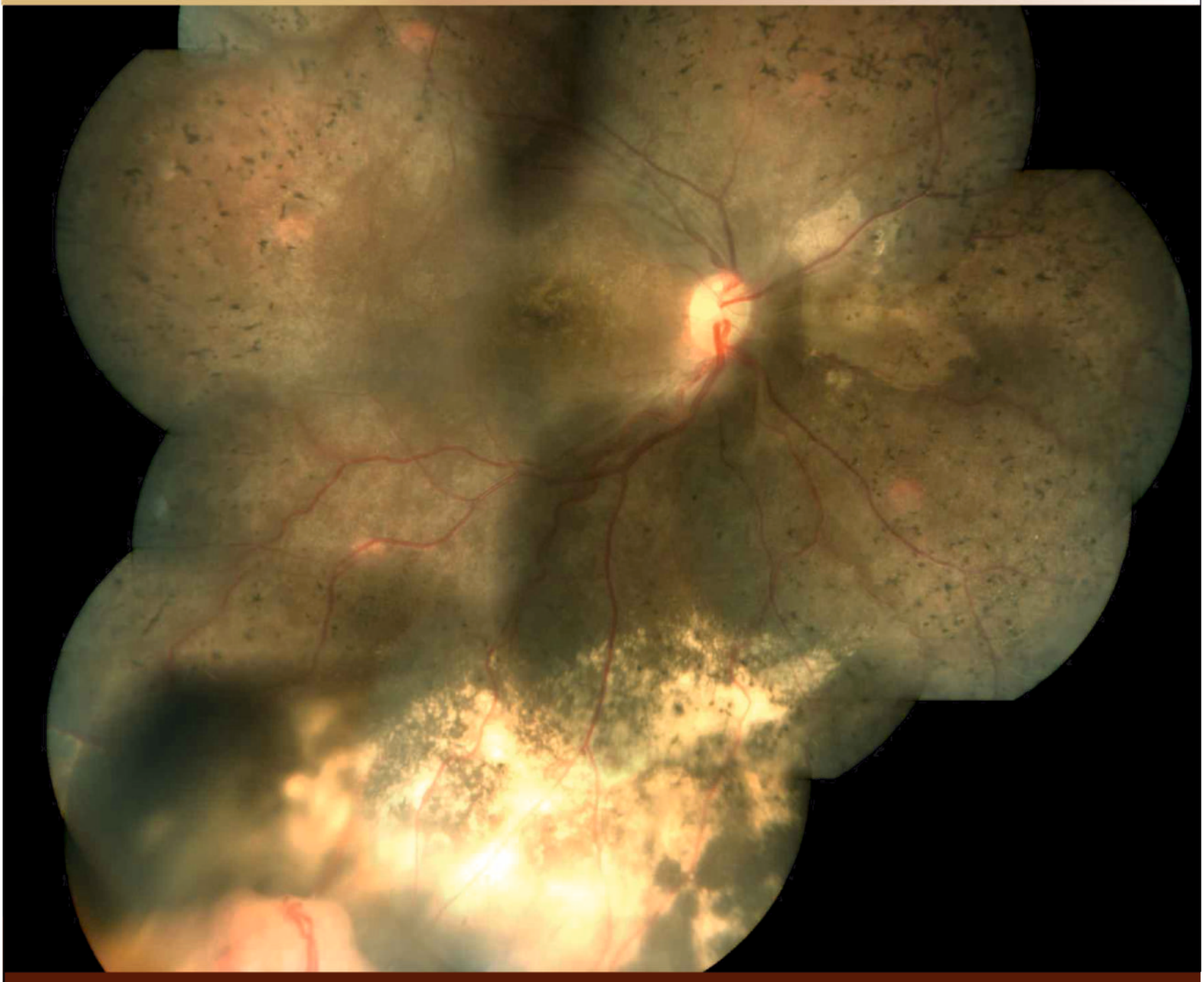
SEPTEMBER 2018

The Official Newsletter of the

VITREO RETINAL SOCIETY - INDIA



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RAZUMAB™

Ranibizumab 0.5mg Injection

Revives Vision Empowers Possibilities

Approved medication for wAMD, DME, RVO & mCNV[1]

Revived Vision of 50,000* + Eyes

Abridged Prescribing Information

Active ingredient: Razumab contains Ranibizumab solution for intravitreal injection 10 mg/mL vial (2.3 mg/0.23 mL). **Indication:** Wet Age-Related Macular Degeneration (wAMD), Diabetic Macular Edema (DME), Macular Edema Following Retinal Vein Occlusion (RVO), Visual impairment due to choroidal neovascularization (CNV) secondary to pathological myopia (PM). **Dose and method of administration:** Ranibizumab 0.5 mg (0.05 mL of 10 mg/mL Ranibizumab solution) is recommended to be administered by intravitreal injection once a month (approximately 28 days). **Contraindications:** Ocular or periocular infections and hypersensitivity to Ranibizumab. **Warnings and precautions:** Endophthalmitis, retinal detachments, increases in intraocular pressure and thromboembolic events. **Adverse reactions:** The most frequently reported ocular adverse reactions following injection of Ranibizumab are: eye pain, ocular hyperaemia, increased intraocular pressure, vitritis, vitreous detachment, retinal haemorrhage etc. **Drug interactions:** Drug interaction studies have not been conducted with Ranibizumab. **Use in specific populations:** Pregnancy Category C, Nursing Mothers: It is not known whether ranibizumab is excreted in human milk. **Overdosage:** More concentrated doses as high as 2 mg ranibizumab in 0.05 mL have been administered to patients. No additional unexpected adverse reactions were seen. **Incompatibilities:** In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products. **Storage and handling instruction:** Store refrigerated between 2 °C to 8 °C in the carton to protect from light. Do not shake. The preparation should not be allowed to freeze. Keep out of reach and sight of children.

1. Myopic Choroidal Neovascularization

*Internal Data

Editorial Board

Guidelines for the manuscript submission in
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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From the President's Desk

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Dear Members:

It gives me great pleasure to write a forward for the final issue of the newsletter for the year 2018 as my term as the President of the VRS-I is ending. The purpose of any scientific society is to disseminate latest scientific information, create an environment for effective scientific deliberations and finally improve fellowship and partnership between fellow Vitreo Retinal surgeons.

Over the years there has been a long debate within the governing council of the VRS-I about the need and purpose of this newsletter. In this context it is important for me to congratulate Dr Vishali Gupta and her team for having brought out systematically many useful issues of the newsletter over the last two years. Personally I feel this can be an avenue for young Vitreo Retinal surgeons to display their inherent talent. This newsletter can be a platform for many of them as a stepping stone for future publications in large peer reviewed journals. Our society is blessed with a large number of young dynamic and innovative surgeons. The mushrooming of various retina forums across the country is a clear indication that there is a phenomenal potential for our society to shine at international level.

As I lay down office as the President of the Society, it is my dream that this newsletter grows into a scientific journal of international repute in the coming years. It is necessary for young, vibrant and dynamically oriented retina specialists to take this forward. Let me conclude by once again thanking the governing council and its members for having participated effectively in the publication of this newsletter. One of the important achievements of this governing council has been involvement by each and every member in some form of activity. This should continue in future.

With kind regards and best wishes

Dr A Giridhar
President, VRS-I

From the Honorary Secretary 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. Vishali Gupta. The local organizing committee lead by Dr. Shorey and Dr. Sharma is working tirelessly to ensure a perfect Meeting for all of us.I am delighted to know that the lastissue of VRSI newsletter in 2018 is being published. I am sure that you will find thearticles 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. I request you all to participate enthusiastically in the activities of VRSI.

Dr Raja Narayanan
Secretary, VRS-I

From the Convenor Scientific Committee Desk

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Dear Members

It gives me great pleasure in bringing out the third volume of VRSI newsletter for the year 2018. The current issue focus on the controversies and challenges that all of us face in our day-to-day practice. I am extremely thankful to all my colleagues, who despite being busy vitreo-retinal surgeons, have worked hard to contribute and share their experiences and give expert tips that shall be extremely valuable for the young surgeons. However, we are certainly missing submissions from our members and do encourage them to submit their cases, images as well as original articles to contribute to the newsletter and share their experiences with other members of the society.

We are also looking forward to see you all for the annual meeting of VRSI to be held in Jaipur between 29th Nov till 2nd 2018 with pre-conference Retinal Imaging Symposium (RISHI 3). The participation by international faculty as well societies is tremendous and we are certain that you will truly enjoy both the scientific contents as well local hospitality. Our local hosts Dr Raj Kumar Sharma and Dr Pavan Shorey are working extremely hard to make sure that this is a memorable event and your participation shall certainly make it one.

Once again, I sincerely hope that you enjoy reading this newsletter and look forward to your comments and suggestions.

Dr Vishali Gupta
Scientific Committee, VRS-I

Current practice pattern for the management of persistent macular holes

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Macular hole (MH) is one of the common causes of reduced central vision. Internal limiting membrane (ILM) peeling has increased the surgical success rateto 90-95% resulting in MH closure.[1] Persistence of MH after pars planavitrectomy remains the most common complication seen in approximately 10-12% of the cases. Various causes for a persistent MH are - persistent vitreomaculartraction (VMT), insufficient tamponade or non- compliance to prone position. Re-surgery in the form of repeat vitrectomy with enlargement of the ILM rhexis, with or without autologous platelet concentrate and additional gas tamponade or light/heavy silicone oil tamponade have been tried for the closure of persistent or recurrent macular holes. [2-5] It is extremely important to know when to intervene in a case of persistent MH after the first surgery to achieve a higher chance of anatomical closure.[6,7] We will discuss the preferred practice pattern with a few of the leading vitreoretinal surgeons- A. Giridhar (AG), Cyrus M. Shroff (CMS), Hany Hamza (HH), Pramod Bhende (PB) and Mahesh P. Shanmugam (MPS). The questions and summarization of the answers by the experts has been prepared by Manisha Agarwal (MA).

MA-Q1.What is your definition of a persistent macular hole? How long after the primary surgery would you like to wait for the hole to close?

AG: A macular hole which does not close after a primary surgery is a persistent macular hole. Closure of macular hole occurs during the first week after the surgery. Therefore any hole that persists at the end of one week after surgery usually does not close later.

CMS: We generally do an OCT one month after the primary macular hole surgery and if the MH is still open we would term it a failed or persistent MH. Recently with Swept source OCT we have been able to identify MH closure as early as the first post-operative day.

HH: Persistent macular hole is defined as a persistent full thickness defect in the neurosensory retina 3 weeks after vitrectomy. The persistent edema at the edge of the hole as well as the slightly elevated edges help to differentiate between non-closure of the hole after primary surgery and type -2 closure.

PB: If the hole remains open 1-2 weeks after surgery, unlikely it will close, though I would still prefer to wait for 6-8 weeks before advising a re-surgery.

MPS: Persistent macular hole is one that has not closed after absorption of the gas. I would intervene if there were inadequate intravitreal volume of gas for effective tamponade and a persistent hole. Hence intervention may be even as early as 1 week or 1 month. If one is able to serially document narrowing of the hole with progressing approximation of the edges on OCT, there is a possibility of hole closure even in the absence of gas. In such cases one may watch closely for spontaneous resolution.

Summary (MA) - Persistent macular hole is a hole which remains open after the primary macular hole surgery with absorption of the gas tamponade or a maximum of two weeks after silicone oil tamponade**.** We may have a persistent or a recurrent macular hole. Recurrent MH is the one which had closed after the primary macular hole surgery, but has reopened. The results of the re-operation are better for recurrent macular holes in comparison to persistent MH.[8] The best time for re-surgery is when the eye is not inflamed and there is no effective gas tamponade with no possibility of closure of MH.

MA -Q2. What factors in terms of BCVA, size and etiology of the macular hole do you consider before you advise a re-surgery for a persistent macular hole?

AG: Once we have a persistent macular hole, the decision to re-operate is more based on the OCT characteristics rather

than the visual acuity. Presuming that in all patients we have done a proper ILM peeling, the etiology of failure after the primary surgery are:

a) Improper ILM peeling
b) Inadequate ILM peeling
c) Inadequate tamponade
d) A very large primary macular hole which fails to close.

Therefore we need to define what exactly the cause is before we decide on further management.

CMS: We would generally advise a re-surgery for any persistent MH especially if we are unsure about the amount of ILM peeling during the primary surgery and of the compliance with the prone positioning.

HH: In terms of visual acuity I have not encountered any patient with a persistent open macular hole with vision better than 0.2 and the persistence of the central scotoma can be quite disturbing to the patient as an indicator of failure of the first surgical procedure. Therefore vision has never been the issue in deciding for reoperation. Persistent open macular hole is clearly the cause of persistent visual symptoms that are the basis of deciding for the primary surgery. With the use of the inverted ILM flap technique we could achieve closure of the macular holes larger than 1500 u in some cases. Therefore with very few exceptions of very large macular hole size is not the issue. On the other hand, etiology and associated pathology can influence my decision to re-operate patients with unhealthy RPE at the base of the hole caused by trauma in traumatic macular holes as well as myopic macular holes with extensive chorioretinal degeneration at the posterior pole have very poor functional outcome. In these cases I explain to the patient that surgery is not useful and that no visual improvement is anticipated and we decide together not to re-operate.

PB: If I have attempted surgery once and the patient comes back with persistent MH, I generally ask the patients, if he/she would like to take a second chance. But at the same time I would explain about guarded visual prognosis. I still believe in prone positioning and if patient is not compliant for prone position, I would prefer not to take second chance. Eyes with obvious traction (on OCT or clinically), smaller holes, underlying healthy RPE, elevated edges of the hole probably are the better candidates for re-surgery.

MPS: Smaller idiopathic holes with good pre-surgery vision have a better prognosis if operated early. BCVA <6/60, holes >1000 microns, associated with retinal atrophy (as in post CME, myopia etc.), failure despite a well performed primary surgery (adequate ILM peel or inverse flap large holes, appropriate tamponade etc.) would be factors against advising a re-surgery.

Summary (MA): Visual acuity is an important deciding factor for the primary macular hole surgery along with other factors such as etiology, size and duration of the macular hole. However these play a less important role while deciding for a re-surgery. We need to evaluate the cause of failure of the primary surgery including inadequate ILM peel, features on OCT such as persistent VMT or a very large size of macular hole. However if non-compliance to prone positioning has been the cause of failure one needs to discuss with the patient before deciding for a re-surgery or think of changing the tamponade such as heavy silicone oil.[9]

Q3. What are the OCT features that you consider pre-operatively which help you decide for a re- surgery ?

AG: If the edges of the macular hole are lifted and we find cystoid changes we would immediately advise such eyes a repeat surgery. Therefore my decision to re-operate on a failed macular hole is based on the SD-OCT features.

CMS: Both the size and the configuration of the macular hole are important. If the walls of the hole are sloping like a drawbridge, then this generally indicates a better prognosis. Holes with flat straight edges are more difficult to close and we would consider an inverted ILM flap technique for these cases.

HH: The presence of persistent edema and elevated edges of the macular hole are good prognostic indicators that favor surgery. Also the presence of a regular layer of healthy RPE at the base of the hole favors re-surgery.

PB:.Obvious traction, smaller holes, underlying healthy RPE, elevated edges of the hole, probably are the better candidates for re-surgery. Look for the presence of ILM on OCT suggestive of an inadequate peel during the primary surgery.

MPS: Size of the hole (narrowest part of the hole), presence / absence of retinal atrophy of the hole margins (thinning of the retina with absence of intraretinal fluid), health of the underlying RPE, redundancy of the hole (presence of fluid and thickened margins) and associated factors such as presence of epiretinal membrane .

Summary (MA): Evaluation of the OCT of a persistent macular hole plays a vital role in prognosticating and deciding for a re-surgery. The good prognostic factors are small size persistent holes <1000 microns, swollen lifted edges of the hole, cuff of SRF, healthy underlying RPE and poor prognostic signs are large flat holes, RPE atrophy and disruption of the ellipsoid zone. An obvious persistent traction on OCT warrants a re-surgery.

Q4. If there has been a type-2 closure after the first surgery with no improvement in vision ? Would you advise a re-surgery

AG: Now-a-days I am not coming across cases where there is a type-2 closure. During the primary surgery itself I decide whether to do a routine ILM peeling or one of the flap techniques. Therefore the chances of a type-2 closure are very remote.

CMS: Generally not.

HH: Type 2– closure is a successfully repaired hole so I do not advise a re-surgery.

PB: No

MPS: Depends on factors such as hole size prior to the primary surgery, duration of the hole, health of the underlying RPE, presence / absence of retinal atrophy of the hole edges, age of the patient, ability to maintain prone position, patient's inclination for further improvement, other eye status etc.

Most often the holes that achieve type 2 closure after a properly performed surgery are larger, may be associated with factors such as CME, resulting in tissue loss or may have been treated with techniques such as inverse flap already. Hence I would most often not intervene in such a situation.

Summary (MA) : Type-1 closure is more often encountered however a Type - 2 closure often occurs in larger macular holes secondary to trauma, CME etc. which have other factors associated and therefore unlikely to benefit by a re-surgery.

MA-Q5. What is the ideal time for intervention in case of a failed macular hole surgery ?

AG: The ideal time would be 3-4 weeks after primary surgery.

CMS: We would generally wait for the gas to absorb and would give a chance by strict prone positioning before re-operating, usually after a month.

HH: I usually wait for 4 weeks before doing an OCT after the primary surgery . If the hole is still open I re-operate within 4-6 weeks after the primary procedure. There is no point to wait and the sooner the intervention the better the visual outcome.

PB: Earlier the better, but if duration is more than 6 months, I would prefer not to offer the option of re-surgery.

MPS: The earlier the better – in a persistent hole in the early post-op period wherein there is no more intraocular gas for effective tamponade, a simple OPD - FGE (fluid gas exchange) may aid hole closure. Hence the intervention may be as early as a week (in case air tamponade had been used in the primary surgery).

