (14%).[3,7]ARMD changes can be early, like RPE alterations and drusen; or late, like macular CNVM or geographic atrophy. Advanced age at presentation can explain the accompanying signs of ARMD in PEHCR.[3,6,7]. 69% of eyes also shows RPE alterations and drusen in the periphery.[3,13]

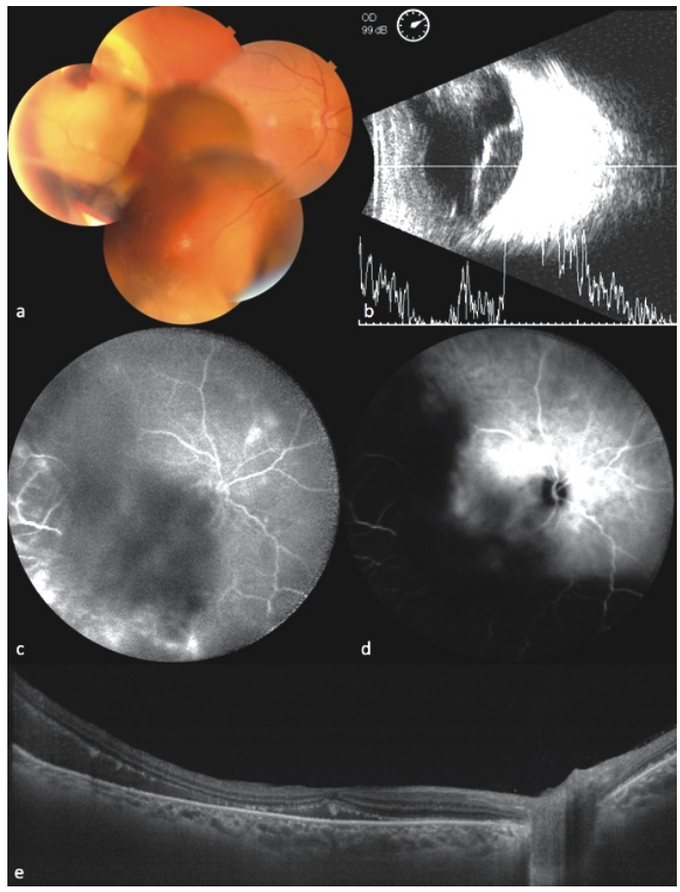

Fig. 2: PEHCR presenting with massive serous exudation. a) Color fundus photo montage showing mound of altered and fresh subretinal haemorrhage in the temporal periphery with surrounding exudative retinal detachment. b) Ultrasound A and B scan showing retinal detachment in temporal quadrant. c) UWF-FFA showing blocked fluorescence corresponding to the lesion.d) UWF-ICGA showing blocked cyanescence corresponding to the lesion. e) Swept-source OCT showing extension of subretinal exudation into the macular area with subretinal precipitates.

Bilateral involvement can be seen in upto 75% cases, or higher if inactive stage of RPE sequelae is included.[3-5,7,13]RPE alterations or drusen can be seen in upto 42% of contralateral eyes.[3]

The introduction of ultrawide field imaging has changed the way PEHCR is diagnosed, classified, and managed.Earlier studies which predated the era of ICGA, usedonly FFA as the mainstay for diagnosing PEHCR, and failed to identify peripheral polyps associated with PEHCR in cases where they could have been present**(Fig. 1b, Fig. 3)**.FFA revealed either blocked fluorescence due to subretinal pigment epithelium haemorrhage or subretinal haemorrhage; or irregular hyperfluorescence in the area of RPE changes, and rarely the characteristic lacy hyperfluorescence diagnostic of CNVM.[2-4].Goldman et al published a series of 10 patients with peripheral PCV as a cause of IPCV, all confirmed by ICGA and/or FFA along with OCT.[8]In their initial series, Mantel et al could delineated a pathological

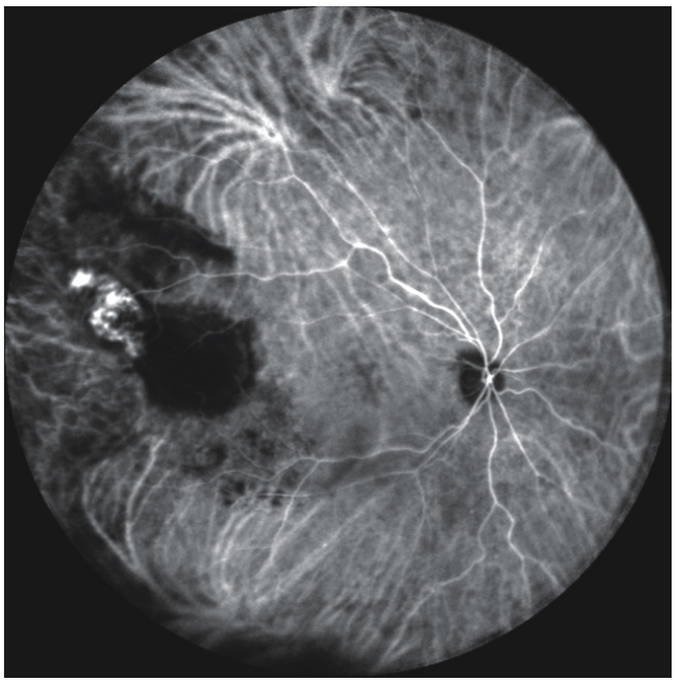

Fig.3: Peripheral polyps in PEHCR. UWF-ICGA of the right eye showing blocked cyanescence in temporal mid-periphery with branched vascular network and polyp-like lesions at the temporal edge of the PEHCR lesion.