Summary (MA): If the decision is made to re-operate then earlier the re-surgery better are the anatomical and visual outcomes. Very often done between 4-6 weeks after the primary macular hole surgery.

MA-Q6. Is additional ILM peeling advised for repeat surgeries and if yes, what should be the extent of the re-peeling ?

AG: Additional ILM peeling is recommended in eyes where the initial ILM peeling has been very small. We have compared the size of the ILM peel and the closure rates and we have shown that for small and medium size holes what is more important is the removal of the ILM from the edge of the macular hole. We have shown a good closure rate with just a 3 mm ILM peel.In re-operation therefore if the initial ILM peel is around 3 to 4 mm, I would increase it to around 7 mm. Otherwise I would just do a fluid air exchange (FAE) and re-inject gas and we have achieved very good results in such cases.

CMS: In general yes. We generally peel from arcade to arcade at primary surgery. In case smaller area has been peeled we would enlarge the area during the re- surgery.

HH: First of all let me stress the point that there is no common consensus as to what is the proper size of ILM peeling. I am not an advocate of extensive ILM peeling during the primary procedure from arcade to arcade but my technique of ILM peeling entails peeling to 1.5 disc diameter around the edges of the hole. If during re-operation I find incomplete peeling was done during the previous vitrectomy then I enlarge it to my preferred size of 1.5 disc diameter. Keep in mind that the ILM can be your backup plan for closing the macular hole by using it as a graft or flap. So by doing an extensive peeling you lose this option.

PB: If adequate peeling is not done and ILM is available to peel, I would prefer to peel till the arcade. It is important to counter check the details of the surgery including the extent of the ILM peel if one has an access to the previous surgery notes.

MPS: ILM peel extending up to the arcades superiorly and inferiorly, to disc nasally and at least 2 disc diameters temporally.

Summary (MA) : It is important to review the previous surgery details and the extent of the ILM peeled. If adequate ILM peeling has not been done then it maybe further extended ,usually till the arcades. However if adequate ILM peel has been already done then one may have to use alternative methods for closing the macular hole.

MA-Q7. What is the technique of ILM peeling used by you for persistent macular holes after an adequate ILM peel has been done arcade to arcade during the first surgery? Temporal peel/hinge flap/free flap or any other technique of ILM peel. When to use which one ?

AG: If there is an adequate ILM peeling and the topography of the macular hole shows a cystoid change I will not indulge in any further ILM peeling and just do a FAE and inject gas (short acting 20 to 25% SF6).

CMS: In case ILM still remains close to the MH, then a hinge flap would be preferred, however if ILM has been extensively removed from around the hole then would require a free ILM flap or full thickness retinal graft.

HH: If I find enough ILM to do a hinged flap then I go for this option. Unfortunately this is only possible if during the primary vitrectomy the ILM has not been peeled properly and its remaining peeled edge is very close to the edge of the macular hole. More commonly I go for a free ILM graft.

PB: If ILM is already peeled up to the arcade, then there is not much choice left. If the hole edge is elevated, I can even try simple reinjection of C3F8 gas and prone positon. The other option would be free LM flap. We have now couple of reports attempting full-thickness retinal transplant or use of amniotic membrane or lens capsule to cover the macular hole. I do not have personal experience with any of these techniques.

MPS: Considering that adequate ILM peel has been done in the primary surgery, a free flap / graft is what would be feasible.

Summary (MA): The ILM peeling if done inadequately during the primary surgery then one may do a hinge flap technique of ILM peel during re-surgery. However if no ILM is available till the arcades and has been already peeled then the only options are retinal graft(autologous retinal transplant) or free ILM flap.

Q8. Your technique of doing a free ILM flap?

AG: I have tried removing a bit of the ILM from the edge of the previously removed ILM and I have placed it inside the macular hole. But I have not been very happy with the outcome and I have not done many cases.

CMS: We feel that bimanual surgery really helps in this maneuver as the flap has a tendency to get dislodged and may fly away. Once an area of ILM is located the free flap should be peeled carefully. It's better to take a generous flap as it tends to shrivel up and become smaller. It is best to do this under PFCL & slide the free flap to the MH. After placing the flap remove PFCL and then do a gentle fluid air exchange, keeping the backflush tip nasal to the disc.

HH: First step is to stain the ILM using brilliant peel dye outside the macular hole. Under perfulorocarbon liquid, I go for an area of the retina just below the inferior arcade and using a Tano scraper I start making an incision in the ILM marking the borders of the graft. Using an Eckardt ILM forceps, I peel the ILM starting from the periphery to the center all around . The behavior of the ILM is different outside the arcade and it is more fragile. Sometimes the graft tears and you have smaller fragments that you transfer one at a time to the macular hole. The ILM graft is usually sticking to the jaws of the forceps and using a bimanual technique and chandelier, I move the ILM forceps towards then macular hole and using a second forceps with the jaws closed I try to disengage the ILM or ILM fragments and place them inside the hole. If you grasp the ILM using the second forceps it will stick to its jaws as the first one and you are in a vicious circle. Therefore keep the jaws of the forceps closed so that the out smooth surface of the tip of the forceps is used as a spatula to release the free graft. I also try to push the graft inside the hole and under its edges so as to minimize the possibility of it's displacement during FAE. During FAE aspirate the PFC liquid over the optic disc and you can move the globe so that the nasal retina is more dependent .Do not aspirate over the macular hole otherwise you will lose the free graft. I do not recommend the use of viscoelastic as sodium hyaluronate to keep the ILM graft in place as the viscoelastic itself can act as a barrier preventing hole closure.

PB: Harvest the flap preferably along the previously peeled edge and stuff it within the hole.

MPS: Staining under air is preferable to identify an appropriate area for harvesting the graft. An area proximal to the arcades is preferable (assuming that the ILM within the arcades has been peeled earlier) as the ILM is less fragile. An appropriately sized ILM is harvested with the aid of the forceps and gently inserted in to the hole taking care not to disturb the RPE beneath. A bimanual approach with chandelier illumination is preferable, but it is possible with a unimanual approach as well. I would switch off the infusion before the forceps is removed from the eye to minimize the fluid currents and place a drop of viscoelastic on the flap before turning the infusion back on. A careful and gentle (slow) FAE with the flute placed nasal to the optic disc will prevent the graft from being sucked out through the flute needle.

Placing the ILM flap at the hole can also be performed beneath a PFCL bubble by harvesting the ILM just adjacent to the bubble and dragging it close to the retina, beneath the bubble to the hole. The PFCL aids the placement and prevents displacement. However, there is a strong possibility of displacement of the graft when removing the PFCL and the visualization through PFCL may make placement of the graft difficult.

Caution: Some scissor action forceps generate suction at the tip acting as a flute needle – this may make the process of placing the ILM flap in the hole difficult. Similarly a rough edge at the tip of the forceps may adhere to the ILM making it difficult to transfer it to the hole.

Summary (MA): ILM is more fragile outside the arcades and less within, therefore preferable to take the ILM flap from within the arcades, if available. Bimanual technique may make the process easier of harvesting the ILM flap and placing it over the macular hole preferably under a bubble of PFCL. A very slow and careful FAE keeping the flute at the nasal edge of the optic disc is mandatory to avoid the inadvertent suction of the free flap of the ILM.[9]

MA-Q9. Have you used lens capsule graft for persistent macular holes, if yes then what is your technique and do you combine with ILM peel ?

AG: No I have not used lens capsule graft for persistent macular hole.

CMS: No

HH: I have no experience with the use of lens capsule as a graft but it seems to be an interesting technique.

PB: No

MPS: Yes. If the patient is to undergo combined cataract surgery, the anterior lens capsule is preserved after capsulorhexis; in a pseudophakic patient a bimanual posterior capsulectomy can be performed. An adequately trimmed capsular fragment is then used to plug the hole. The capsular graft is used when an adequate ILM free flap is not possible – hence this would be in eyes wherein adequate ILM peeling has been done earlier and further ILM peeling is not possible due to the fragility of the extramacular ILM in the particular patient.

Summary (MA): This is better known as autologous lens capsular flap transplantation. The anterior or the posterior lens caplsule is harvested after a routine phacoemulsification surgery. The lens capsule is trimmed and kept a little larger than the size of the macular hole. Either side of the lens flap can be placed over the retinal pigment epithelium(RPE). The lens flap is tucked under the edges of the macular hole so that is not displaced. This is followed by a careful FAE and gas tamponade with post op prone positioning.[10]

MA-Q10. Any experience with full retinal graft for a persistent macular hole? If yes then your technique of doing it and do you combine it with ILM peel? Any possible complications encountered by you?

AG: No

CMS: No experience with full thickness retinal graft.

HH: I have 2 cases of full thickness retinal grafts for closure of recurrent macular hole. I only used this technique after failure of ILM peeling and free ILM grafts so ILM peeling was already done in previous procedures. The technique starts by marking the area of the graft with endolaser. The graft should be 1.5 times larger than the size of the hole. I usually select an area in the upper nasal or lower nasal mid retinal periphery for ease of accessibility and dissection. Using a 41 g needle I inject BSS in the sub-retinal space in the center of the laser marked graft area . I inject LPFC in the posterior pole . Next using a bimanual technique with a scissor and forceps I cut the retinal graft free from the retina and then drag it with forceps under LPFC and place it over the macular hole. Releasing the graft from the forceps in the same way as previously described for ILM grafts but is much easier as the full thickness retina in not as sticky as the free ILM graft. Next you do a limited fluid /air exchange until you reach the level of PFC and then start injecting silicone oil and continue with a direct LPFC-Silicone oil exchange. This is the last step to avoid displacement and loss of the flap which would happen if one was to do a LPFC-air exchange, and this is what happened to me in my first case and I had to take a second graft from the retina during the same procedure and close the hole. Please note that when you move the graft you keep its orientation as it was in its original position so you have the photoreceptors facing the RPE cells. Once the graft is displaced you will not be able to know its correct orientation anymore and that is the reason I had to take a second graft. Sometimes minor bleeding occurs from the bed of the graft or the edges of the cut retina but this is self- limiting and stops within minutes with elevation of intraocular pressure.

(Fig:-1a-d)

Fig.1a Persistent macular hole after vitrectomy and ILM peel, silicone oil injection and silicone oil removal

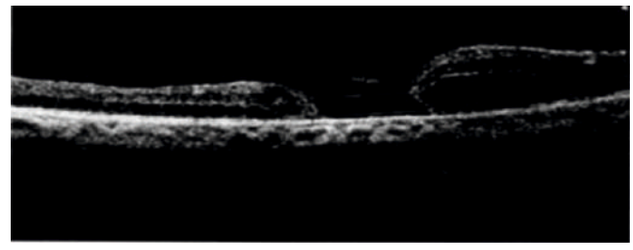
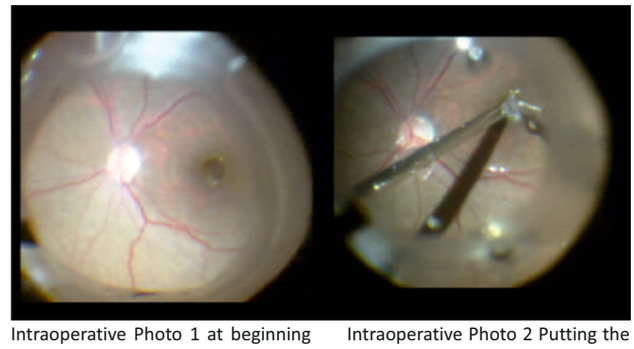


Fig:1b- Persistent macular hole after free ILM flap



Intraoperative Photo 1 at beginning of Surgery showing the open MH after free ILM Graft

Intraoperative Photo 2 Putting the full thickness Graft in place

Fig.:- 1c

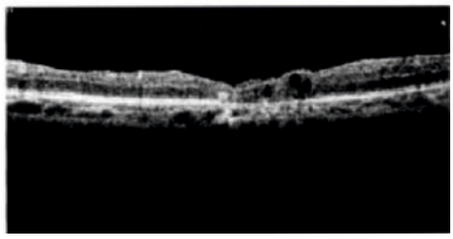


Fig-1d
Postoperative OCT at 8 weeks after Full thickness Graft

PB: No experience. Though the early reports are promising, I am not very comfortable with technique at this stage. Would like to wait for the long term results.

MPS: No experience yet

Summary (MA)- Full thickness retinal graft is usually the last option for patients who have a persistent macular after everything has failed including a free ILM flap. This is a relatively new technique described and not many articles are published in literature. Wu AL et. al. have used the same technique as described by Dr. Hany except that they have used a drop of autologous fresh blood over the retinal graft to stabilize it. The fresh blood soon becomes a clot on the surface of the macula, and the retina graft and blood clot seals the hole in a few minutes as a macular plug[11]

MA-Q11. What is the technique adopted by you for a persistent macular hole in a myopic patient ?

AG: In a myopic patient with persistent macular hole, we need to look into the topography of the hole and the anatomical structure of the posterior pole. These are factors which may be the cause for macular hole surgery failure. I usually go for ILM flap during the primary surgery in such situations.

CMS: Technique remains the same. Prefer 23G in these long eyes. Contrast is poor and often requires repeated ILM staining.

HH: For a myopic patient I first assess the situation of the first surgery. If the ILM has not been peeled I go for an inverted ILM flap. I never recommend ILM peel in these cases. If the ILM has been peeled before I go for a free ILM graft. The ILM in myopic macular hole can provide the additional tissue needed to bridge the defect and overcome the stretching force on the retina caused by scleral expansion.

PB: Varies from case to case. Would like to ensure that all the vitreous is removed, followed by ILM peeling if present. If staphyloma is very deep, can consider combining with macular buckle. If there is underlying severe RPE and choroidal atrophy, I would defer the surgery.

MPS: Myopic macular holes may be associated with macular schisis or a frank macular detachment.

In myopes, even an experienced surgeon may miss the schitic layer of cortical vitreous and hence repeated staining with triamcinolone and brilliant blue green dye is essential. I would stain the ILM under air in myopes, allowing dye contact for 30 seconds. The stained ILM can be used as a handle to peel the epiretinal proliferation / cortical vitreous.

In cases with intact ILM: An inverse flap may be necessary considering myopic macular holes are usually larger and often not associated with rolled edges (less redundant retina and less tissue to bridge the hole).

In cases with adequately peeled ILM: A free ILM flap / anterior / posterior lens capsule / amniotic membrane graft may be necessary.

In eyes with macular detachment: In eyes with persistent ILM, ILM peeling under PFCL may be necessary. Repeated staining and ensuring the absence of cortical vitreous is immensely important in these eyes. In these eyes, the holes are usually larger and the primary goal of the surgery is to attach the retina, closure of the hole being a secondary objective. Hence a free ILM flap / lens capsule / amniotic membrane graft may be used after drainage of subretinal fluid preferably from a extrafoveal retinotomy. The atrophic RPE and poor visualization of the hole after FGE make the process of placing the graft difficult in these cases. In cases with recurrent detachment and persistent hole, additional steps such as a macular buckle, laser photocoagulation of the hole margins may be necessary to prevent recurrence of retinal detachment.

Summary (MA): In myopic patients foveal retinal detachment may precede the onset of MH formation. Myopic macular holes behave differently from an idiopathic macular hole due to associated factors such as posterior staphyloma and macular schisis. Intraoperatively one may encounter problems in reaching the posterior pole with instruments due to longer axial length. This may be taken care by making the sclerotomies slightly posterior and using 23 gauge instruments which are longer. Less contrast is available for appreciating the stained ILM which may require longer duration of staining preferably under air. The most crucial step of complete posterior vitreous detachment (PVD) is difficult to achieve due to the presence of vitreoschisis and a posterior vitreous cortex maybe found adherent to the retina. Multiple times of staining with triamcinolone and brilliant blue green dye

maybe required to ensure a complete PVD. Presence of a persistent macular hole with retinal shortening and posterior staphyloma may warrant the need of a macular buckle.[12,13]

MA-Q12. Your preferred tamponade for a persistent macular hole surgery? Do you prefer using gas, silicone oil or heavy silicone oil ?

AG: My preferred tamponade is again gas; I usually do not use silicone oil. Most often I use 25% SF6 and in some cases where I feel the longer tamponade is required I use C3F8.

CMS: C3F8 gas tamponade

HH: I either use SF6 gas or silicone oil. I have no experience with heavy silicone oil. The choice of tamponade depends on how well I achieved my surgical goal in terms of using an adequate hinged ILM flap or put a large free graft inside the hole rather than multiple tiny ILM fragments.

PB: First choice would be C3F8 gas with prone position for 16 hours a day for 2-3 weeks. If patient has to fly may consider 1300 CS oil. I do not think there is any added advantage of heavy silicone oil. I still believe in prone position. And if patient is unable to maintain prone position, I would not go for re-surgery.

MPS: I would use long acting gas such as C3F8. I seldom use silicone oil – in situations with inability of the patient to maintain prone position.

Summary (MA)- Longer acting gas such as C3F8 is the preferred tamponading agent used in re-surgeries for persistent macular holes. However in situations like the patient is unable to maintain a prone position or has to have an air travel in near future then silicone oil maybe considered. Silicone oil tamponade is essential for an autologous retinal transplant surgery. The rationale for the use of heavy silicone oil(Densiron 68) as described in literature is that it may provide an advantage by following the foveal contour and the edge of the posterior retina providing an effective tamponade leading to hole closure.[14]

MA-Q12. What is the duration of the post-operative prone positioning that you recommend after a re-surgery?

AG: I usually recommend 4-5 days post-operative prone positioning.

CMS: 2 weeks

HH: In recurrent macular holes I recommend 5-7 days of prone position.

PB: 16 hours a day for 2-3 weeks.

MPS: A longer acting gas tamponade is usually preferred and I would advise a week of prone positioning, 10 hours / day with a break of 10 minutes every hour.

Summary (MA): There is no uniform consensus on the duration of the post op prone positioning however for the primary surgery it is usually advised for 3-5 days and it is usually longer than this after a repeat surgery for a persistent macular hole.

MA-Q13. What has been the correlation between anatomical and functional outcomes in cases of persistent macular holes?

AG: In a recent report published by our group we have analyzed 25 patients who were operated for persistent macular holes. All cases have undergone re-operation in the form of fluid air exchange with C3F8 gas injection followed by face down positioning for 5-7 days. Based on the size of the macular hole 17 of the 25 eyes had large persistent macular hole. Statistically there was no correlation between the size of macular hole and anatomical closure rate. The mean interval between the primary and the secondary surgery was 4.3 months. Eyes with an interval of less than 3 months had better closure rates when compared to eyes which were operated more than 3 months after the first surgery. 16 of the 25 cases showed closure after 2nd surgery. There was improvement in BCVA after re-surgery in eyes where the macular hole was closed. Eyes which had irregular or rounded edge in the OCT pre-operatively had better closure rates. [15]

CMS: Anatomically fair, but the visual outcome is generally poor.

HH: In many cases it is unpredictable. If you have a type 2 closure then vision is generally poor and function is not regained. However patients with early postoperative type 1 closure of the hole can have significant visual improvement. Generally patients continue to improve for up to 6 months. Patients with delayed reoperations after the failure of the first surgery also have less chance of improvement and this is the reason I recommend early reoperation. Since closure of the hole represents only one factor which is of course crucial for visual improvement, the unpredictability of visual outcome is simply due to the effect of other factors as etiology (traumatic, myopic or idiopathic), condition of RPE, chronicity of the macular hole and the ability to restore outer retinal layers after successful closure which is still beyond our scope of therapeutic options.

PB: If hole is closed, there is a definite improvement in quality of vision. Few patients even experience 2-3 lines improvement. Visual improvement is relatively better following re-surgery, in eyes with reopened MH than with persistent MH. Other factors such as duration, underlying RPE atrophy or scarring, etc. also are important contributors for final visual outcome.

MPS: Persistent macular holes if operated early do have same visual results as primary surgery. Long interval from primary surgery, technique used such as inverse/free ILM flap, iatrogenic macular damage arising from attempts to close the hole may limit visual recovery.

Summary (MA): The anatomical closure of the persistent macular holes maybe achieved by using one of the many techniques described. However the visual outcomes are unpredictable and depend on a number of factors and the most important being the time interval between the primary and the secondary surgery. The earlier the re-surgery the better are the results. The other factors being the status of the underlying RPE, etiology and size of the macular hole etc.[16]

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Panel Discussion: Controversies in Surgical management of optic pit maculopathy

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Optic disc pit is a rare, isolated, unilateral, congenital condition which is asymptomatic per se, but results in a variable visual loss when the pit is situated on the temporal aspect of the optic nerve head.[1,2] The visual loss follows the dissection of fluid from the optic pit into central macula, resulting in splitting of retinal layers (retinoschisis), and macular detachment. The intra- and submacular fluid waxes and wanes initially and finally settles spontaneously; often with concomitant visual loss from outer retinal and pigment epithelial atrophy.[1-3] Treatment is therefore required in most symptomatic cases, though the modalities for treatment are innumerable, reflecting the controversy about the best treatment option.[2] We addressed three eminent vitreoretinal specialists, with considerable clinical and research experience at premier ophthalmic institutes in India, for their opinions on this disputable subject.

1. Given the fluctuating course of maculopathy in optic pit and the young age of presentation, what are your criteria for surgery vis-à-vis:

a. Best-corrected visual acuity at presentation

b. Complaint/documentation of a significant recent decline in vision (about 2 Snellen lines)

c. Age of the patient

d. Clinical features of maculopathy (on OCT, autofluorescence etc.)

Dr. MR Dogra (MRD): Our Criteria for surgery in optic pit maculopathy is significant visual loss or documentation of progressive visual deterioration.

Dr. Mahesh P Shanmugam (MPS): Younger patient with history of recent vision loss and schisis involving the fovea would be an indication for surgery. Patients presenting with squint and poor vision (<6/60) would be relative contraindication for surgery considering possible poor visual outcome.

I would watch a patient presenting with 6/6 vision and / or those with fovea spared schisis until documented vision loss occurs. It need not be 2 Snellen vision loss –any documented vision loss will be an indication for surgery as optic disc maculopathy is associated with poor vision without treatment.

Dr. Jay Chhablani (JC): I usually advise surgery in the range of 20/50 or worse or with recent vision loss. Usually the age group is in mid 30s. OCT indications for surgery are neurosensory detachment or outer lamellar hole or gross schisis extending the whole length.

Dr. Dhananjay Shukla (DS)[Panel summary]: The panelist s are in agreement that a patient with excellent vision (6/6) should be observed. Dr. MPS specifies that ANY definite, documented visual loss (to 6/9, say) qualifies for surgery: this aggressive approach is seconded by two of the largest recent studies, which included patients with 6/6 vision with central scotoma or metamorphopsia.[1-4] Dr. JC points that the maculopathy should correspond to the visual loss: indeed, multilayered macular schisis, submacular fluid and outer lamellar hole are poor prognostic signs and warrant early surgery, even at 6/12-6/9 vision.[1]Similarly hypoautofluorescent signals in fundus autofluorescence (FAF) imaging – a sensitive marker of pigment epithelial (RPE) atrophy, should alert the surgeon to chronicity of maculopathy and need for intervention. However, all macular fluid, even if symptomatic, is not necessarily catastrophic, as pointed out by late presentations of the congenital pits (Dr. JC). A young adult or child with a few schitic changes in the macula (esp. if inner retinal) with good vision (6/12 or better) may be observed on periodic follow-ups with OCT and FAF **(Figure 1A)**; delayed surgery in such a case may not compromise outcomes.[1,2] However, this is a hypothetical situation: most such children are probably not symptomatic and vigilant enough to alert the parents and visit an ophthalmologist in the first place. Poor vision (<6/60) is indeed poor prognostic marker (Dr. MPS) but probably not contraindication to surgery as the most recent and largest

studies testify.[1,2,4,5]

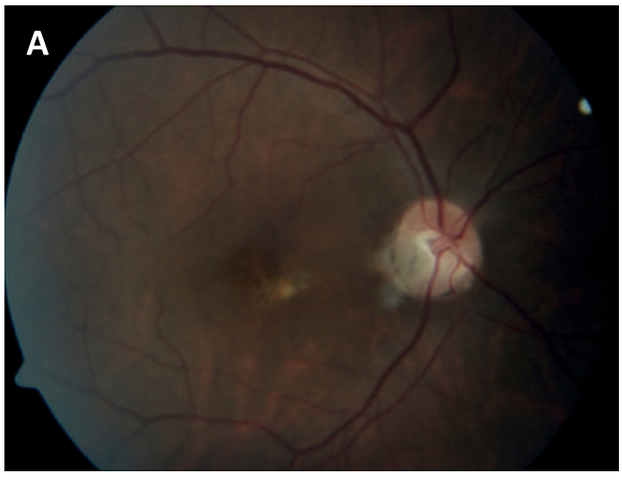
A rare case of bilateral optic disc pits: ***both of which are better left alone***

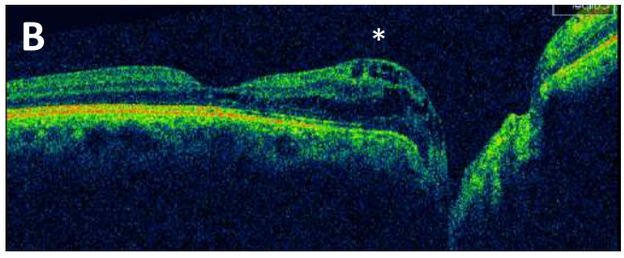
A. The right eye (RE) of this 22-year old man has best-corrected visual acuity (BCVA) of 6/6p. Note the small pit with subretinal precipitates nasal to the fovea, which appears flat clinically.

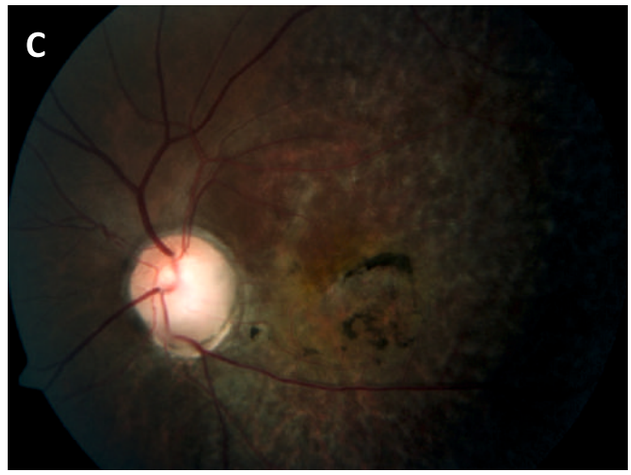
B. OCT RE shows a localized multilayered schisis along the temporal margin of the optic pit (asterisk). The central fovea shows a small cyst with preservation of the outer retinal bands

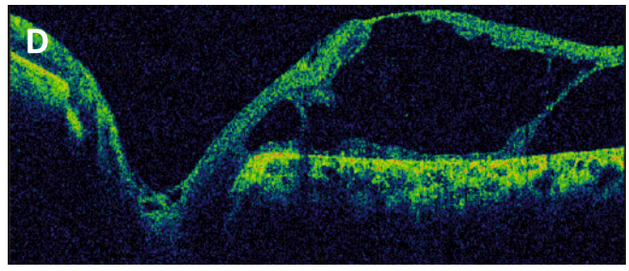
C. Left eye (LE) shows a much worse BCVA of 3/60 with extensive and severe retinal pigment epithelial atrophy, which indicates spontaneously settled macular detachment resulting from a large temporal pit.

D. OCT LE shows hollow schitic cavities with widespread vertical and horizontal destruction of most of the sensory retinal layers, and vertically connecting Muller's cells.









2. Please mention the basic steps (with brief explanation) you feel are critical to surgical success in vitrectomy:

a. Core vitrectomy
b. Removal of the posterior hyaloid attachment
c. Air/gas injection
d. Any other steps you consider essential.

MRD: Critical step in vitrectomy for optic pit maculopathy is meticulous removal of the posterior hyaloid attachment. This step is crucial to close the conduit between optic pit and macular detachment near the optic disc demonstrated on OCT scan passing through this area. Other steps are optional and may likely help in faster resolution of fluid but has no role in primary management of optic pit maculopathy.

MPS: Removal of posterior hyaloid attachment and gas tamponade – the traction exerted by the posterior hyaloid on the retina adjacent to the pit keeps the tract open resulting in schisis detachment. Hence removal of posterior hyaloid is important. I would use triamcinolone repeatedly to identify the vitreous and aid its removal.

JC: PVD induction with complete resolution of the hyaloid is the most important step during the surgery. I look for the membranes (glial tissue) over the disc on OCT scans pre-operatively and ascertain the removal of this membrane during surgery. Complete removal of posterior hyaloid needs to ensured, therefore, ILM peeling become must. While

removing ILM, just ensure that ILM is peeled completely along with thin membrane over the disc. I prefer to give 12% C3F8 tamponade with a week of prone positioning.

Summary (DS): There is panel consensus on the most essential step in vitrectomy for management of optic pit maculopathy: induction of posterior hyaloid detachment, presumably after core vitrectomy. Indeed, there is also consensus in the literature on culpability of vitreous traction on the passage of fluid from the optic pit into macula in spite of continued debate on the source of fluid.[2]Drs. MPS and MRD (see below) recommend intraoperative use of triamcinolone acetonide, more than once if required, to ensure identification and complete removal of posterior cortical vitreous, particularly difficult in small children; as also used in the 2nd largest surgical study on pit maculopathy to date (MACPIT study).[5] Dr. MRD would stop at PVD induction in the primary surgery, and this strategy is supported by the largest, and most recent studies with the longest follow-up.[1,2,4,6]Dr. Jay includes ILM peeling and longstanding gas tamponade in the list of essential procedures. ILM peeling indeed ensures completeness of PVD removal (though triamcinolone use could be a safer alternative),[2] and gas tamponade (both short- & long-term) is seconded by the MACPIT study.[5]The high risk of cataract, especially with prolonged tamponade, is however a deterrent to the use of a long-acting gas.

3. Please mention the additional steps you recommend (routinely/SOS, with explanation):

a. Laser barrage to the isthmus between optic nerve head and macula

b. ILM peeling

c. ILM peeling with foveal sparing

d. Stuffing the pit with ILM

e. Stuffing the pit with scleral plug

f. Stuffing the pit with…any other substance

g. Any other step.

MRD: We have given up Laser barrage to the isthmus between optic nerve head and macula as it leads to more damage and has no rationale. ILM peeling and stuffing is perhaps more damaging in the presence of thin cystic overlying retina. Stuffing optic pit with any tissue lacks rationale as conduit between optic pit and macular detachment is away from pit and would close by apposition of retina achieved by meticulous posterior hyaloid removal.

MPS: I do perform 2 rows of circumferential laser photocoagulation to the margin of the pit with minimal energy, preferably with red laser – this is to further augment the chances of surgical success and decrease recurrence of fluid. ILM peeling though not mandatory can be useful to identify fine epiretinal membranes involving the peripapillary area. I would consider doing a fovea sparing ILM peeling if there is a risk of deroofing the fovea. Stuffing the pit with ILM or other material is reserved for recurrent cases as the maneuver of stuffing can result in damage to the nerve fiber layer. I have used ILM and lens capsule to stuff the pit in recurrent cases.

JC: As I said before, I perform ILM peeling involving fovea along with membrane removal over the disc. Along with I have tried stuffing the pit with ILM and fibrin glue. The results with glue have been very satisfying **(Figure 2A-D)**. Just to be careful that the glue shouldn't be at the macula but just at the disc. The glue can be easily trimmed.

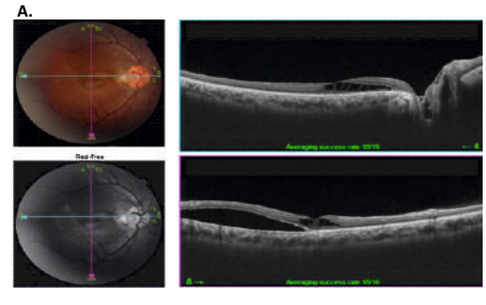
Summary (DS): As expected, the panelists' opinions begin to diverge as soon as adjunctive procedures come into play. Drs. MPS and JC routinely employ laser and ILM peeling respectively during vitrectomy; and stuff the pit with tissue from ILM, lens capsule and fibrin glue, occasionally or during re-surgery. Dr. MRD stays steadfastly at his original stand, irrespective of the circumstances. As already mentioned, for primary surgery there is a consensus in the recent literature on minimal surgery with short tamponade or none at all.[1,2,4-6] And it makes intuitive sense since laser demarcation doesn't affect fluid seepage throughinner retinal layers of the papillomacular bundle between the pit and macula, unless it reaches upwards from RPE and compacts (thus damaging) the inner retina in this zoneof densely packed neural tissue.[2] ILM peeling, though my personal favorite step,[7] may predispose the wafer-thin outer lamellar holes to de-roofing, and should probably be reserved for re-surgery, since most studies appear to fare well without it. The same is apparently true for stuffing the optic pit.[1,2,4-6]

Early surgery for optic pit maculopathy

*Figure 2 courtesy Dr. Jay Chhablani, LVPEI

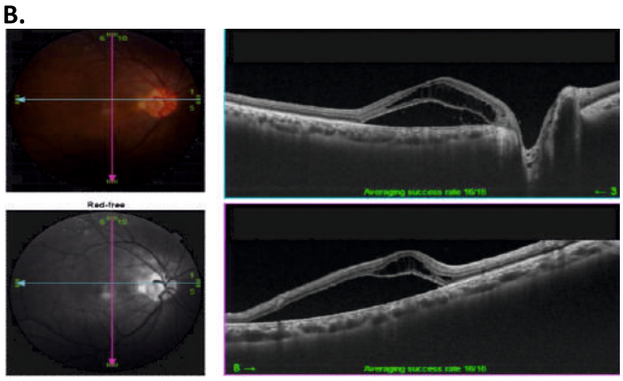
- A. A 27 year-old man presented with a baseline BCVA RE of 6/15 and optic pit with central macular schisis and large serous detachment (SRD) inferiorly
- In view of the SRD, vitrectomy with internal limiting membrane (ILM) peeling and fluid-air exchange was performed; fibrin glue was used at the margin of the pit.

A.



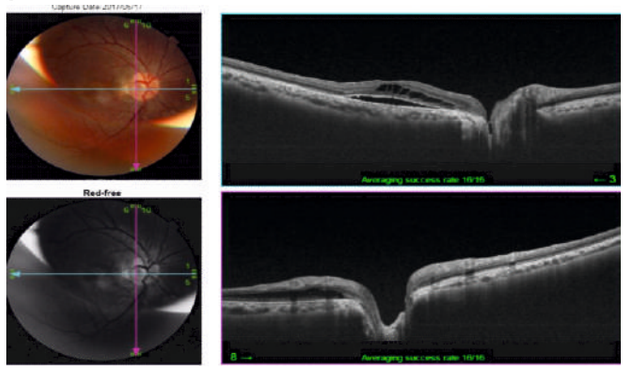
- B. Two weeks after vitrectomy, a slight worsening of the schisis, and extension of the SRD under central macula with a marginal drop in BCVA to 6/18 was observed.

B.



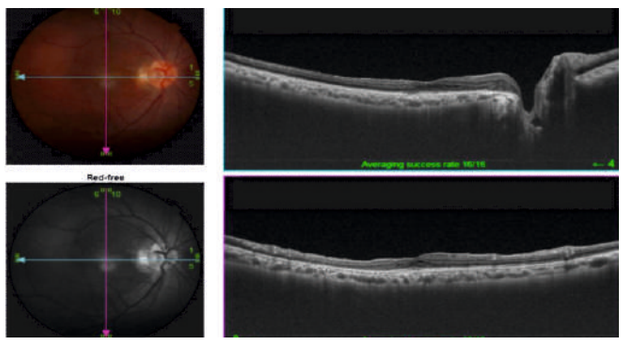
- C. Over the next 4 weeks, BCVA gradually recovered, and then improved to 6/12, with re-settlement of SRD recorded on OCT

C



- D. A year after the surgery, nearly normal foveal contours have been restored with a couple of small non-foveal cystic spaces. BCVA has now improved to 6/9.