vascular network, not visible on FFA, in 6 eyes using ICGA;but could not visualize polyps in any patient.[6]Later, the same group, using ultrawide-field FFA, ICGA and OCT spectralis in a series of 48 patients, could visualize polyp-like structures in 33 eyes (69%) and an abnormal choroidal vascular network in 24 eyes (50%), with dome-shaped PED over the lesion on OCT. They noticed that polyps were more frequently present at the border of the lesion than under it (79% vs 27%), whereas the CNVMwas located mostly under the lesion than adjacent to it (67% vs 42%). Frequent peripheral choriocapillaris closure and dilated shunting vessels was also observed.[13]

Treatment

There are no definite treatment guidelines for PEHCR in literature. As the disease has a self-limiting course, and it resolves spontaneously leaving RPE sequelae or fibrosis, treatment is traditionally indicated only if the vision is affected. Various treatment modalities include laser photocoagulation, cryotherapy, anti-vascular endothelial growth factor (VEGF)injection, combination therapy and vitrectomy. Shields et al observed all the cases in their series and noted progression only in 10 of 173 eyes. However, it's important to notice that 21 of the cases in their series had undergone treatment in the form of vitrectomy or laser photocoagulation or photodynamic therapy before presentation.[3]Rishi et al used combination therapy with antiVEGF followed by focal laser and achieved good visual outcome.[10] Kim et al used combination therapy and reported stable vision in 3 of 5 patients in their series.[9]Pinarci et al observed 11 eyes of 23 eyes (47.8%), and treated the rest with bevacizumab injections. They found that 3 eyes (13.04%), showed progression and decreased vision despite consecutive injections.[4] Goldman and colleagues achieved mixed results with bevacizumab in 4 of 8 eyes which were treated.[8]Cebeci and associates used bevacizumab/ranibizumab in 5 of 21 patients and found that mean VA improved from 0.81 logMAR to 0.73 logMAR.[7] Siebel et al presented favourable anatomical outcomes in symptomaticpatients with PEHCR after intravitreal injections of anti-VEGF agents.[14]Recent report by Sax et al showed resolution of vitreous haemorrhage and subretinal haemorrhage with aflibercept injection.[15] Goel reported favourable outcome in patients who presented with vitreous haemorrhage and underwent vitrectomy.[16]

Our experience

We diagnose and monitor our PEHCR cases using UWF-FFA, ICGA and swept-source OCT. We prefer combination therapy, when possible, in cases where macula is involved or threatened **(Fig.4)**.Vitrectomy is done in cases of vitreous haemorrhage along with antiVEGF injection. In view of the potentially vision threatening course,we have a low threshold for treatment incases of PEHCR which have a history of PEHCR-related vision loss in the contralateral eye.

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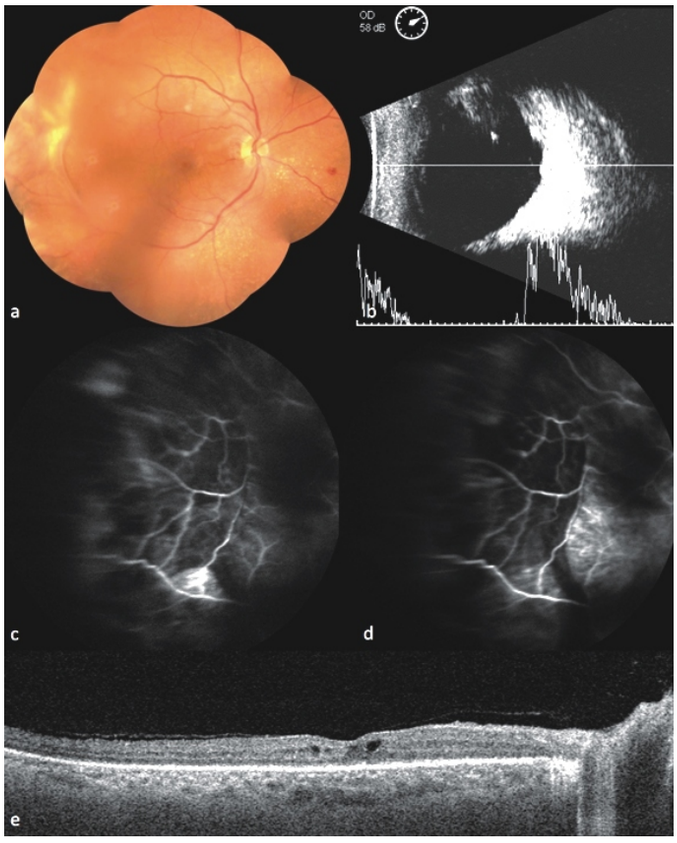

Fig.4: Resolution of PEHCR (shown in Fig. 2) after combination therapy with serial antiVEGF injections and focal laser. a) Color fundus photo montage showing resolution of subretinal mound and exudation with development of fibrotic scar in the temporal periphery with few surrounding RPE changes. b) Ultrasound A and B scan showing resolution of retinal detachment. c) UWF-FFA showing blocked corresponding to the lesion with mild hyperfluorescenceinferotemporally. c) UWF-ICGA showing blocked cyanescence corresponding to the lesion with mild hypercyanescenceinferotemporally. d) Spectral-domain OCT showing resolution of subretinal exudation with development of cystoid spaces.