D.



4. Have you tried any other surgical alternative in optic pit maculopathy?

a. Only gas injection with laser barrage

b. Posterior scleral buckling

c. Any other surgery.

MRD: At present I am only doing triamcinolone acetonide assisted meticulous posterior hyaloid removal without any air fluid exchange or gas tamponade as primary procedure in these cases. Procedure is short and simple and needs no postoperative positioning. This simple procedure is showing encouraging results which we are in process of publication shortly.

MPS: I have tried only laser photocoagulation without gas injection in cases where the peripapillary subretinal space (separation between the retina and the scleral margin of the optic disc is narrow in height and extent. The inflammatory infiltrate / fibrin resulting from the laser photocoagulation blocks the passage temporarily, ultimately resulting in approximation of the retina to the underlying choroid / sclera at the pit margin.

Trial of conservative treatment is an option in cases where the visual prognosis is in doubt and in apprehensive patients. A failed laser does not result in adverse effects unless the photocoagulation is intense, thereby resulting in visual field defects.

JC: I have done only gas injection with laser barrage but unsatisfactory results. My preferred approach is laser photocoagulation, if no success, then PPV+ILM peeling+glue/ILM graft filling.

Summary (DS): Another can of worms opens with this tricky though essential question. Drs. MPS and JC have both attempted non-surgical (or rather pre-surgical) barrage photocoagulation of the disc margin, alone or with gas: Dr. JC had disappointing results; Dr. MPS' outcomes are not known. They both steadfastly stick to their guns (*firing blanks most probably*); indeed, barrage laser doesn't harm in most cases even if it fails, irrespective of the wavelength used.[2] Their stand receives unexpected support from a recent study which showed remarkably successful outcomes with gas and laser alone, and lack of adverse effect of primary failure on subsequent vitrectomy.[8] I have also tried laser barrage and gas injection (with frustrating results), but now have settled on vitrectomy as the only treatment for optic pit maculopathy (Dr. MRD). Intuitively too, performing a precise barrage with low power, as well as obtaining a large, intact gas bubble and positioning it over pit margin (especially in a child or young adult) appears to be more problematic than a simple vitrectomy.

Not surprisingly, none of us has experience with posterior scleral buckling for optic pit maculopathy. Though Greek authors continue to demonstrate spectacular results over a

decade of follow-up,[9] the surgery remains ***Greek*** to the rest of the world; and most of the vitreous surgeons (yours truly included) loathe stepping out of their comfort zone![1,2]

5. Given that maculopathy continues to improve postoperatively for a year or more:

a. When do you decide to re-operate a case?

b. How do you re-operate (gas injection; re-vitrectomy +adjuvant procedures, etc.)?

MRD: I re-operate if there is recurrence of maculopathy with visual loss. I again look for any residual posterior hyaloid and remove it. This is followed by air fluid exchange. Internal drainage is done through the optic pit or separate small retinotomy created in macular detachment temporally. This is followed by SF6 gas tamponade.

MPS: The OCT gives a good idea about the possibility of subsequent success of the procedure. Partial resolution of the intra or subretinal fluid when compared to the pre-op OCT and closure of the passage are indications of subsequent success. No improvement in fluid / worsening and persistence of the passage would be indication for re-intervention. Significant subfoveal RPE atrophy as seen clinically and on autofluorescence imaging, long-standing disease, elderly patient and a large macular hole would be relative contraindications to resurgery.

JC: The most important aspect in the management of this disease is to understand and explain to the patient is that the recovery of foveal contour and resolution of fluid takes long time, upto 7-8 months. Re-appearance of schitic cavity after complete resolution could be an indication for re-surgery.

Summary (DS): The key issue in re-surgery is to differentiate between recurrence and **delayed resolution** of macular fluid. While the former is a clear indication for repeat intervention, the latter is the norm in the postoperative course of optic pit maculopathy. As Dr. JC points out, the maculopathy may take close to a year to settle. So when progressive flattening of maculopathy is observed, it is prudent to withhold any intervention up to a year after primary vitrectomy

(Figure 2).[1,2,5,6]

How to re-operate is the next issue, which depends partly on the details of the first intervention. If triamcinolone wasn't used to look for more-than-one layers of anomalous PVD, residual vitreous may still be detected by using triamcinolone, and must be removed first (Dr. MRD). If no residual vitreous is found, additional procedures like laser demarcation of the pit (if not done earlier), ILM peeling, plugging the pit, and long-acting gas tamponade are legitimate options (Drs. MPS & JC).[2] ILM removal serves to eliminate the residual tangential traction, ensures complete removal of cortical vitreous and fine epiretinal membranes, should preferably be performed up to the pit margin, and in a fovea-sparing manner if there is risk of secondary macular hole formation (Drs. MPS & JC).

If the above procedures (complete vitreous removal, laser barrage, ILM peeling, plugging the pit) have already been performed during the primary vitrectomy, complete fluid-air exchange and long-acting gas tamponade (silicone oil - normal or heavy - is probably an overkill) with strict prone position for 10-14 days may still benefit some cases, if the RPE is healthy and photoreceptors viable (assessed well by OCT and FAF).

6. When do you decide not to intervene in a case of pit maculopathy?

MRD:I always try surgery foroptic pit maculopathy afterproper counseling. All pros and cons including chances of recurrence are explained in detail.

MPS: Response same as for the previous question.

JC: Early schitic change without any neurosensory detachment with good visual acuity (up to 20/40) can be observed. Presence of gross RPE changes in surrounding area defines poor visual prognosis and can be best left alone.

Summary (DS): As Dr. JC points out, there are two diametrically opposite scenarios for observing a case of optic pit maculopathy: we have already discussed the deferral of surgery on a young patient (*see question 1& discussion above*). A more vexed issue is when to give up further intervention; or when to say NO to surgery first time: a challenge most surgeons are unable to cope with. Drs. JC & MPS refer to a key parameter: Gross RPE atrophy, when clinically evident or on FAF imaging, indicates the inability of RPE to dry up macula, as well as the non-viability of photoreceptors, predicting poor anatomical & functional outcomes **(Figure 1B).** Surrogate prognostic markers include advanced age (reflects on RPE and photoreceptor viability again) and a large macular hole, generally consequent to a de-roofed extensive macular schisis (Dr. MPS). Importantly, the lateral extension of schisis is more important: (Dr. JC) we have reported excellent visual and anatomical outcomes in presence of near-full thickness macular holes in pit maculopathy if the vertical extension was not aggravated by horizontal extension.[7]

To sum up the panel discussion, surgical management of optic pit maculopathy is a multi-layered issue, like the schisis itself. The inclination for surgery has followed a parabolic curve. The initial reluctance of surgeons to step into a precarious situation resulted in laser barrage of the pit and injection of air or gas… later followed by vitrectomy with increasing complexity of adjunct procedures…till the minimally invasive trend of vitrectomy arrived, and shrunk more than merely the size of entry. Today, while there is a reasonable agreement on the need for treatment and the basic surgical modality, there is a dichotomy of opinion on the details like surgical adjuvants and re-surgery. This lack of consensus is not necessarily a cause for worry. Since success rates with the various surgical alternatives are excellent, one has that many more options (including non-surgical ones, to some extent) to choose according to the patient profile, complexity of the case, and the surgeon's comfort level. Consensus also prevails on delaying re-surgery for about a year, if the slow anatomical recovery is carefully monitored. It is also probably high time for the Indian vitreoretinal fraternity to accumulate and report the large collective Indian experience in high-impact international literature, rather than frittering away personal experiences on small-scale media.

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Anti VEGF in ROP: Pros and Cons

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India and other middle-income countries are experiencing the 'third epidemic' of retinopathy of prematurity (ROP). ROP is responsible for blindness in over 50,000 children worldwide. India has over 3.5 million preterm births annually, between 30-54% of those 'at risk' develop ROP of which, approximately 5-15% require treatment.It is estimated that nearly 18,000 infants go blind every year in India from the disease.

Whereas the 'gold standard' for ROP treatment is still laser photoablation delivered by indirect ophthalmoscopy, which has a very high proportion of successful outcome if performed on time and adequately well, intravitreal injections of anti vascular endothelial growth (VEGF) agentsis a relatively newer mode of treatment that has been shown to be useful.

However, like any new treatment, the pros and the cons must be evaluated before it is widely accepted.The hitherto unresolved issues in the use of Anti-VEGF in ROP are:

1) Choice of anti VEGF agent (eg Avastin, Lucentis, EyeLea, Others)
2) Indications for its usage (Type 1 ROP and / or APROP?)
3) Dosing and timing of administration (adult dose, half-adult dose, one-third adult dose, others)
4) Schedule of follow-up (how often and for how long)
5) Detecting and managing recurrences
6) Safety – ocular and systemic (currently, the single most important unresolved issue)
7) Medico-legal aspects (especially its “off-label” use in the light of the recent DGCI ban (and subsequent recall) for Anti VEGF in adults and safety aspects)

This article is not a comprehensive guideline for the use of Anti-VEGF in ROP, but hopes to provide an overview of the current scenario. In the absence of evidence based data and published guidelines, we must tread cautiously in its use in infants.

Anti-VEGF biology:

Bevacizumab is a full-length monoclonal immunoglobulin G (IgG) antibodywhile Ranibizumab is an anti-VEGF-A monoclonal antibody fragment. Aflibercept is a fusion protein comprising of the second and third Ig domain of human VEGFR1 and VEGFR2respectively and the Fc region of a human IgG1. Both ranibizumab and bevacizumab bind to all human VEGF-A isoforms while aflibercept binds with multiple isoforms of human VEGF-A, VEGF-B and placental growth factor.

The physical properties of these agents are relevant in ROP, which is a disease that has a rapid tempo of progression and regression **(Table1).** Hence the drug may 'outlive' its requirement in the vitreous or systemic circulation.

Table 1: **Physical properties, vitreous and systemic half-life of commonly used anti VEGF in ROP.**

Anti VEGF agents	Molecular weight (kDa)	Vitreous half life (days)	Systemic half-life (days)	Geometric mean ratio of systemic exposure (1st dose) (nAMD)	
				C_{max}	C_{min}
Bevacizumab	149	6.7	20	9 fold	310 fold
Ranibizumab	48	9	0.09	1	1
Aflibercept	115	7.13	5-6 (avery)	5 fold	37.3 fold

NAMD: neovascular AMD

How Anti-VEGF is absorbed and transported:

The mechanism of absorption of bevacizumab is unknown. Several mechanisms that have been postulated are: simple passive diffusion, an active transporter/receptor pathway, leakage through the extracellular space or absorptive endocytosis.In infants the retina does not contain tight junctions (TJs) and has 15- to 20-nm-wide intercellular spaces. In addition, intravitreal bevacizumab (IVB) can be transported across their is vascular endothelial and ciliary body non-pigment epithelial TJs into the bloodstream, and through conventional aqueous humor outflow pathways. Finally, in

ROP eyes the endothelial cell gap junction increases. This may allow more drug to pass through the BRB into the bloodstream.

Serum Bevacizumab appears after 2 days of intravitreal injection, peaks at 14 days and persistsuntil 60 days. Wu et al however showed that the IVB group had more significant serum VEGF suppression whereas the serum VEGF levels did not change significantly after IV ranibizumab treatment.Intravitreal Aflibercept (IVA) demonstrated significant reduction in serum levels of VEGF until 12 weeks of administration similar to IVB but the suppression with IVB was greater **(Table 2).**

Table 2:Serum VEGF level at different time intervals post intravitreal injection

Anti VEGF	Baseline VEGF levels (pg/ml)	VEGF levels at 2 weeks(pg/ml)	VEGF levels at 4 weeks(pg/ml)
Bevacizumab	693.70 ± 437.97	34.07 ± 28.15	25.34 ± 15.87
Aflibercept	406.98 ± 90.91	47.42 ± 22.59	71.17 ± 33.56
Ranibizumab	405.0 ± 161.4	395.6 ± 235.3	332.4 ± 207.7

Bevacizumab (Avastin) in ROP:

The BEAT ROP (Bevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity) study:

BEAT ROP was a prospective, randomized, stratified and multicenter trial to assess intravitreal bevacizumab monotherapy for zone I or zone II posterior stage 3+ ROP. It had two arms: infants receiving intravitreal bevacizumab (0.625 mg/0.025 ml) and conventional laser therapy, bilaterally. The primary ocular outcome defined was recurrence of retinopathy of prematurity in one or both eyes requiring retreatment before 54 weeks' postmenstrual age. 150 infants were enrolled (total sample of 300 eyes); 143 infants survived to 54 weeks' postmenstrual age, and the 7 infants who died were not included in the primary outcome analyses. Out of 150 infants,67 infants had zone I disease and 83 zone II posterior disease.

The rate of recurrence for zone I and posterior zone II combined was significantly higher with conventional laser therapy than with intravitreal bevacizumab 26% [19 of 73 infants] vs. 6% [4 of 70 infants]. A significant treatment effect was found for zone I retinopathy of prematurity (P=0.003) but not for zone II disease (P=0.27). The rate of recurrence with zone I disease alone was significantly higher with conventional laser therapy than with intravitreal bevacizumab 42% [14 of 33 infants] vs. 6% [2 of 31 infants]

The rate of recurrence with zone II posterior disease did not differ significantly between the laser-therapy group and the bevacizumab group (12% [5 of 40 infants] and 5% [2 of 39 infants]. After intravitreal bevacizumab therapy retinopathy recurred in four eyes (bilateral in two infants) with macular dragging and retinal detachment in two eyes (bilateral). Retinopathy recurred in nine eyes (one unilateral and four bilateral), with macular dragging in six eyes but no retinal detachment after laser therapy.

Unfortunately, the study did not assess the safety of the drug. For an assessment of mortality at a 5% significance level and with 80% power, a sample of 2800 infants would have been required to determine whether intravitreal bevacizumab, as compared with conventional laser therapy, was associated with a significantly increased death rate. An assessment of local or systemic toxicity would require an even larger sample. However there were more deaths in the IVB group than the laser group in the BEAT-ROP study, but this was not statistically significant.

They concluded that intravitreal bevacizumab monotherapy as compared with laser therapy showed a significant benefit for zone I but not zone II disease in infants with stage 3+ retinopathy of prematurity.

Dose of the intravitreal injection in ROP:

The BEAT ROP study used a dose of 0.625 mg/0.025ml of bevacizumab but no rationale was provided for the same. The neonate's eye is approximately one-third smaller than the adult's eye and the volume of the vitreous is also smaller than calculated, due to the big size of the neonate's lens. Therefore, the size-adjusted dosage of a neonate has been calculated to be 0.4 mg. However, achieving dilution of this dose is a challenge. The outcomes of different doses have been summarized in **Table 3.**

Table 3:Anatomical outcome with different dose of Bevacizumab

Dose of intravitreal bevacizumab	0.625mg	0.250 mg	0.125 mg	0.063 mg	0.031 mg
Study eyes	Study eyes	11	16	24	10
Re-treated for early failure (<4 wks)		0 (0%)	0 (0%)	3 (13%)	0 (0%)
Re-treated for late recurrence of ROP		2 (18%)	4 (25%)	5 (21%)	0 (0%)
Re-treated for persistent avascular retina		3 (27%)	2 (13%)	3 (13%)	3 (30%)
No retreatment required		6 (55%)	10 (63%)	13 (54%)	7 (70%)
Fellow eyes *(injected dose was 1 level higher than the study eye)*	10	16	23	8	
Re-treated for early failure (<4 wks)	0(0%)	0(0%)	3 (13%)	0(0%)	
Re-treated for late recurrence of ROP	2 (20%)	4(25%)	5(22%)	0(0%)	
Re-treated for persistent avascular retina	3(30%)	2 (13%)	3 (13%)	3 (38%)	
Retreatment not required	5 (50%)	10 (63%)	12 (52%)	5 (63%)	

Adapted from: Wallace DK, Dean TW, Hartnett ME et al. A Dosing Study of Bevacizumab for Retinopathy of Prematurity: Late Recurrences and Additional Treatments. Ophthalmology. 2018

Technique of injection:

The problems encountered during intravitreal injection in preterm infantsare due to short axial length, thicker crystalline lens, anterior location of ciliary body and underdeveloped

pars plana. These predispose the infant to iatrogenic anterior retinal tears. The use of the standard long needle that is "half inch"may lead to contralateral retinal tears. Lens touch is a known complication. The underdeveloped immunity and the associated comorbidities in preterm infants predispose them to endophthalmitis.

Gauge of the needle:

In BEAT ROP trial 5/16th inch (7.93 mm),31-gauge needle was used while the RAINBOW study used 1/2 inch (12.7 mm) 30-gauge needle. Wright et al reported in a histopathological analysis that when a standard 30g 1/2 inch (12.7 mm) needle was fully introduced in vitreous cavity, damage may be caused to the posterior pole in the infant eye. A 4 mm 32 G needle seemed to avoid these complications while effectively depositing the drug in the vitreous cavity.