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ORIGINAL ARTICLE

Features of Fellow Eye Lesions in Polypoidal Choroidal Vasculopathy

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Background

To describe the features of fellow eye of patients diagnosed with Polypoidal Choroidal Vasculopathy (PCV).

Methods

A longitudinal study of patients diagnosed with PCV in the first eye and who developed exudative lesions in the fellow eye was performed. PCV was classified into the following sub-types -1. Macular: polyp located within 1000 µm from center of fovea; Peri-papillary: located within one disc diameter from the margins of the disc; Peripheral: located outside the arcade. The ICG features of the first affected eye were noted and compared with the fellow eye for the presence of polyp, location of polyp and presence of BVN.

Results

Eighteen patients who developed exudative lesions in the fellow eye during follow-up were included in the study. The ICG in the first eye showed presence of polyp in all the patients, and polyps were present in the fellow-eye in 15(83.33%) eyes. Polyps were not present in 3 fellow eyes. Twelve (66.66%) eyes had BVN in the first affected eye and the fellow eye showed BVN in 6 (33.33%) eyes. In the first eye, PCV was predominantly haemorrhagic at presentation in 12eyes, and exudative in 6eyes, while in the fellow eye, PCV was hemorrhagic in 6eyes, and exudative in 12 eyes.

Conclusion

In patients with bilateral PCV, fellow eye may have different features as compared to first eye. Polyps and BVN may not always be present in the fellow eye.

Polypoidal choroidal vasculopathy (PCV) was first described by Yannuzzi in 1982.[1]

It is characterised by polypoidal dilatation of choroidal vessels with a branching vascular network (BVN).[2]PCV been regarded as a subset of exudative age-related macular degeneration (AMD) because of its clinical similarities to exudative AMD. However, it remains controversial whether PCV is a true distinct entity or a variant of type 1 choroidal neovascularization (CNV), despite reportedly different clinical characteristics, natural course and response to treatment.[3] Both PCV and CNV due to AMD usually show characteristics of an occult lesion on fluorescein angiography. However, indocyanine green angiography (ICGA) shows a cluster of subretinal hot spots in PCV, typically associated with a branching choroidal vascular network (BVN).

The prevalence of PCV amongst patients diagnosed with neovascular age related macular degeneration is as high as 24.5% [4]to 54.7%[5] in Chinese and Japanese population respectively, compared to 4% to 9.8%in Caucasians.[6,7]

PCV is bilateral at presentation in 15% of patients. The polyps are seen in the macular region in 92% Asians while there is an even distribution of polyps in the macular and peripapillary location amongst the Europeans.[3] In a cross-sectional study conducted by Hwang et al,[8]among 14 patients diagnosed with

PCV, ICG performed at baseline in the fellow eyes showed polyps (18.2%),or BVNs only (45.4%). In another cross-sectional study by Byeon et al,[9] nineteen patients (25%) had bilateral PCV. Minor ICGA abnormalities were observed in 22 patients, including choroidal vessel hyperpermeability or RPE pigment changes in the asymptomatic fellow eyes.[9]Most of the studies studying the fellow eyes have been cross-sectional studies. We report the results of a longitudinal study of patients who initially presented with PCV in one eye, and we studied the charactersitics of exudative lesions and time taken to develop the disease in the fellow eye.

Methods

A longitudinal study of patients diagnosed with PCVon the basis of FFA and ICG (HRA-2; Heidelberg Engineering, Dossenheim, Germany) was performed. Consecutive patients with PCV presenting to the Retina Service of L.V. Prasad Eye Institute, Hyderabad, from May 2007to June 2015 were included. Informed consent were obtained from all the participants in the study. The local institution review board approved the study, and all the procedures adhered to the tenets of the Declaration of Helsinki.

Patient Eligibility

Inclusion Criteria

Patients with 1) PCV with unilateral eye involvement at baseline; and 2) Minimum follow up of 2 years were included.

Exclusion criteria

Patients with 1)Absence of ICG documentation of PCV; and 2)Coexisting disease such as diabetic retinopathy, epiretinal membrane, retinal vascular obstruction were excluded.

Ocular examination

Systemic history of Diabetes Mellitus, Hypertension and systemic medication history was taken. Baseline ocular examinations included measurement of best corrected visual acuity (BCVA) by snellen chart, slit lamp evaluation and indirect ophthalmoscopy. The BCVA at first and last visit of both first and fellow eye was taken for analysis. The clinical features like subretinal exudates, sub retinal haemorrhages were evaluated to classify PCV into hemorrhagic, if there was subretinal hemorrhage more than 1 disc diameter, or exudative. The time taken for the other eye involvement was noted.

Indocyanine Green Angiography

ICGA was conducted using a confocal laser scanning system (HRA-2; Heidelberg Engineering, Dossenheim, Germany). PCV was diagnosed on the basis of typical changes observed on ICGA, and the presence of BVN of inner choroidal vessels with polypoidal vascular dilation at the border and/or inside of the BVN was noted. Polyp was defined as early nodular hyperfluorescence arising from choroidal circulation noted within the first 6 minutes of dye injection. Branch Vascular Network was defined as abnormal vascular network appearing within 1 minute of dye injection. Based on ICGA, PCV was classified into following sub-types with relation to the location of polyp / abnormal vascular network -1. Macular: located within 1000 µm from center of fovea; Peri-papillary: located within one disc diameter from the margins of the disc; Peripheral: located outside the arcade

Outcome Measures

The location, and presence or absence of BVN was noted. The ICGA features of first affected eye were noted and compared with the fellow eye for the presence of polyp, location of polyp and presence or absence of BVN. BCVA was converted to logMAR for analysis.

Results

Eighteen eyes of 18 patients were studied. The mean age was 55.66 years at the time of diagnosis of PCV in the first affected eye. Among 18 patients, 5(28%) were male and 13(72%) were female. Three patients had Diabetes, 5 had Hypertension, and 2 patients were on antiplatelet therapy.

Visual Acuity

The mean BCVA of the first affected eye at first visit was 0.74(20/100) and at final visit was 0.88 (20/150), while the mean BCVA of fellow eye at first visit was 0.45 (20/60) and at final visit was 0.52 (20/70).

ICGA features

Table 2 shows the distribution of polyps in the first and fellow eyes. Figure 1 shows the images of a patient from our study with

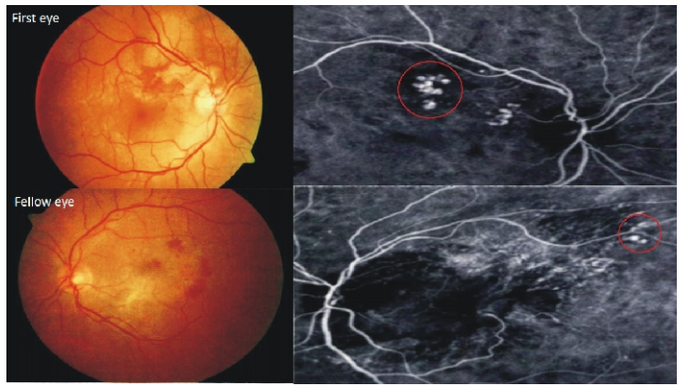

Fig-1: The first affected eye (top) shows macular and peripapillary polyps with absence of a branching vascular network (BVN), whereas the fellow eye shows extramacular polyps with a BVN at the macula.

varied distribution of polyps in both the eyes. In the first affected eye, the polyp was located peripheral (outside the macula),whereas in the fellow eye the polyp was macular. Polyp was present in all the patientsin first affected eye, and second eye showed polyp in 15 (83.3%) eyes on ICG. In first affected eye, the polyp was macular (9), peripapillary (3), macular and peripapillary (3) and peripheral (3), and in the fellow eye, it was macular (8), peripapillary (2), macular and peripapillary (4), peripheral (1). Polyps were not present in 3 fellow eyes. (Figure-2) Twelve (66.66%) eyes had BVN in the first eye and the second eye showed BVN in 6 eyes (33.33%).

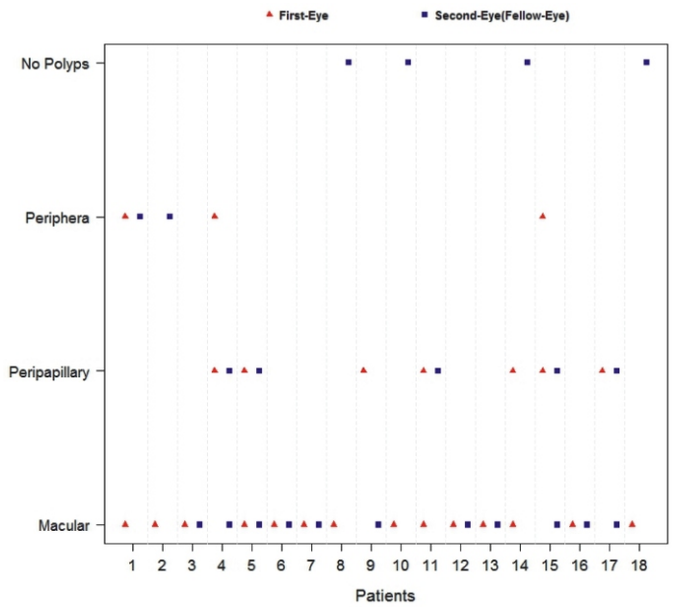

Fig-2: Scatter graph showing the distribution of lesion in the First and Fellow eyes. One eye may have multiple locations of polyps.

Hemorrhagic and Exudative PCV

In the first affected eye, hemorrhagic PCV was noted in 12 (66.66%) eyes, and exudative PCV was noted in was 6 (33.33%) eyes, while in the fellow eye, haemorrhagic PCV was noted in 6 (33.33%) while exudative PCV was noted in 12 (66.66%) eyes.(Figure 3)

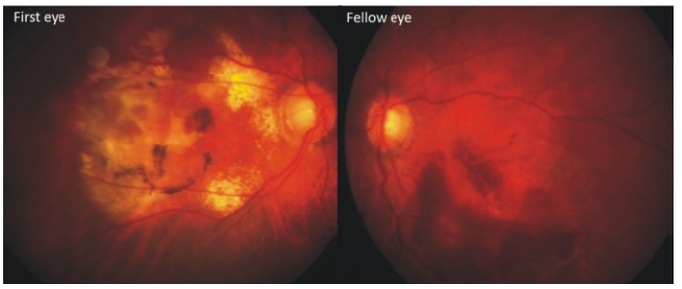

Fig-3: The first affected eye shows extensive exudation and macular scar, and the fellow eye shows submacular hemorrhage without exudation.