The steps of intravitreal injection are as follows:

1. Anaesthesia: Choice of sedation depends on the treating ophthalmologist; while some prefer topical anaesthesia, othersuse sedation or even general anesthesia.
2. Instil betadine 5% in the conjunctival sac
3. Use a self-retaining infant speculum
4. Distance - 1.0 mm to 1.5 mm from temporal corneoscleralimbus (note that the BEAT ROP study reported 2.5 mm, which is likely to damage the retina)
5. While injecting the needle the tip should be kept parallel to the visual axis to avoid inadvertent injury to either the lens or the posterior retina. A stabilizing instrument should be used if the procedure is performed using topical anaesthesia to avoid injury due to sudden head movements. Care should be taken not to insert the needle till hub in case a 30 G is used
6. Instil topical antibiotic at the end of procedure

Recurrence after anti –VEGF:

Understanding recurrences in the BEAT ROP study:

Moshfeghi has elegantly argued that the increased recurrences in the laser arm compared to the injection arm in the BEAT-ROP study may have been wrongly interpreted. The final end point for assessment in the BEAT ROP study used was 54 weeks PMA for recurrence. The age of treatment was significantly different (34.5 $\pm$1.4) in the bevacizumab group when compared to (33.7$\pm$1.6 weeks) in laser group respectively. Assuming a normal distribution, if one standard deviation above the mean is taken for bevacizumab group, the infants could have been treated at 35.9 weeks and not recurred till 27.8 weeks after treatment- that is 63.7 weeks PMA. This is 13.7 weeks after the primary end point of 54 weeks. Similarly, for 2 SD, the recurrence would not have occurred until 72.3 weeks PMA that is 18.3 weeks after primary outcome. This highlights that approximately 47.7% (2 SD) recurrences would have been missed in the bevacizumab arm. For zone 1 ROP, there was a significant difference between recurrence of retinopathy, 14 of 33 infants in the bevacizumab compared to 2 of 31 infants in the laser therapy group (p=0.003). In laser group if one SD is taken into account the treatment would have been at 35.3 weeks and would not have occurred till 13.1 weeks which is 48.4 weeks of PMA which is well within primary outcome. Thus the number of late recurrence in intravitreal arm would have been greater than what was reported.

Diagnosing a recurrence:

Recurrences are characterised by recurrence of plus disease and/or neovascularizationat both the initial ridge or new extraretinal proliferation at the advancing edge. APROP recurrences are seen more commonly at the advancing edge. The other characteristic of recurrence is decreased extent of retinal vascularization. These vessels can be mistaken as hemorrhage and thus difficult to identify. The broader vitreoretinal adhesions between both anterior and posterior ridges along with altered adhesion strength at the vitreoretinal interface leads to retinal detachment.

Timing of recurrence:

The period of recurrence of ROP after bevacizumab may be delayed with a critical 10-week recurrence window ranging from 45 to 55 weeks, adjusted age (AA), with a mean of 51.2 weeks AA. Sometimes, the recurrence can be as late as 65 weeks AA. In contrast, ranibizumab reactivation may be earlier at a mean of 5.9 weeks. **Table 4** summarises various studies with respect to the age at recurrence and rate of recurrence with anti VEGF. Increased risk of recurrencesare seen in APROP, infants with increased duration of hospital stay and decreased birth weight. Infants with APROP were found to have a 5-fold increased risk of recurrent disease developing when compared to infants with stage 3 plus ROP.

Table 4: Summary of studies with rate and age of recurrence with anti VEGF

Authors	Type of ROP	Sample size	PMA at treatment (weeks)	PMA at Recurrence	Recurrence Rate	Subsequent treatment
Castellanoset *al*	Type 1 ROP	6 eyes of 3 infants (IVR)	33-42		0%	
Chen *et al.*	Type 1 ROP	31 eyes of 16 infants (IVR)	36.4		0%	Laser
		41 eyes of 21 infants(IVB)	36.8	41.6		
Wong et al	Zone 1 or posterior Zone2 disease	6 eyes of 4 infants (IVR)	35.7		83%	Laser
		4 eyes of 2 infants (IVB)	32.4		0%	
Erol et al	Type 1 ROP	15 eyes of 8 infants (IVR)	34.4 ± 1.8	41 ± 3	40%	Laser
		21 eyes of 12 infants (IVB)	35.3± 1.7	50	10%	
Tandon et al	APROP	28 eyes of 14 infants (IVB)	33.5±2.3	35.0±2.8	6.80%	Laser
	ROP in zone 1 and 2 posterior with plus disease	30 eyes of 15 infants (IVB)	36.3±1.7		0%	
Mintz-Hittner et al	Stage 3+ zone 1: 41 infants Stage 3+ zone 2: 181 infants APROP: 19 infants	471 eyes of 241 infants	35.9±2.6	51.2±4.6	7.20%	Repeat intravitreal bevacizumab
Chan et al	Type 1 ROP: APROP 4 eyes of 2 infants, Poor pupillary dilatation and persistent iris vessels 5 eyes of 3 infants	10eyes of 6 infants (IVR)	36.2±1.9	44weeks 2 days	60%	Laser, surgery

Advantages of intravitreal anti VEGF injection:

Some of the potential advantages of intravitreal anti VEGF are:

Refractive Error:

A few studies **(Table 5)** suggest that the refractive error (i.e. myopia) is lower in injected eyes compared to laser treated eyes. However, long-term refractive changes, axial length changes and lenticular contribution to refractive error have not been assessed.

Table 5: Refractive outcome in various treatment modalities

Authors	Number of eyes	GA	Mean SE±SD (D), anti-VEGF	Mean SE±SD (D), laser±anti VEGF	P value
Harder et al	IVB: 23eyes (12 infants)	25.2±1.6	***-1.04+4.24***	-4.41+5.50	***0.02***
	Laser: 26 eyes (13 infants)	25.3±1.8			
Chen et al	IVB	26.6 ±1.7	-0.98 ± 4.05	−2.40 ± 3.13	***<0.001***
	IVB+Laser	24.7± 2.2			
Hwang et al	IVB	24.2±1.0	Zone 1: -4.3±3.4	-11.2±11.0	0.09
	Laser	24.8 ± 1.2	Zone 2: 0.3±2.0	-5.5±4.6	***0.004***
Kuo et al	IVB	27.33±2.94	−1.67 ± 1.69	−1.73 ± 1.29	>0.05
	Laser	27.43±2.93			
Lee et al	IVB	26.6 ±1.6	0.2±4.4	Laser : -2.0 6 4.0	***<0.001***
	Laser	26.6 ±2.5		IVB+Laser: -1.5 6	
	IVB+Laser	24.8±1.9		3.2	
Chen et al	IVB	27.06 ± 2.43	−0.65 ± 3.83		0.19
	IVR	26.54 ± 2.28	−0.12 ± 1.12		
Lin et al	IVB	26.50±2.14	3.26		0.35
	IVR	26.15±2.08	0.46+1.36		

Complete vascularisation post treatment in ROP:

Leporeobserved that in laser treated eyes the overall risk of abnormal angiogenesis is lower in the ablated retina compared to eyes treated with anti-VEGF since there are large avascular areas with abnormal arteriolar branching indicating continued abnormal angiogenesis. Whereas it is widely agreed that like peripheral ischemic retinopathies like FEVR, ROP treated with anti-VEGF would also require peripheral laser ablation, there is no consensus at this time on 'when' to laser. If possible, angiography must be performed to determine the extent of the peripheral avascular retina along with the location of the leading and active edge that would 'leak' on angiography to aid the boundary for laser therapy.

Macular and Foveal development:

Vogel et al observed that bevacizumab treated eyes were associated with more rapid outer retinal thickening whereas earlier inner retinal layer extrusion and delayed EZ development was associated more with laser treated eyes. Foveal depression was found to be absent in 63.6% of the IVB-treated eyes compared to 91.7% of laser- treated eyes. However long term foveal photoreceptor remodelling, abnormal foveal avascular zones, superficial and deep capillary plexus changes (on OCT-angiography) in IVB eyes suggest that these subclinical changes require future consideration.

Complications:

Systemic complications:

VEGF is responsible for angiogenesis elsewhere in the body especially in a developing neonate. In the nervous system, it acts as anangiogenic and neurotrophic agent which has gliotrophic properties and promotes neuronal, neurite, and neuroprotection functions. It also maintains the blood brain barrier.

Lien et al reported asignificant mental and psychomotor impairment at 24 months in 'IVB with laser' group compared to 'laser alone' group. Similarly, the odds ratio of developing severe psychomotor defect was 5.3 times when compared to the laser group. There were increased odds of developing low mental development index in IVB with laser or IVB alone when compared to laser although not statistically significant. Morin et al reported increased odds of developing severe neurodevelopmental disabilities in infants treated with IVB when compared to laser alone. Another study by Castellanos et al however, reported no neurodevelopmental impact after 5 years.

Lung alveolarisation has been shown to be regulated by VEGF. Broncho-pulmonary dysplasia (BPD) has been reported in cases where there has been disruption in the angiogenesis signalling. Upto37.5 % of babies in the IVB group have required intubation, compared to a fewer in the laser group.

Ocular Complications:

Bilateral choroidal rupture, cilio choroidal ischemia, hypotony, exudative detachment and endophthalmitis have been reported after IVB therapy.

VRSI Guidelines and anti- VEGF for ROP:

The VRSI has laid down guidelines for 'off label' use of intravitreal bevacizumab in adults. . The guidelines encompass procurement and storage of bevacizumab, fractionation of bevacizumab and guidelines for intravitreal injection. The updated guidelines on intravitreal injection technique and monitoring have been proposed based on a review of existing literature and an expert panel discussions. It is of critical importance to note the VRSI society does not currently 'officially endorse' the use of Anti-VEGF in ROP or in infants.

After the ban on anti-VEGF use (in adults) was revoked, there is still considerable uncertainty on the legal stand of the use of these agents in infants. A recent Indian ROP Society (iROP) survey (unpublished data) showed that several centers have stopped treating both eyes on the same day, some have stopped bevacizumab altogether and use only ranibizumab and others have stopped all anti-VEGFagents for ROP. There are some centres however, that use anti-VEGF agents as the first line for monotherapy for all treatment requiring ROP. In the absence of guidelines, we are exposing ourselves to possible medicolegal scrutiny.

With long term studies including the RAINBOW (Novartis sponsored trial for Ranibizumab in ROP) is still awaited, we must use this drug cautiously. Whereas it has significant utility in zone 1 or posterior zone 1 ('zone half' cases) APROP, its indiscriminate use must be avoided at all cost.

A special consent, long-term follow-up for ocular and systemic outcomes, early identification and laser therapy for recurrences or persistent avascularity of the peripheral retina and long term vision, refraction and neurodevelopmental assessment must form the cornerstone of anti-VEGF management in ROP until we have evidence based guidelines.

A suggested guideline for anti-VEGF in ROP is summarized below that may be practical in the Indian scenario:

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- Workshops on Retinal procedures
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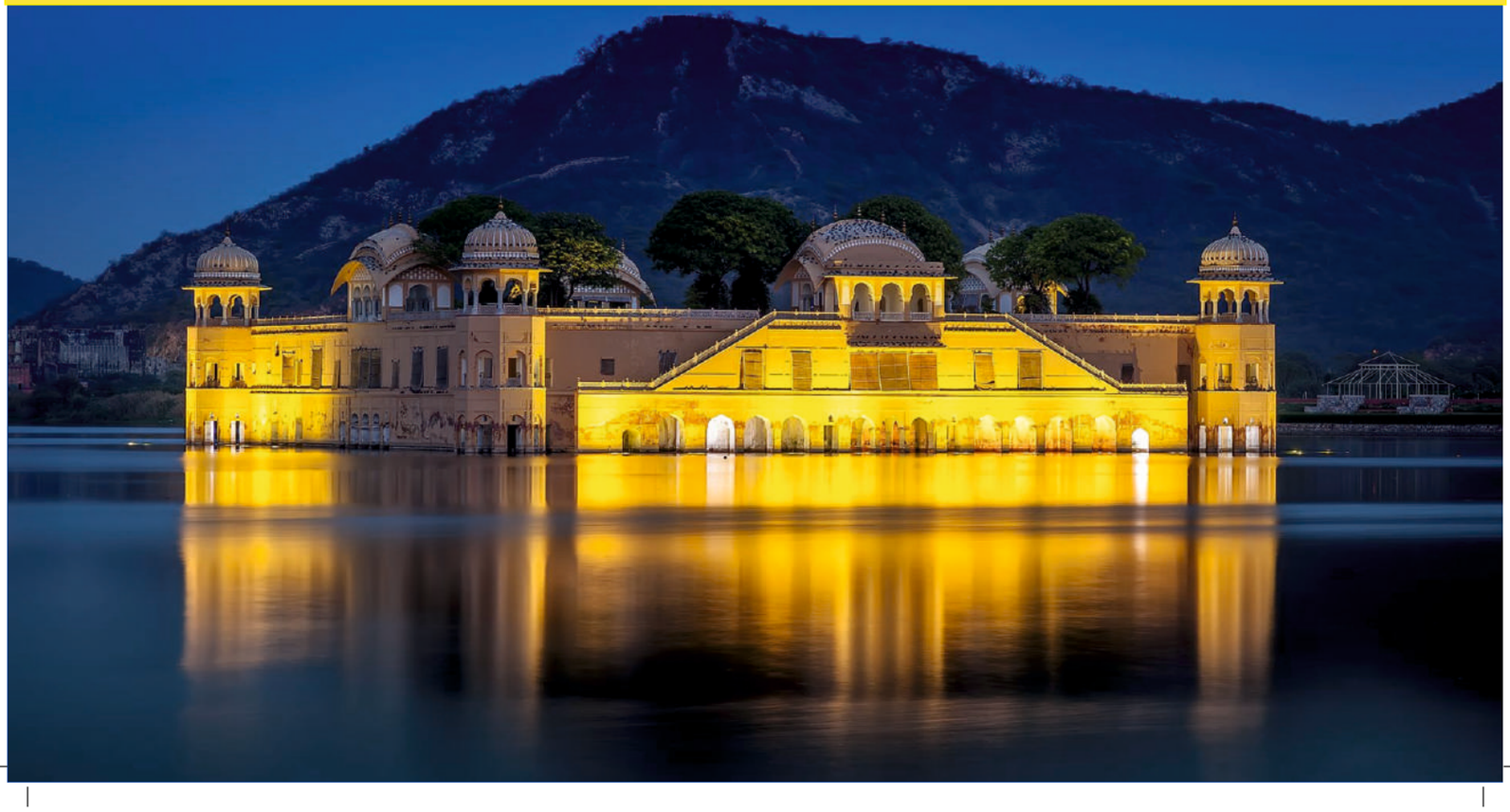

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OCT ANGIOGRAPHY: Ornament or Armament?

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Imaging in the field of retina has witnessed a sharp development in the last few decades with the advent of optical coherence tomography (OCT) which has enabled retina specialists to make a detailed anatomical evaluation of retina in a non-invasive manner[1].The next area of interest was development of means to non-invasively study the vasculature and blood flow of retina. The available non-invasive techniques like ultrasound , blue field entoptoscopy, and laser Doppler velocimetry had restricted use because of poor reproducibility, difficulty of application and large variation in parameters of blood flow among human beings.[2,3] A major landmark was achieved in 2013 when OCT angiography (OCTA) establisheditself as promising non-invasive tool for evaluating vascular details of retina. Although the initial period fetched criticism for OCTA on account of multiple imaging artefacts, rectifications in algorithms were soon brought about which overcame the initial limitations. As of today, OCTA has definitely established its role in certain specific diagnoses where the insights offered by it cannot be matched by any other imaging modality.

Basics, Principles and Artefacts

OCTA effects a mapping of the blood flow of the retina and choroid by performing serial B scan OCT images of the same cross-sectional area. It then detects the difference of the back-scattered signal intensities to deduce the movements of erythrocytes in blood vessels. The decorrelation of signal amplitude from the repeated consecutive B-Scans provides a contrast between the static and non-static tissues, thus enabling 3-dimensional visualisation of the retinal and choroidal vasculature. [4-8] The scanning speed of OCT machines hence directly correlates to the quality of imaging in OCTA. The newer generation of OCT machines, including the swept source OCTs with high scanning speeds of up to 1,00,000 scans per second, have provided a strong platform for further advances in the field of OCTA in the times to come.

A distinct advantage afforded by OCTA is its ability to provide en face visualisation of vessels in different layers of retina by providing segmentation of the layers of interest. This sole feature bestows a distinct advantage over the conventional angiography techniques by proving vascular details of retina, layer by layer, enabling identification of isolated abnormalities in individual vascular plexuses of retina. (**Figure 1)** When compared to fluorescein angiography (FA) and indocyanine green (ICG) angiography, the test is non-invasive and hence safer, quicker, less cumbersome and much easier to perform. It lacks the potential perils of using a dye,that range from minor problems like nausea to issues as severe as anaphylaxis. The limitations of the present models of the machine, and OCT Angiography today, however, include a smaller field of view, higher artefacts and inability of the machine to detect leakage from vesselsas well as poor delineation of lesions with low flow such as microaneurysms,fibrovascularchoroidal neovascular membranes (CNVM).