The mean duration for appearance of clinical signs between the first affected eye and fellow eye was 13.5 months.

Discussion

Our longitudinal study shows that in patients with bilateral PCV, the fellow eye may have different features as compared to the first eye. The location of polyp in the fellow eye may not be the same location as in the first affected eye. Many similarities have been described between AMD and PCV, however, the cytokine profiles have been noted to be different among these diseases.[10]The presence of polyps in different locations in two eyes of the same patient may suggest a different etiology for PCV compared to AMD, which typically involves the central macula. Usually, extramacular PCV is not associated with BVN (Figure 1). The presence of polyps may be due to high choroidal blood flow, which is associated with increased choroidal thickness. While a neovascular membrane is essential for the diagnosis of exudative AMD, the absence of a branching neovascular network (BVN) in many of our cases of PCV suggests a different mechanism for the development of PCV. Choroidal ischemia inducing CNVM in AMD may not be a factor in PCV, which may be more likely due to increased choroidal flow leading to secondary changes in the choroidal vessels such as polyps. This could also explain the fact that polyps could be located anywhere on the posterior pole in PCV, although secondary macular involvement may occur due to the exudative process.

Our study shows that hemorrhagic and exudative PCV may occur in the two eyes of the same patient. This could be due to different flow characteristics in the choroidal polyps, such that low flow with leakage may lead to more exudation. High flow velocity of blood in polyps may lead to rupture of polyps causing significant hemorrhage.

Some of our patients did not develop polyps in the fellow eye, even though they developed subretinal fluid, pigment epithelial detachment, and BVN in the fellow eye. This could indicate a different level of lesion (superficial or deep) in the choroid in the 2 eyes, or different flow charactestics in the choroidal blood vessels. One of our patients who developed exudative changes in the fellow eye without polpyp, did not develop polypoidal lesions even after 2 years of follow-up.

Patientscan present either as exudative or haemorrhagic PCV in the fellow eye irrespective of the type of involvement of the first eye. The fellow eye polyp may be present with or without BVN, and significantly, in some cases, polyps may not be noted in the fellow eye.

The age of presentation of PCV is earlier than that for Age related macular degeneration (AMD), and we found similar results, which is comparable to the previously published reports.[3,11] In our study, we noted that the visual acuity in the fellow eye was better than the first affected eye at the time of presentation. This could be because of early presentation, and the fact that

these patients were on regular follow-up because of the disease in the first eye.

Our study limitation includes the small number of patients, and the lack of ICG angiography at regular intervals during the asymptomatic phase in these patients. However, our study provides longitudinal data on patients with PCV who developed exudative disease in the fellow eye.

In conclusion, our study suggests that PCV may present with variable features in the 2 eyes of the same patient, with significantly different characteristics compared to AMD. The absence of polyps in some of the fellow eyes suggests that PCV canot be ruled out by the absence of polyps. The broad variations of clinical features in these patients suggest that PCV and AMD may not be part of a spectrum of a single disease entity.

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Table 1. Baseline characteristics (N=18)

Mean Age	55.6 years
Gender male to female	13:5
Systemic hypertension	5
Diabetes	3
Mean interval between first and second eye disease	13. 5 months

Table 2. Distribution of polyps in the first and fellow eye

Eye	LOCATION OF POLYPS				
	Macular	Peripa-pillary	Macular and Peripa-pillary	Peripheral	No Polyps
First Eye	10	2	3	3	0
Fellow Eye	8	2	4	1	3

CASE REPORT

Pneumatic displacement combined with tPA and Anti VEGF for sub-macular bleed secondary to PCV

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Keywords
Polypoidal choroidal vasculopathy;
Anti VEGF; Pneumatic displacement

Abstract

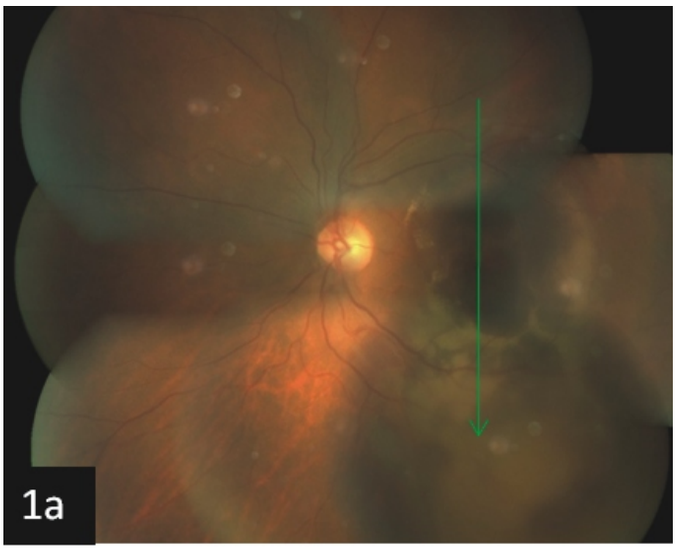
Sub-macular bleed is associated with various conditions like Polypoidal choroidal vasculopathy, Retinal artery macroaneurysm, pathological myopia, trauma etc. Without treatment, it could be devastating as the long standing hemorrhage can cause toxic damage to the photoreceptors. The intervention is either pneumatic displacement of heme with or without dissolution with a tissue plasminogen activator or surgical removal with vitrectomy, simultaneously adding treatment adjuvant directed to the cause. We here describe a case of a 55 year old healthy gentleman with sub-macular heme managed well with pneumatic displacement with gas and tPA with Anti VEGF and then subsequently with Anti VEGF monotherapy.

Introduction

Polypoidal choroidal vasculopathy (PCV) is recognized today as a vital cause of exudative maculopathy in Asians, which is typically characterized by serous macular detachment, serous or hemorrhagic pigment epithelial detachment, subretinal hemorrhage, and occasionally visible orangered subretinal nodular lesions. [1]The definitive diagnosis is by multimodal imaging, which includes ICGA, OCT and OCTA. The treatment protocol currently is in form of Anti VEGF injection, Photodynamic therapy (PDT), or vitrectomy for non clearing hemorrhage. [1] We here describe a case of a 55 year old healthy gentleman with sub-macular heme managed well with pneumatic displacement with gas and tPA with anti VEGF and then subsequent Anti VEGF monotherapy.

Case Report

A 55 year old healthy gentleman presented to us with complains of sudden onset decreased vision in the left eye since the past 10 days. The best corrected visual acuity in was 20/20 and 20/80 in the right and left eye. On fundus examination **(Fig 1a)**, the left eye showed a large red colored sub-macular bleed with yellowish sub-retinal deposited material temporal and inferior to the fovea extending beyond the inferior arcade. Swept source OCT **(Fig 1b)** analysis showed homogenous hyperreflective subretinal material, multiple tall, notched pigment epithelial detachments (PED) with underlying back-shadowing, multiple hyperreflective dots in the outer plexiform/nuclear layers and a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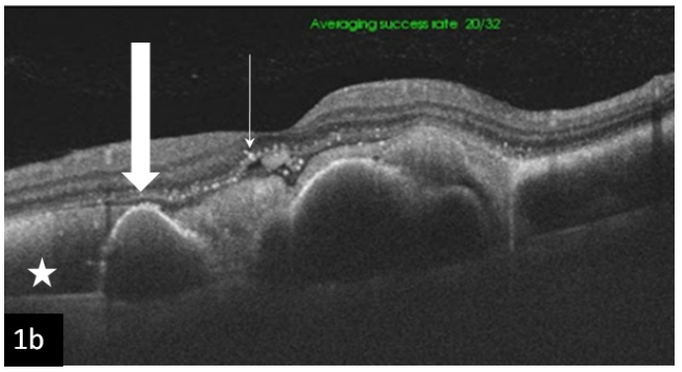


Fig-1: 1a is the colour fundus photo of left eye showing a red colored sub-macular bleed with yellowish sub-retinal deposited material temporal and inferior to the fovea extending beyond the inferior arcade. 1b is the swept source OCT showing homogenous hyperreflective subretinal material, multiple tall, notched pigment epithelial detachments with underlying back-shadowing, multiple hyperreflective dots in the outer plexiform/nuclear layers and a well maintained foveal contour.

well maintained foveal contour. The sub-foveal choroidal thickness(SFCT) could not be commented upon because of the back-shadowing, but the choroid in the right eye on OCT was thickened (SFCT- 420 microns). FFA **(Fig 2a)** showed a hypo-fluorescence at the area of hemorrhage with visible overlying retinal vessels with a late onset point leak. The parallelICGA **(Fig 2b)**showed a hotspot in the mid phase which increased in intensity in the late phase. This hotspot on ICGA corresponded to the notch of the sub-foveal PED, confirming it to be a polyp.

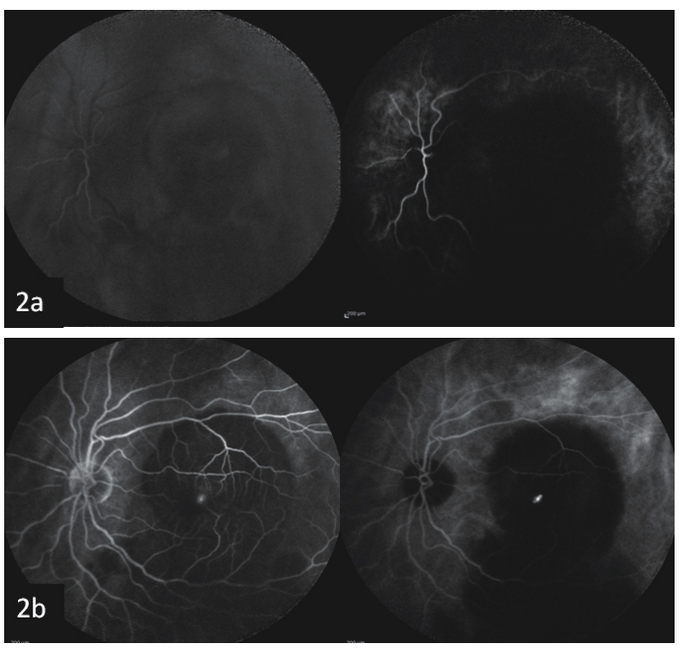
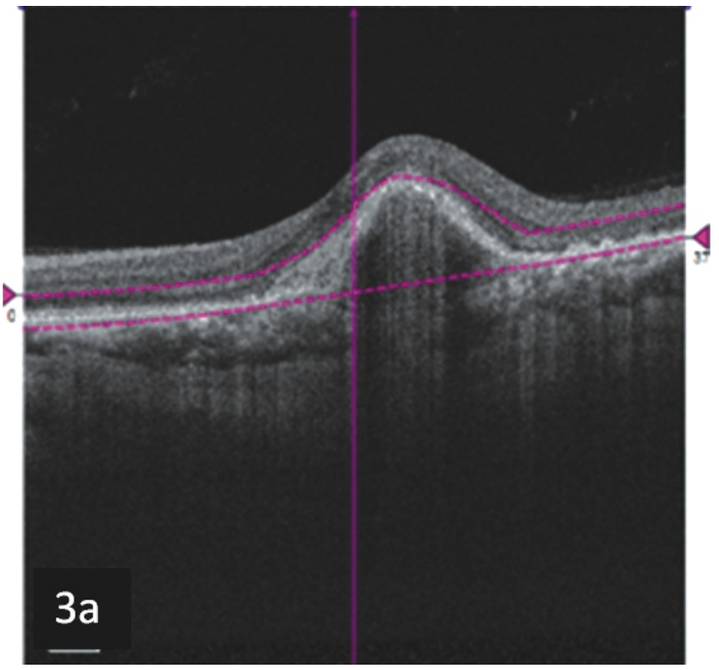