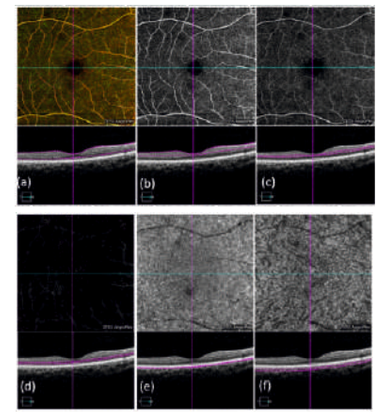

Figure 1: The Normal OCTA - A 6 x 6 mm OCT Angiogram and corresponding B scan images with segmentation of normal fundus of a 45 years old maleon Carl Zeiss Meditec CIRRUS™ HD-OCTshowing (a) Depth coded full thickness angiogram (b) OCT Angiogram of superficial inner retina(c)OCTA of deep inner retina (d)OCTAof outer retina showing absence of vasculature with some projection artefact from the vasculature of superficial layers(e) OCTA of choriocapillaris (f) OCTA of choroidal vasculature

The initial days of OCTA did witness multiple disturbing artefacts due to eye movements, eye blinking and also due to projection of the vasculature of superficial layers onto the deeper layers resulting in interpretational errors.Any eye movement was interpreted by the machine as a decorrelation

and depicted as a white line while any blink was interpreted as no movement and depicted as a black line. Motion artefact correction was soon introduced to counter artefacts resulting from eye movements using the eye tracking system and orthogonal registration which did improve the image acquisition drastically, but also resulted in a few new artefacts like doubling of the retinal vessels, stretching defects and crisscross defects. These, however, were less of an issue compared to motion artefacts.**(Figure 2)** Projection artefacts have to some extent been dealt with by improved segmentation and software updates like the slab subtraction method and Projection Artefact Removal (PAR). [9]

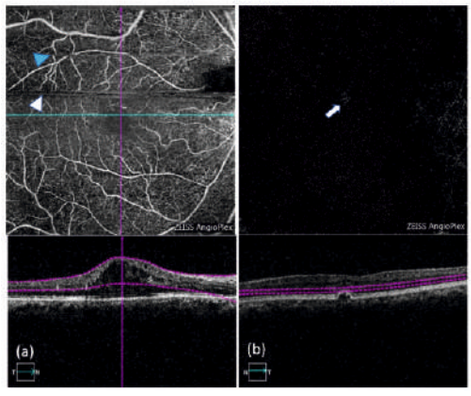

Figure 2: ARTEFACTS - OCT Angiogram and corresponding B scan images with segmentation of two common artefacts on Carl Zeiss Meditec CIRRUS™ HD-OCT (a) OCTA of superficial inner retina showing motion artefact (blue arrow head) due to eye motion and black line defect (white arrow head) due to blinking (b) OCTA of outer retina showing projection artefact over the area of PED giving a false impression of presence of vasculature in the layer.

As far as the field of view is concerned, the en face acquisition areas range from 2x2 mm to 12 x 12 mm in different machines available but the number of B scans per second remains the same in all these slabs. The quality of the images thus is highest with the smallest acquisition area and decreases as the acquisition area increases. The future looks promising with Carl Zeiss, Inc (Carl Zeiss Meditec, Dublin, CA) developing an automatic wide-field montage software, which will employ motion tracking to track the eyes and fusemultiple images acquired together into a wide-field montage OCTA image. [10]

An important fact to be remembered is that various commercially available machines for OCTA differ significantly in the algorithm, scanning speed, signal spectrum, wavelength, axial resolutionand method of motion artefact correction used (table 1) and hence the images acquired from different machines are not exactly identical. [11]

	SSADA(Optovue)	OMAG(Zeiss)	OCTARA(Topcon)
Algorithm	Intensity/amplitude variance	Amplitude+Phase variance	Amplitude de-correlation
Motion artefact correction	Orthogonal registration	Eye tracking system(FastTac)	Orthogonal registration
Signal spectrum	Split spectrum	Full spectrum signal	Full spectrum signal
Axial resolution	Compromised	Intact	intact
Scanning speed	70,000 A-scan/sec	68,000 A-scan/sec	100,000 A-scan/sec
Wavelength	840	840	1050

Table 1 Comparison of various parameters used by the three well established OCTA machines

OCTA, normal retina and the vascular plexuses

One of the most appreciated features of OCTA, today, is its excellent ability to enable En Face visualisation of vascular plexuses of retina individually. This includes the superficial and deep capillary plexuses noted everywhere along with the additional intermediate or middle capillary plexus at macula and the peripapillary capillary plexus near disc. Furthermore, the imaging system also provides distinct images of the choriocapillaris as well as the choroidal vasculature. Although Park et al [12] have documented the middle capillary plexus at macula which is qualitatively and functionally distinct from the superficial and deep capillary plexus, it has not yet been widely adopted. All the commercially available machines provide automatic segmentation only for the superficial, deep vascular plexuses and the choriocapillaris. Each of the available machines differ slightly from each other in the level of automatic segmentation for visualising these plexuses accounting for minor differences in the images from different machines. The segmentations can also be changed by the user while analysing the images. [13,14]

OCTA and Dry Age Related Macular Degeneration (ARMD)

The ability of OCTA to detect early signs of neovascular changes in cases with dry ARMD non-invasivelyand promptly. [4] This enables imaging on more frequent intervals, there by increasing the chances of early detection of choroidal neovascular membrane whenever it is formed. An important fact to be remembered is thatdrusens in dry ARMD cause projection artefact immediately above them by strongly reflecting the refracted waves giving a false impression of presence of vascularisation above them. The same also results in decreased signals from choriocapillaris immediately below the drusens. [9]The same holds true in the presence of pigment epithelial detachment and caution needs to be

exercised whenever an interpretation of choroidal neovascular membrane (CNVM) is made in the presence of PED or drusens solely on the basis of OCTA. The question of whether the loss of choriocapillaris signal below the drusen also represents decreased flow or is completely due to shadowing from the contents of drusen remains to be answered and would need further elaborate studies.**(Figure 3)** Geographic atrophy on OCTA shows extensive areas of choriocapillaris loss which often extends beyond the margins of the atrophy suggesting propensity of progression. Serial OCTA in patients with dry ARMD does help detecting changes in the vasculature and early CNVM formation in these patients.

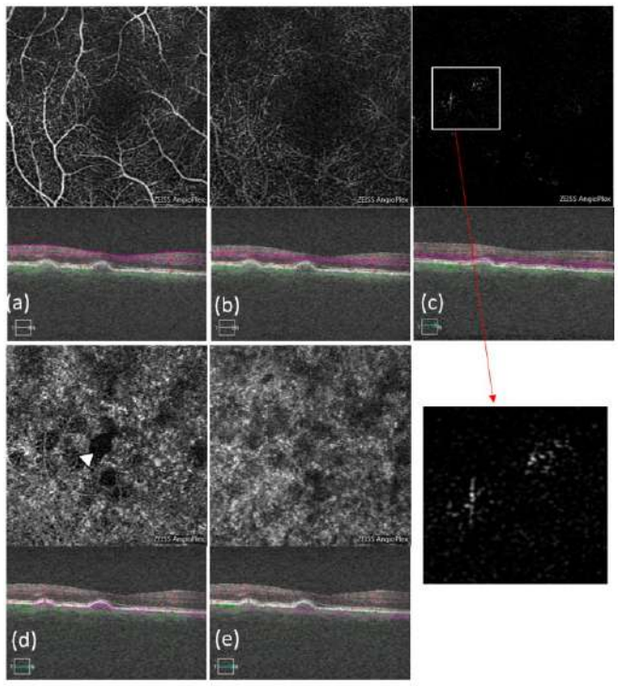

Figure 3: DRY ARMD - OCT Angiogram of a 60 year old male with Dry ARMD. OCTA of superficial inner retina(a) and deep inner retina (b) are normal. OCT Angiogram of outer retina (c) shows absence of vasculature except for areas overlying the drusens which show projection artefacts from the vasculature of superficial layers (magnified view in inset) (e) OCT Angiogram of choriocapillaris shows areas of shadowing defects below the drusens resulting in a false negative flow pattern (f) OCTA Angiogram of choroidal vasculature showing less severe false negative flow pattern below the drusens.

OCTA and Wet ARMD

OCTA has slowly established its role in the management of Wet ARMD by elegantly delineating CNVMs as networks of abnormal vessels noted in the layer of choriocapillaris and in the outer retina. **(Figure 4)** Although the sensitivity and specificity of OCTA is definitely less than that of fluorescein angiography in explicitly delineating a CNVM, onesignificant advantage of OCTA, borne from enface visualisation, is its ability to better distinguish type 1 and type 2 CNVM. The ability to detect CNVMs, though, gets compromised in the presence of haemorrhage as well as when the flow through the CNVM is less due to predominant scarring and fibrosis. In a comparative study of OCTA with FA in detecting CNVMs in 48 eyes, a sensitivity of 50 percent and a specificity of 91 percent indetecting CNVMs was noted, attributing a small sample size as well as large amount of haemorrhages in few cases as the underlying cause for limited detection by OCTA. [15] Nevertheless, the non-invasive nature of the investigation as well as its ease of performance and repeatability do favour its increasing use in the near future for diagnosis as well as monitoring of CNVMs secondary to wet ARMD as well as other causes.

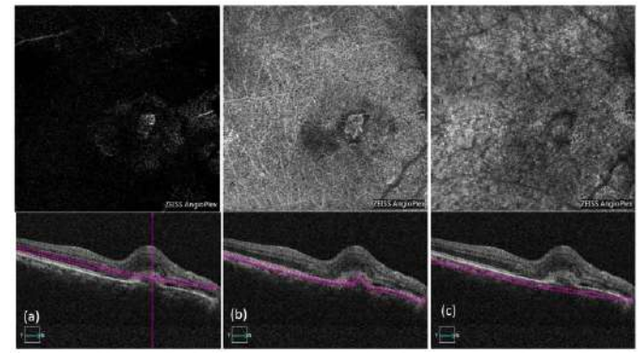

Figure 4:WET ARMD –OCT Angiogram of a 62 year old male with a CNVM. OCTA of outer retina (a) shows thepresence of abnormal network of vasculature clearly delineating the CNVM. OCTA of choriocapillaris (b) andchoroidal vasculature (c) shows the extent and severity of the lesion.

OCTA and Diabetic Retinopathy

OCTA has been extensively evaluated in various studies for its potential role in proving markers to predict the progression of diabetic retinopathy in various stages of the disease. It helps visualise microaneurysms, foveal avascular zone, neovascularisations, retinal vessel density and non-perfusion areas in the posterior retina thereby providing insights into the stage and extent of retinopathy.

OCTA has helped localise microaneurysms and studies have shown that a greater number of microaneurysms are located in the deep vascular plexus compared to the superficial capillary plexus.[16,17] Also, some lesions like small neovascularisation tufts or areas of focal leaks which are seen as hyperfluorescent dots on FA and interpreted as microaneurysms can be better differentiated on OCTA. **(Figure 5)** On the other hand, OCTA may miss microaneurysms when they undergo recanalization and sclerosis as they would then become low flow lesions making it barely detectable. Fluorescein angiography and OCTA are thus complementary to each other in evaluating the extent and distribution of microaneurysms.

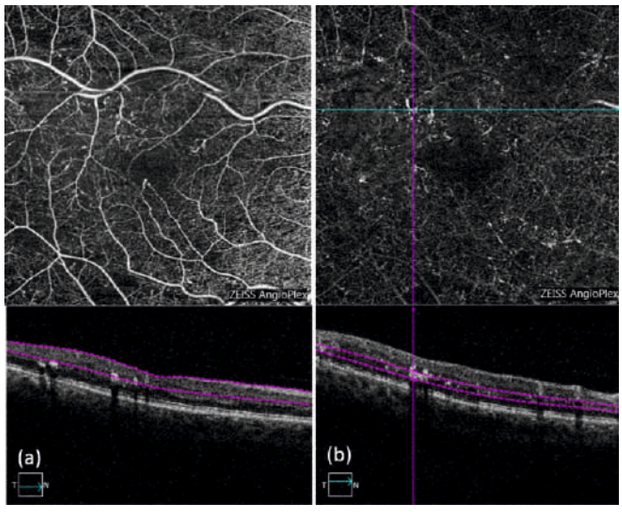

Figure 5:MODERATE NPDR –OCT Angiogram of a 52 year old lady with moderate NPDR (a) OCTA of superficial inner retina shows the presence of microaneurysms scattered in the posterior pole and near the edge of FAZ (c) OCTA of deep inner retina shows the presence of microaneurysms as well as some projection artefacts due to the presence of hard exudates.

Enlargement of the Foveal avascular zone (FAZ) has been found in almost all studies on diabetic retinopathy. [18 – 22] However, a clear correlation between this enlargement of FAZ and visual acuity has not been found in the recent studies. [23,24]. OCTA has proved to be an excellent tool to track changing FAZ areas. Progressive enlargement of FAZ represents advancement of the disease with degradation of capillaries.

Vessel density of both SCP as well as DCP has been found to reduce continually in patients with diabetic retinopathy and hence serial measurement of the same is another useful tool in monitoring the severity and progression of the disease. [18,19,25,26] Projection artefact from the SCP into the DCP was a problem in the past but with software updates, characterisation of DCP is now possible without significant artefacts from SCP.

Neovascularisation in diabetic retinopathy is, unquestionably, best detected by FA due to the characteristic leak seen. Inability of OCTA to detect leakage is a big limitation, compared to OCTA when dealing with patients of proliferative diabetic retinopathy (PDR). However, the structural details of the neovascularisation are better delineated on OCTA compared to FA due to the lack of leakage. In the present era, when intravitreal pharmacotherapy is being looked at as an alternative to pan retinal photocoagulation (PRP) for PDR, OCTA may have a major role in monitoring the size of the neovascularisation following every intravitreal injection. OCTA can also be used toevaluate and monitor the extent of capillary non-perfusion areas in the various layers of the posterior retina. [16,17, 25]**(Figure 6)**

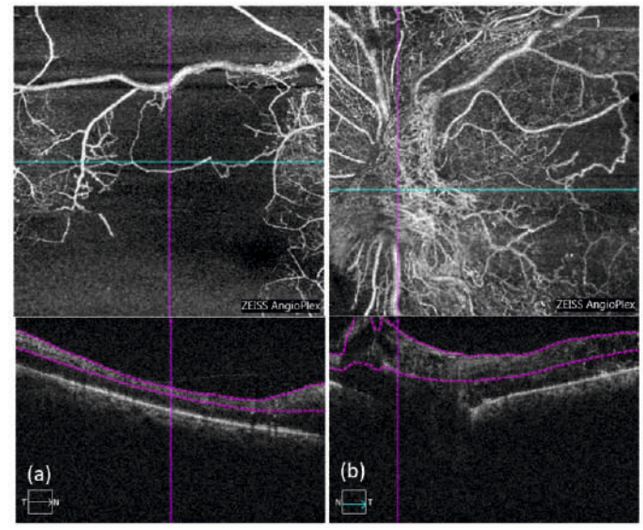

Figure 6:PDR –OCT Angiogram of a 66 year old male with PDR. (a) OCTA of superficial inner retina shows the extensive area of capillary dropout and non-perfusion (b) OCTA of deep inner retina shows the presence of severe neovascularisation of the disc.

The role of OCTA in diabetic macular edema (DME) is hampered by the inability of OCTA to detect leakage. Studies have shown that the mean vessel density on OCTA is lower in patients with DME compared to patients without DME [19,26]. The extent of associated ischaemia in patients with DME can be evaluated with OCTA.

OCTA and Paracentral Acute Middle Maculopathy (PAMM)

In recent years, a new entity Paracentral Acute Middle Maculopathy or PAMM was described, where isolated ischaemia occurs in the intermediate and deep capillary plexus of retina, with the appearance of characteristic hyperreflective bands in the middle layers of retina on OCT.[27] These hyperreflective bands on OCT were thus found to actually represent ischaemia. [28] It can occur as an isolated event in otherwise healthy individuals or in association with vascular disorders like central retinal vein occlusion and central retinal artery occlusions. It can also be associated with systemic co-morbidities. [29]The OCTA typically depicts diffuse patchy attenuation and pruning of the DCP in these cases compared to a relatively normal or a mild attenuation in SCP. **(Figure 7)** [27] PAMM eventually results in thinning of the inner nuclear layer (INL) and a permanent compromise in the quality of vision in the eye. OCTA has thus been a useful tool in the recognition of this entity and give the underlying explanation for vision loss in these patients.

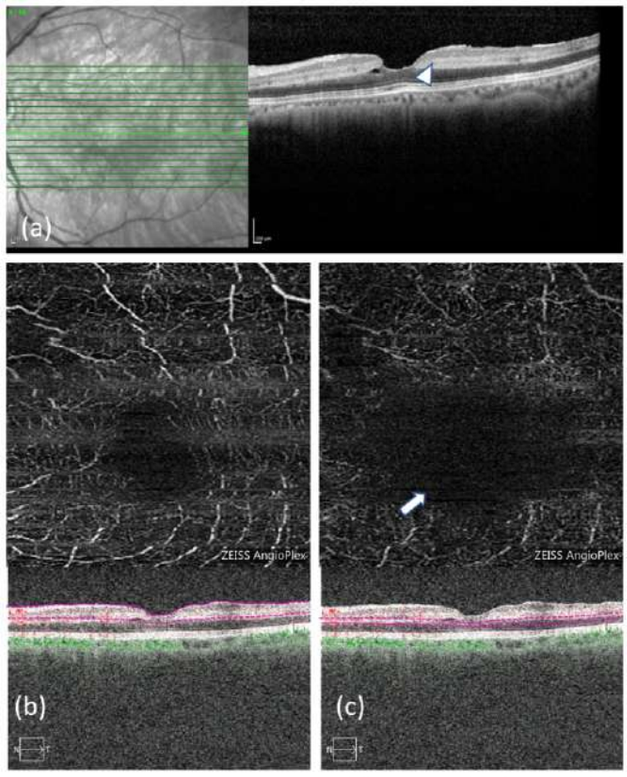

Figure 7: PAMM - OCT Angiogram on Heidelberg Spectralis of a 68 yearlady with PAMM (a) SD OCT done showing hyperreflective band in the middle layer of retina. (b &c) 6 x 6 mm OCTA and corresponding B scan images with segmentation of the same patient on Carl Zeiss Meditec CIRRUS™ (b) OCTA of superficial inner retina shows the presence of mild attenuation of the vessels of superficial capillary plexus (c) OCTA of deep inner retina shows the presence of diffuse patchy attenuation and pruning of the DCP.

OCTA and Macular Telangiectasia (MacTel)

Macular telangiectasia is characterised by the presence of capillary abnormalities around fovea.[30—34]FA has been the gold standard for diagnosing MacTel by highlighting the telangiectatic vessels showing diffuse hyper fluorescence in the late phase. A major limitation of FA has been its inability to show the fine details of capillary changes which are masked by the diffuse hyperfluorescence. Also, FA fails to give the details of vascular changes in the deeper layers of retina. These issues have been well addressed by OCTA and is a useful tool for detailed evaluation of the vascular changes in different layers of retina during the various stages of the disease.**(Figure 8)** The early stages of MacTel 2 show telangiectatic vessels with increased intervascular spaces, abnormal vascular anastomosisand the patchy loss of capillary network in the SCP and DCP that begin temporally and progress with advanced stages of the disease[35,36] Later stages also show brush-like localised branching of vessels with right-angled dipping around areas of RPE hyperplasia in the SCP and DCP. Advanced stage of the disease (stage V) with scarred CNVM reveals dense vascular network corresponding to the areas of scar along with the presence of complete distortion of foveal avascular zone, gross capillary rarefaction and dilated vessels that can be traced through different layers of retina with abnormal anastomosis. [35]

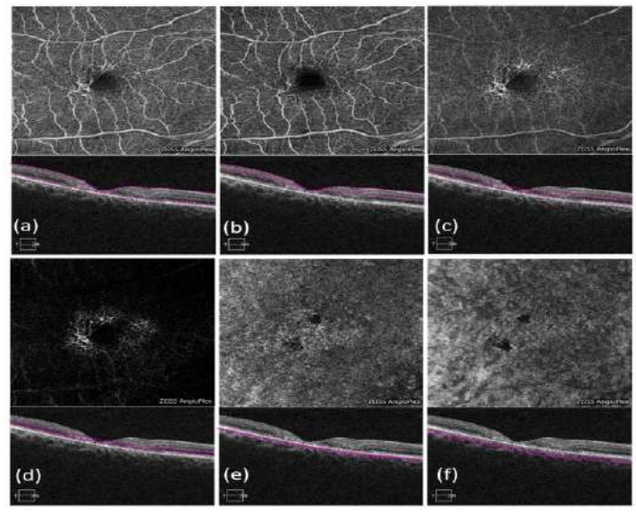

Figure 8: MacTel – A 6 x 6 mm OCT Angiogram of a 56 year old lady with MacTel Type 2 done (a) Full thickness OCT angiogram (b) OCT Angiogram of superficial inner retina(c) OCTA of deep inner retina and (d) OCTA of outer retina show telangiectatic vessels with increased intervascular spaces, abnormal vascular anastomosis and the patchy loss of capillary network (e) OCTA of choriocapillaris and (f) OCTA of choroidal vasculature show few areas of flow void.

OCTA and Polypoidal Choroidal Vasculopathy (PCV):

Polypoidal choroidal vasculopathy presents with characteristic branch vessel networks (BVN) and polyps in the choroidal vasculature which is best detected on indocyanine green angiography (ICGA)[37]. Studies on OCTA in PCV have demonstrated capability to identify most of the polyps and all the BVNs when specifically looked for with manual segmentation [38,39]. However, the need for manual segmentation raises question about the ability of OCTA to independently identify these lesions in the absence of ICGA. Also, not all the polyps are detected by OCTA as the polyps with smaller calibre and low flow rate are missed. Nevertheless, it is a useful tool with potential to understand and monitor the vascular changes in PCV and has even provided major insights into the exact anatomical locations of BVNs and the polyps.

OCTA and Vascular Occlusions:

Retinal vascular occlusions are a leading cause of defective vision amongst the retinal diseases. The utility of OCTA in cases with vascular occlusions has been now well established.

In cases with retinal artery occlusion (RAO), OCTA has been shown to lucidly delineate areas of decreased vascular perfusion in the SCP and DCP, corresponding to areas of delayed perfusion on FA and also corresponding to the inner retinal changes noted on OCT in these patients. [40]Although

diagnosis of RAO is mainly done on the basis of clinical examination findings and FA, OCTA does have the potential to provide useful information in prognosticating these cases.

In central retinal vein occlusion (CRVO) and branch retinal vein occlusion (BRVO), OCTA has been found to provide details of the capillary non-perfusion (CNP) areas in the posterior pole.**(Figure 9)** It was noted that scans with larger acquisition area of 8mm x 8mm have been more efficient in picking up the extent of CNP areas in these cases compared to 3mm x 3mm scans, the utility is however limited by the inability to detect the peripheral CNP areas compared to FA[41]. Mastropasqua et al studied the vessel density in the SCP, DCP and choriocapillaris in the foveal and parafoveal zone and found that in patients with BRVO and CRVO having macular oedema, vessel density significantly decreased in these layers. The maximum effect was noted to be on the DCP which did not recover after intravitreal dexamethasone. Vessel density is thus another potential parameter to assess the extent of damage caused by vessel occlusion in these cases [42]. Neovascularisation of the optic disc and elsewhere in retinal vein occlusions can also be detected and monitored by OCTA, although not as efficiently as by FA.

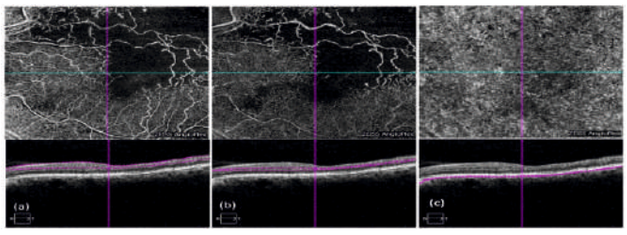

Figure 9: STBRVO - OCT Angiogram of a 42 year old lady with Superotemporal BRVO (a) OCTA of superficial inner retina and (b) deep inner retina shows the presence of extensive capillary non perfusion areas in the superotemporal quadrant. (c) OCTA of the choriocapillaris is normal.

OCTA and Retinal Angiomatous Proliferation (RAP)

Retinal angiomatous proliferation, also known as type III CNVM, typically presents with intraretinal haemorrhage and cystic retinal changes often accompanied by OCT findings of an underlying pigment epithelial detachment (PED) or intraretinal pigment migration. [43, 44]It is best confirmed by FA and ICG which show the feeding and draining retinal vessels associated with the leaking RAP lesion. The promise provided by OCTA has been its ability to detect early vascular changes in these cases before the progression to CNVM. Projection artefactsare a major limitation of OCTA in detecting the same as the presence of intraretinal pigment migration amplifies this artefact. Bhavsar et al have demonstrated, in a case report, the use of a Projection-resolved OCTA technique to retrospectively identify the early vascular changes of RAP-like vessel dilatation in the DCP five months before the appearance of a fulminant RAP lesion in a patient.[45]

CONCLUSION:

OCTA is definitely a technological boon which has the potential to revolutionize imaging in retinal vascular and degenerative diseases. It has provided insights into the intricate details of the vascular structures of retina with hitherto unseen precision. The most novel aspect of this imaging technique has been its ability to segment the retina and provide en face images of vascular details of the layer of choice. The accuracy of OCTA in delineating the vascular details has been found to come close to histopathology. Although FA and ICG are the current gold standard techniques for imaging vascular details of retina and choroid, OCTA has the definite advantages of being a non-invasive technique and lacking any of the side-effects associated with dye injection apart from being less time consuming. Nevertheless, OCTA is still evolving and the major challenges it faces today are its smaller field of view and its inability to detect leakage when compared to FA and ICG. Also, the imaging artefacts associated with OCTA are still an issue and need further honing in time to come. While OCTA, today, serves as a diagnostic to supplement structural OCT, FA and ICG, with continued advances, the day is not far when OCTA might take pole position amongst retinal imaging modalities.

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ICG in clinical practice : Where does it help?

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Indocyanine green angiography was first used by cardiologists as an indicator of cardiac output. Subsequently it was used by hepatologists to study hepatic blood flow and hepatocellular function.

ICG was first used to image human choroid by Flower and Hochheimer in 1972[1], however its use was limited due to poor fluorescence and inability to get good quality images on infrared camera. Hayashi and de Laey developed filter combinations with sufficient sensitivity for near-infrared wavelengths. They were also instrumental in the transition from still-frame to dynamic imaging by introducing videoangiography.

In 1992, Guyer et al. introduced the use of a 1024 × 1024-line digital imaging system to produce high-resolution ICGA[2].Finally, Yannuzzi and coworkers described a system, which had appropriate flash synchronization and image storage capability thus permitting high-resolution and long-duration ICGA.

ICG is a tricarbocyanine dye. Its structural formula is 2,2'-indo-6,7,6',7'-dibenzocarbocyanine sodium salt with a molecular weight of 774.96 Da.ICG absorbs light in the near-infrared wavelength. The maximum absorption is at 790 nm, while the maximum emission occurs at 835 nm. These optical properties allow penetration through macular pigment, melanin, blood, and pigment.

About 98% of ICG is bound to plasma protein. ICG is excreted mainly by liver. ICG disappears from vascular compartment at the rate of 18–24% per minute, and after 20 minutes less than 4% remains in plasma.

ICG's high molecular weight in combination with the high percentage of dye bound to plasma proteins, reduces the amount of dye that exits from fenestrations in choroidal vessels. This makes it very suitable for studying the choroidal vasculature.

The rate of side-effect is low: 0.15% with mild events (nausea, vomit, sneezing, pruritus), 0.2% with moderate events (urticarial, syncope, pyrexia, nerve palsy), 0.05% with severe events (bronchospasm, laryngospasm, anaphylaxis). However patients with a history of definite iodine allergy should not be given the dye, because of possibility of anaphylaxis.

Food and Drug Administration has classified ICG as a pregnancy category C drug, meaning that adequate studies for its safety have not been conducted.

INDOCYANINE GREEN ANGIOGRAPHY INTERPRETATION

Normal eye

ICGA, one can recognize an early phase when the retinal artery is not yet filled, a midphase when both arteries and veins are filled, and a late or recirculation phase more than 10 minutes after injection. First the haler's layer gets filled followed by satler's layer and then choriocapilaris. One can clearly visualise the vortex veins in widefield angiography.

Exudative age-related macular degeneration

Indications of ICGA in ARMD

1. In case of non response to anti VEGF treatment
2. In presence of huge PED
3. In presence of subretinal haemorrhages
4. In cases of direct evidence of orange coloured polyp like lesions on slit lamp biomicroscopy.

Type 1 choroidal neovascularization

The Macular Photocoagulation Study recognized two forms of occult CNV:

(1) a fibrovascular pigment epithelial detachment (PED)

(2) a late-phase leakage of an undetermined source (LLUS).

In case offibrovascular PED, ICGA may delineate the presence of a neovascular network usually located along the edges of the PED. Moreover, dynamic ICGA may reveal a feeder vessel that can be treated with laser photocoagulation if it is located outside the foveal region.

In case of LLUS, which may represent 36–78% of occult CNV,dynamic ICGA may differentiate an occult form of CNV from retinal angiomatous proliferation (RAP)[3]. Considering that one-fourth of patients with an LLUS have a RAP and that an early diagnosis of these lesions is crucial for the functional prognosis.Yannuzzi et al. found that 39% of lesions classified as poorly demarcated occult lesions by fluorescein angiography were well defined by ICGA.

Type 2 choroidal neovascularization

In classic CNV, ICGA improves visualization of the fine structure of the neovascular network allowing the choroidal and retinal circulation to be distinguished. This high spatial and temporal resolution permits identification of choroidal vessels that feed into the CNV (Fig 1).

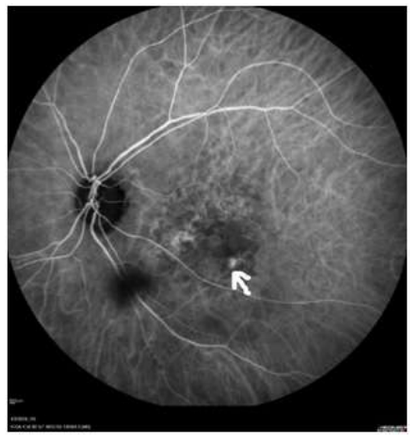

Fig 1. Case of CNVM showing abnormal branching vasculature over posterior pole with feeder vessel.

In early phases, ICGA shows a dark rim which corresponds to a whitish ring on infrared imaging and a discrete neovascular network surrounded by a hypocyanescent margin which is more visible after 15 minutes. Watzke et al.[4] showed that 87% of eyes with classic choroidal neovascular membranes were hypercyanescent with distinct edges.

It has been reported that VEGF inhibitors are more effective in controlling immature vessels, whereas a VEGFinhibitor along with a platelet-derived growth factor (PDGF) inhibitor appeared to show a synergistic effect for controlling the growth of mature vessels.

Mature, larger choroidal vessels may be readily differentiated from immature choroidal capillaries on ICGA. Thus, in patients with chronic AMD or those who do not benefit from previous treatments with anti-VEGF, ICGA helps to delineate a more mature stage of CNV. This has potential implications for therapeutic decision-making.

Type 3 choroidal neovascularization

Dynamic-ICGA takes up to 12 frames per second and captures progressive filling of the lesion thus allowing detection of very small and recent-onset cases of RAP.

Polypoidal choroidal vasculopathy

This disorder is associated with dilated tortuous choroidal vasculature with polyp like sacculations at the end.It manifests with multiple, recurrent, serosanguineous detachments of the RPE and neurosensory retina secondary to leakage and bleeding from the abnormal choroidal vasculature.

The early phase of the ICG angiogram shows a distinct network of vessels within the choroid (Fig.2,3 & 4). Larger choroidal vessels of the PCV network begin to fill before retinal vessels, and PCV network fills also at a slower rate than retinal vessels. Shortly after the network can be identified by the ICG angiogram, small hypercyanescent “polyps” become visible[5].In dynamic angiography pulsation may also be noted in these polyps.They appear to leak slowly as the surrounding area becomes increasingly hypercyanescent. In the later phase of the angiogram there is disappearance of dye (“washout”) from these polypoidal lesions. ICGA guided Photocoagulation of these polyps has been shown to be helpful in regression of disease. ICG is also used to measure the greatest linear dimension (GLD) of lesion and perform a guided photodynamic therapy.

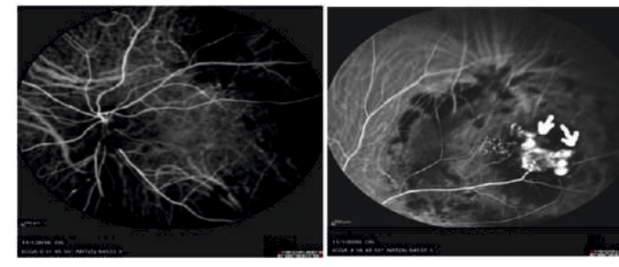

Fig.2.Case of PCV showing extramacular blocked cyanescence with hypercyanescent polyps(arrows).

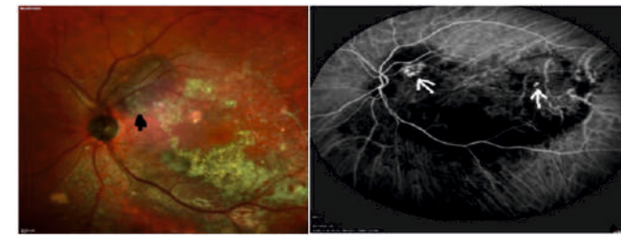

Fig.3. Case of PCV showing ICG with hypercyanescent macularpolyps away from fovea to which focal laser was done.

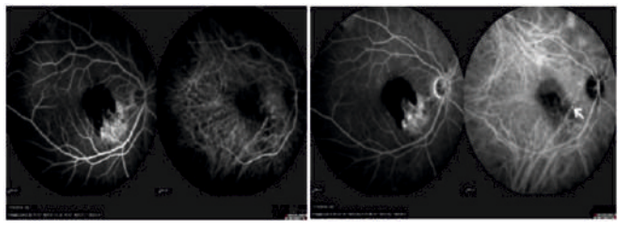

Fig.4.Simultaneous FFA and ICG of a patient of PCV with subretinal haemorrhage showing blocked flourescence on FFA and clearly deleniating abnormal vasculature on ICGA with knobbed polyp(arrow) like ending.

Central serous chorioretinopathy

CSCR is characterized by multifocal areas of choroidal hyperpermeability which is visible on ICGA in the mid and late phases[6].Zones of choroidal hyperpermeability tend to persist in cases of severe and chronic CSC. ICG helps to localise these areas of hyperpermeability and carry out guided treatment with verteporfin photodynamic therapy or laser photocoagulation.Other findings demonstrated in CSC using ICGA include multiple "occult" serous PED, punctate hypercyanescent spots, delays in arterial filling of the choroidal arteries and choriocapillaris and venous congestion. ICGA is very useful in differentiating chronicCSC from Pachy choroid disorder.

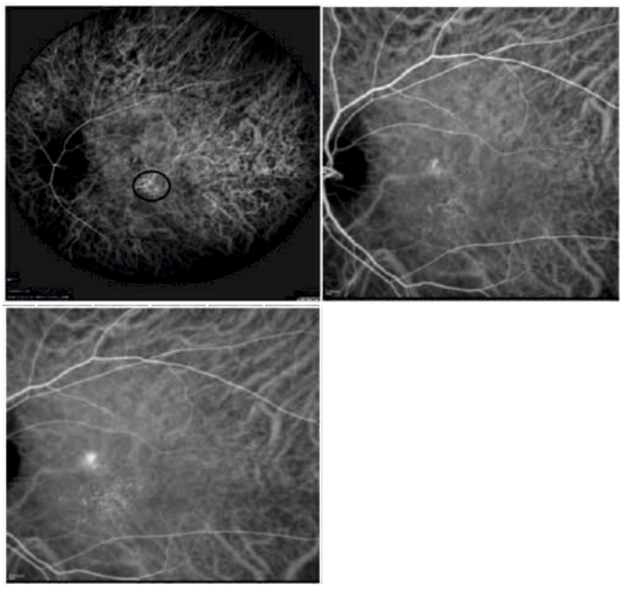

Fig.5.Case of Chronic CSCR showing abnormal hypercyanescent choroidal vasculature in early phase with increasing intensity in late phase. This angiogram was used to measure GLD (encircled) and do a guided PDT.