Fig-2: 2a is FFA+ICGAearly phase showing a hypo-fluorescence at the area of hemorrhage with visible overlying retinal vessels. 2b shows late phase with a point leak in the FFA corresponding to a hotspot in the ICGA.

Since the colour of the heme was dark red, was 10 days old and looked fresh in onset, a pneumatic displacement was planned. To aid the process of dissolution of heme and faster displacement, a tissue plasminogen activator (Alteplase) was used. As we were sure of the diagnosis of PCV, an Anti VEGF was added to address the root cause. There are various approaches of how to administer all three in a single sitting. We have described our technique of doing the same. After painting and draping, we gave intravitreal injection of tPA (0.05ml) and asked to patient to lie supine on the table. After 30 minutes, we re-did the painting and draping and performed anterior chamber paracentesis with 30G needle. Then we injected 0.05ml of Anti VEGF. Again we did paracentesis and allowed the eyeball to be on a softer side of intraocular pressure measured by figure tension method. Then we injected 0.3cc of C3F8 via a 30G needle at one go. After the procedure, we asked the patient to lie down in prone position right away maintaining it for the next 10 days, 12-14 hours a day.

One month later, the vision improved to 20/40, and the sub-macular bleed was partially displaced. The OCT showed reduced hyperreflective sub-retinal material and size and number of PEDs. The patient was then placed on monotherapy with monthly injections of Anti VEGF. After a total of three injections, the vision remained stable at 20/40. The OCT **(Fig 3a)**showed minimal hyperreflective sub-retinal material, reduced hyperreflective dots and few small PEDs. OCTA **(Fig 3b)**done after the last injection showed no membrane complex or flow in the PED. The patient was asked to follow up after 1 month.



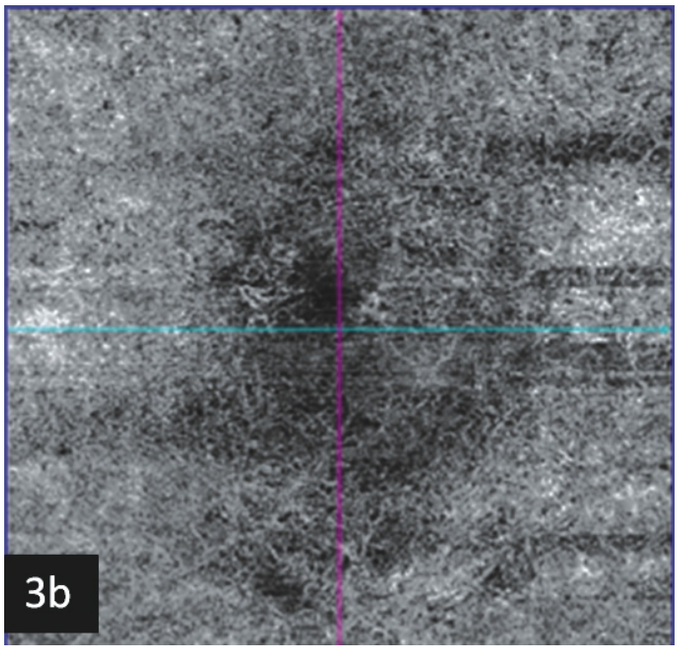


Fig-3: 3a is the OCT scan after 3 injections which show minimal hyperreflective sub-retinal material, reduced hyperreflective dots and few small PEDs. 3b is the OCTA outer slab (ORCC complex) which shows no membrane complex or flow in the PED.

Discussion

Sub-macular bleed can cause severe permanent vision loss owing to mainly three mechanisms. First, by direct toxicity by iron in the hemorrhage; second, by mechanical traction exerted on the photoreceptors by fibrin strands formed during clot retraction process; and third, by interfering between the choroidal and retinal circulation by formation of long standing metabolic byproducts. [2] Hence, displacement or removal of this blood is extremely imperative as soon as possible.

There are multiple aspects and questions to this case, which could have different management perspectives around the world. We have given our best attempt to answer the common ones.

The first question here in this case is lies in the necessity to use tPA along with pneumatic displacement. Since the bleed was more than a week old, and the other areas showed signs of old heme, it is quite a possibility that there might be old clotted heme at the macula also, which might not budge to displacement with gas. Hence, tPA, which is an excellent agent to dissolve the clotted blood, was our choice in this case. [3] Kitagawa et al have proven similar results in their study. [4]

The second question here would be in regard to the frequency of injections now, after alleged stability of the disease. The protocol we follow in such cases is loading dose of 3 injections, followed by treat and extentprotocol by 2 weeks. [5] In case it re-bleeds anytime in between, we go back to monthly injections. The capped period is kept at 8 weeks, so at every 8 weeks, we go ahead and inject, irrespective of stable vision or no new changes on imaging. When do these injections end, is a grave dark terrain to step in and answer.

The third question is in view of the edge of OCTA in diagnosing PCV in comparison to ICGA. Cheung CMG et al. in their recent study proved that cross-sectional OCTA is more sensitive than en face OCTA in detecting flow signal in polyps. [6]OCT signs used to diagnose PCV included notched or narrow-peaked PED, round subretinal pigment epithelium structure or double layer sign. OCTA signs included presence of a localized subretinal pigment epithelium hyperflow signal in the cross-sectional OCTA and/or presence of a focal hyperflow sign in en face OCTA based on outer retina slab with or without a visible membrane complex.[6] Combination of OCT and OCTA achieved 82.6% sensitivity and 100.0% specificity for differentiating PCV from choroidal neovascularization / retinal angiomatous proliferation.[6]

Thus, it is imperative to understand that sub-macular bleed is an emergency condition which requires prompt diagnosis and treatment. Multimodal imaging is the way to go in this era of medicine. Most importantly, a very clear idea of prognosis and treatment plan should be explained to the patient before commencing with the management in such cases.

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Notes

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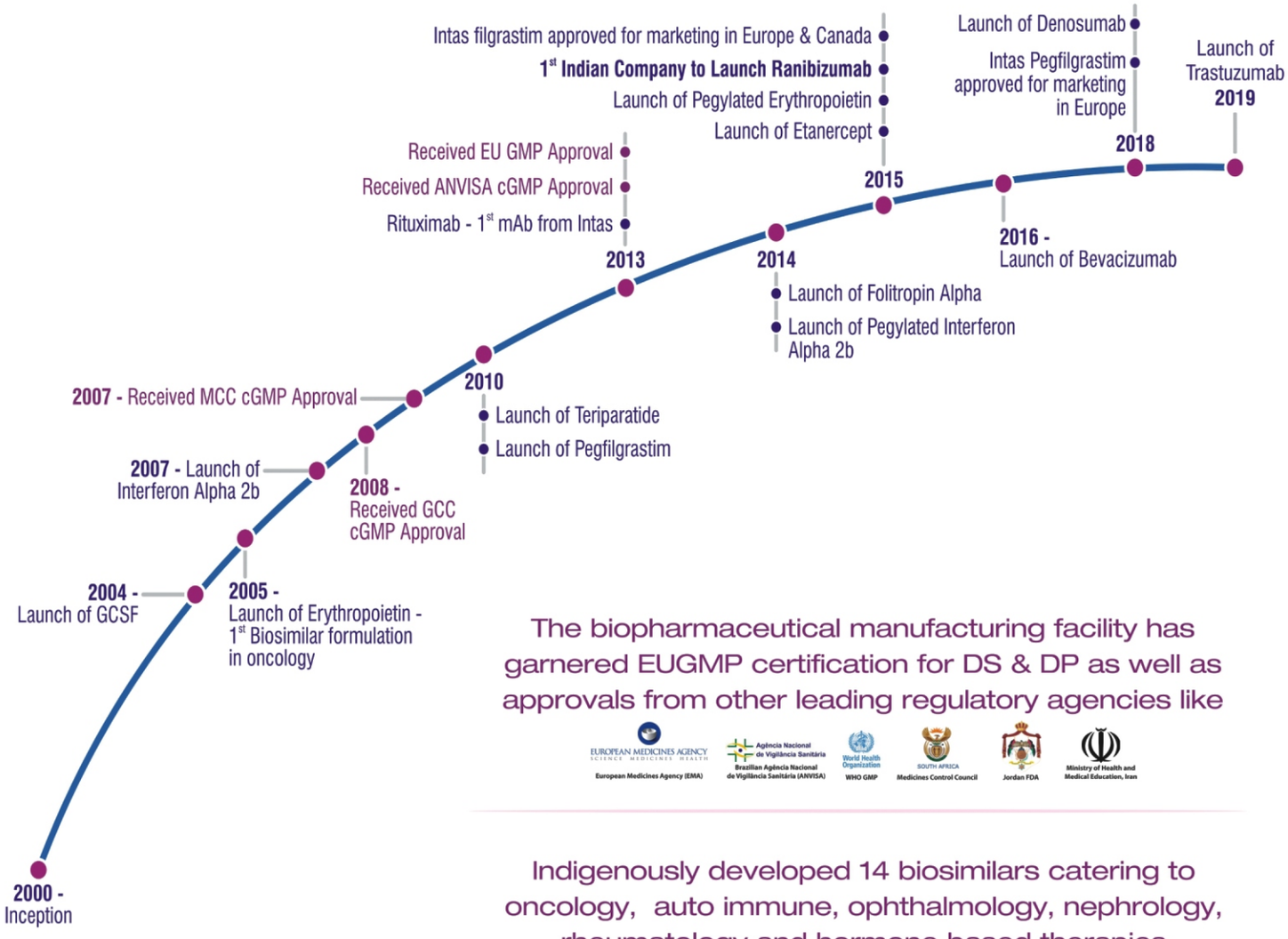

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