Choroidal tumors

Choroidal hemangioma

ICGA is the most useful study for demonstrating the intrinsic vascular pattern of circumscribed choroidal hemangioma. The advantage of ICG dye over sodium fluorescein dye is that it diffuses very slowly out of fenestrated small choroidal vessels as compared to sodium fluorescein. By 1 minute, choroidal hemangiomas completely fill with the dye, showing brilliant hypecyanescence which is diagnostic of this tumor[7].Thetumor vasculature has low resistance and high flow property so it allows rapid flow in and out of tumor. The results in tumor emptying faster than the normal surrounding choroid and thus it appears hypocyanescent in late phase compared to surrounding choroid. This washout sign is very helpful in differentiating choroidal hemangiomas from amelanotic malignant melanoma and choroidal metastases.

Choroidal melanoma

ICGA is capable of identifying tumor vessels which are usually irregularly tortuous, with anarchic branching, dilated and have a parallel course[8]. ICGA is superior to fluorescein angiography as it clearly delineate these vessels.

Multiple evanescent white-dot syndrome

Multiple evanescent white-dot syndrome involves the choroid and the outer retina. ICGA shows a pattern of multiple hypocyanescent areas at the posterior pole and peripheral retina due to slow movement of dye through the inflamed vessels. These spots become visible in the mid to late phases, range in size between 50 and 1000 µm[9]and are apparent in greater numbers in ICGA images than by fundus examination and fluorescein angiography.

Fig.6.A case of multifocal choroiditis showing hypocyanescent lesions in late phase of ICGA which were not visualised by fundus examination or autoflourescence. The lesions were with ill defined margins suggesting activity.

Serpiginous choroidopathy

ICG allows better staging and identification of active lesions in serpiginous chorioretinopathy. The active lesions are characterized by hypocyanescent areas with poorly defined margins.The lesions detected on ICGA may preceed the lesions seen on FFA and may also be larger in size and number as compared to FFA.

Acute multifocal placoid pigment epitheliopathy

ICG of acute posterior multifocal placoid pigment epitheliopathy (AMPPE) shows areas of hypocyanescence in both early and late phases that correlate with the placoid lesions. These lesions may be caused by choroidal hypoperfusion, secondary

to occlusive vasculitis(Fig.7). New, activeandhealed, inactive lesions in AMPPE can both be imaged and differentiated using ICGA.

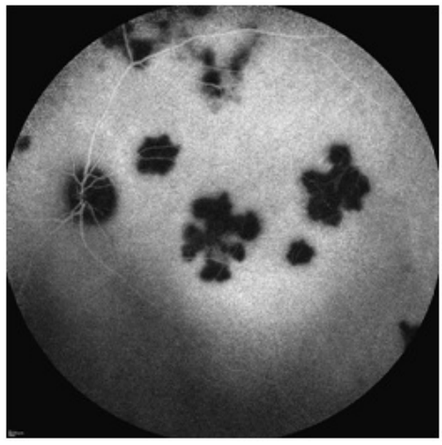

Fig.7 Case of AMPPE showing hypocyanescence corresponding to the placoid lesions.

Acute zonal occult outer retinopathy

In acute zonal occult outer retinopathy, Spaide reported that the peripapillary drusenoid material blocks the choroidal cyanescence in ICG and therefore the involved areas appear hypocyanescent[11].The secondary atrophy of the choriocapillaris produces hypocyanescence as well, which does not affect the cyanescence from the underlying larger choroidal vessels. In some casesICG may show hypercyanescence from the affected areas, due to the lack of photoreceptor outer segments and the lack of minor blocking effect from this layer.

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Gene therapy in Inherited Retinal Diseases

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Introduction

Retinal dystrophies or inherited retinal diseases (IRD) are a group of heterogeneous diseases that are characterized by progressive photoreceptor and/retinal pigment epithelial dysfunction, cell loss and eventual atrophy of retinal tissue. They are a significant cause of bilateral blindness worldwide. The common IRDs include Retinitis Pigmentosa (RP), Stargardt disease, Choroideremia and Leber Congenital Amaurosis (LCA).

Management of IRDs has conventionally been limited to genetic counseling and low-vision rehabilitation. However with the recent surge in research into gene therapy, stem cell therapy and retinal prosthesis, several treatment options are on the horizon. Management of IRDs with gene therapy has been of interest since the discovery that biological information is passed on from one generation to the other by discrete biological material called “genes” encoded in the DNA of the cell and that mutations in various genes are responsible for the occurrence of IRDs.

This article discusses the basics of gene therapy and its current status in management of retinal dystrophies.

Gene therapy basics

The retina is a highly-specialized multilayered structure that include the light-sensitive cone and rod photoreceptor cells that initiate neuronal signaling in response to light stimulation by phototransduction. The photoreceptor cells are supported by the retinal pigment epithelium (RPE), in which the visual cycle takes place.

IRDs are a group of disorders arising from genetic defects in proteins that play a role in development, function, and maintenance of either the photoreceptor/RPE or both. Identification of the genetic defect causing the IRD allows accurate diagnosis, prognosis, and counseling in affected patients, and the exciting prospect of being able to offer therapies as they become available.

IRDs are one of the most genetically heterogeneous diseases in humans. Since the identification of Rhodopsin as the first retinal dystrophy gene in 1990, over 250 genes responsible for isolated(non-syndromic) or syndromic forms of the disease have been characterized to date (https://sph.uth.edu/retnet/, accessed on 29th Aug 2018).

The majority of genes mutated in RP encode proteins that are expressed either in photoreceptor cells or in the RPE. Gene therapy involves gene replacement/gene silencing. Gene replacement is employed for disorders due to loss-of-function mutations and is based on the delivery of a correct copy of the defective gene without removal of the endogenous mutant one. Gene silencing inhibits the expression of the mutated gene via modification of messenger RNA (mRNA) and is applied to disorders caused by gain-of-function mutations. Irrespective of mutation dependent and -independent strategies, vectors are key for successful gene therapy in the eye. Gene therapy therefore uses either a viral or non-viral vector that replaces or silences the causative gene. (**Figure 1)**

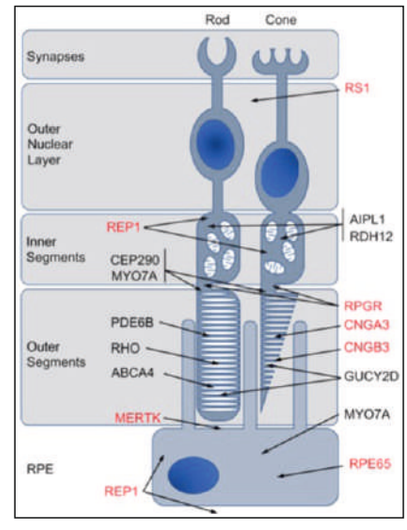

Figure 1. Schematic diagram showing the outer retina and the cellular location of products of the genes targeted by current gene therapy trials (red) and the genes explored for future trials (black).Adapted from Kumaran N et al. Retinal gene therapy. Br Med Bull. 2018;126:13-25.

Viral Vectors

Viruses are obligate parasites of the cells with specific tropism for the cell type and have an efficient delivery system for transfer of genetic material. Decades of research has helped in development of safe and efficient viral vectors suitable for the delivery of the genes invivo. Retroviruses, adenoviruses, adeno associated viruses, herpes simplex viruses and more recently with the advent of nano technology, nonviral gene delivery systems are being considered for gene therapy.

Adeno associated viruses (AAV) have become a very popular choice for the gene therapy delivery system. AAV vectors presents specific characteristics such as low immunogenicity and toxicity, lack of pathogenicity, long-term transgene expression, and relative ease in manipulating genetic elements, making them the safest and most effective viral vector platform for gene delivery into the retina to date. They are replication deficient in their wild type condition. They need infection of another virus eg. Adenovirus (and hence the name AAV) or DNA damage insult to undergo a lytic cycle in the host cell. A variety of clinical trials have been initiated world wide using different serotypes of AAV for various IRDs. Depending on the capsid protein expressed, there are several serotypes identified for the AAV virus of which AAV2 is the most studied. These capsid proteins allow the AAV to infect a specific cell type, thus making the in vivo cell type specificity possible.

Two major limitations of AAVs in the retina are its slow onset of transgene expression, and the vector's limited cargo capacity of 4.7kb. Certain forms of IRDs like Stargardt disease, Usher syndrome Type 1B and LCA10 are caused by mutations in ABCA4, MYO7A, or CEP290 respectively that have cDNA that exceeds 5kb, and these are difficult to treat with AAV.

Lentiviruses (LV) have a large capacity of transgenes and sequences up to 8 kb can integrate their genomes into chromosomesof target cells, supporting long-term expression. Drawbacks of LV are potential insertional mutagenesis, complexity of production, and the large diameter.

Nonviral vectors using nanomaterial-based delivery system, lipid based delivery and more recently magnetic nano particles are being tried. Challenges of these include difficulty in delivery, instability and short-term transient expression.

Genome editing techniques

Genome editing involves correcting the disease-causing mutation within the genome, enabling the cells to produce what is needed to have optimal phenotype outcome. Providing a wild-type copy of the mutated allele via gene therapy to restore a phenotype does not directly impact the pathogenic host gene. In contrast, a genome-editing approach has the potential of correcting the mutation directly in the patient' s DNA.

There are potentially two different approachesto this- an in-vivo approach where by the disease-causing mutations are corrected directly in the retina and an ex-vivo approach in which the mutation is corrected in the patient' s cells in view of future cell transplantation.

Genome editing is especially useful in stem cell transplants where the underlying genetic defect is corrected in the cells using tools like zinc finger nucleases and transcription activator-like effector nucleases (TALEN), and the recent use of Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) and CRISPR associated genes (Cas) system. Genome editing uses has advanced at an exceptionally rapid rate, creating huge impacts on biotechnology and biomedicine.

Diseases treated

Gene therapy for LCA

Leber Congenital Amaurosis (LCA) is an infantile, autosomal recessive variant of RP that was first described by Leber in 1869. Characteristic features include severe vision loss from infancy, nystagmus, and sluggish pupillary response. The fundus usually has a normal appearance, although findings such as salt and pepper pigment mottling, macular coloboma-like appearance, and retinal flecks have been reported. High hyperopia is a common finding.

Till date, mutations in 25 genes currently associated with LCA. The most common mutations include *CEP290* (15%), *GUCY2D* (12%), *CRB1* (10%) and *RPE65* (6%).

RPE65 is a gene-encoding retinoid isomerohydrolase expressed in the retinal pigment epithelium that plays a key role in the visual cycle. Defective RPE65 gene leads to an early onset of degeneration of rods, followed by cones, causing significant visual loss. This leads to RP type 20 and LCA type 2- both of which have been extensively evaluated in pre-clinical models. The earliest animal experiments were with Swedish Briard dog, a naturally occurring animal model with mutated RPE65. The success of the preclinical murine and large-animal models translated into a number of human trials evaluating the safety of injecting AAV vectors containing the human RPE65 codingsequence.

Although not a very common cause of IRD, certain factors have made RPE65 a favourite target for gene therapy. 1. It is an autosomal recessive disease, and therefore amenable to therapy by gene replacement. 2. It was one of the earliest discovered genes for IRDs. 3. RPE65 gene is relatively small in size, and therefore it can be carried by AAV2. 4. The clinical

course of LCA in which photo receptor cell loss significantly lags behind functional loss, provides a window in which retinal function may be restored in theresidual cells. 5. The existence of dogs with an RPE65 mutation as an animal model.

In 2008, three independent studies began phase I clinical trials in order to assess the efficacy of unilateral subretinal injection of the AAV-RPE65 vector in LCA patients carrying RPE65 mutations- Bainbridge et al, Maguire et al and Hauswirth et al. Visual function showed improvement in all three trials with a subjective improvement in visual perception, and a statistically significant improvement in the dark-adapted ERG response. Subsequent phase 1/2 trials showed improvement in light sensitivity, retinal sensitivity on microperimetry and change in pupillary responses.

Following this, Spark Therapeutics conducted a phase III trial enrolling 31 patients, with confirmed genetic diagnosis of biallelic RPE65 mutations, sufficient viable retina, and ability to perform standardized multi-luminance mobility testing (MLMT). Intervention was bilateral, subretinal injection of 1·5 x 10^{11} vector genomes of voretigene neparvovec in 0·3 mL total volume. The primary efficacy endpoint was1-year change in MLMT performance, measuring functional vision at specified light levels. At 1 year, mean bilateral MLMT change score was significantly higher in the intervention group Vs control group. No product-related serious adverse events or deleterious immune responses were noted. In addition, a subset of participants in this study were enrolled in a separate functional magnetic resonance imaging study that showed increased activation of the visual cortex and evidence of improved function and structure of the visual pathways after intervention.

Voretigene neparvovec-rzyl is composed of human RPE65c DNA along with a cytomegalovirus enhancer and a hybrid chicken b-actin promoter incorporated into a recombinant AAV2. Following injection into the subretinal space, AAV2 enters RPE cells. While the viral vector remains in episomal form in the nucleus, without integrating into the host DNA, the enhancer and promoter facilitate expression of RPE65.

In December 2017, the USFDA approved the gene therapy 'Luxturna' ((voretigene neparvovec-rzyl), developed by Spark Therapeutics, to treat children and adults with biallelic REP65 mutation-associated retinal dystrophy.

In addition to RPE 65, multiple other gene therapy trials for LCA are underway for the following mutations: **GUCY2D** (encodes retinal guanylylcyclase-1, a protein expressed in the outer photoreceptors and leading to LCA type 1), **RPGRIP1** (retinitis pigmentosa GTPase regulator protein gene that encodes a structural protein that localizes to the connecting cilium linking the inner to the outer segment), **CEP290** (encodes a centrosomal protein involved in trafficking through the connecting cilia of photoreceptor cells).

Gene therapy for Choroideremia

Choroideremia is a X-linked disorder that leads to progressive degeneration of the photoreceptors, RPE and choriocapillaris, mainly affecting males. Symptoms include night blindness and progressive constriction of visual fields; most affected males are legally blind by their midlife. The causative gene has been mapped at Xq21.1-q21.3; mutations in this gene leads to the loss of loss of function of a protein necessary for retinal cell health, Rab Escort Protein 1 (REP1). The disease has characteristic fundus features that include progressive atrophy of the retina and choroid.

Choroideremia has several attributes that make it an ideal target for gene augmentation therapy. A Phase I/II clinical trial was conducted by MacLaren et al, in which six patients were adminstered AAV2.REP1 genome particles in the subretinal space. At 6 months follow up, all patients showed an improvement in the visual acuity on the ETDRS chart and an increase in the retinal senstivity on the microperimetry.

Spark Therapeutics has sponsored an open-label, dose escalating phase 1/2 trial designed to assess the safety and preliminary efficacy of subretinal administration of investigationalSPK-7001 in choroideremia. The trial has enrolled two dose cohorts of five patients with advanced disease and initial efficacy analysis is expected soon. (Spark Therapeutics. SPK-7001: choroideremia. 2017. Available from: http://sparktx.com/scientific-platform-programs/)

Gene therapy for RP

RP is a heterogenous hereditary disorder resulting in diffuse,progressive photoreceptor loss preferentially affecting rod photo receptors with secondary loss of cones. A mutation in RHO, which encodes rhodopsin,was the first one associated with the disease, but numerous other genetic mutations have subsequently been identified.

The prevalence of RP in India has been much higher than that noted in the Western population. Its prevalence ranges from 1 in 3500 in the US to 1 in 1000 in China. Sen et al. estimated the prevalence of RP as 1 in 930 in the urban population and 1 in 372 in the rural general population of Southern India, aged 40 years and above.Nangia et al. estimated the prevalence of RP as 1 in 750 in the adult population of rural Central India.

MERTK is one of the genes encoding for a tyrosine kinase, required for phagocytosisof photoreceptor outer segments by the RPE and is associated with a rare form of autosomal recessive RP. The genetic mutation and its resultant pathology has been extensively studied in preclinical models mainly because it is the gene mutation in Royal College of Surgeon

(RCS) rats, a popular model for IRDs. A phase-1 clinical trial utilizing an AAV2 vector with an RPE-specific promoter (VMD2) driving MERTK in six patients was published in 2016. However the results were not sustained and further trials are awaited.

The RPGR gene is involved in 70% of X-linked RP and up to20% of all RP. RPGR encodes for a transporter protein in the cilium, connecting the inner and outer segments of photo receptors and suspected to play a role in transporting photo transduction components across the connecting cilium. X-linked RP due to RPGR mutations carries a poor prognosis associated with an aggressive course. Currently, there are two phase 1/2 clinical trials that are going on for gene therapy for X-linked RP with RPGR mutations.

Gene therapy for Stargardt disease

Stargardt disease or fundus flavimaculatus is the most common juvenile macular dystrophy and a common cause of central vision loss in adults under age of 50, with an estimated prevalence of 1:8,000 to 1:10,000. The vast majority of cases are autosomal recessive.

Pathogenesis of Stargardt disease is linked to an abnormal accumulation of lipofuscin in the RPE in the early stages, followed by slowing of the rod and cone retinoid cycles later in the disease. The commonest gene identified for Stargardt disease is ABCA4 (chromosome 1p13-21) for the ABCR retinal ATP transporter protein.

The ABCA4 gene (6.8 kb) exceeds the capacity of the AAV vector and therefore requires equine infectious anemia lentivirus (EIAV) for gene transfer. Subretinal injection of EIAV-ABCA4 was found to be effective in a knockout mouse model. Currently, Oxford Biomedica in coordination with Sanofi is sponsoring an escalating dose phase1/2 EIAV-ABCA4 clinical trial investigating its utility in Stargardtdisease. There are other cell replacement therapies that are underway for Stargardt disease.

Other diseases

There are several clinical trials for diseases including those for Achromatopsia, X-linked Retinoschisis and Usher syndrome (clinicaltrials.gov)

Advantages of using the eye as an end organ for gene therapy

1. Relative ocular immune privilege- limits an immune response to the genetic material injected
2. Tight blood-ocular barrier- limits the systemic spread of the injected material
3. Ease of accessibility directly to the cells of interest
4. Ability to monitor response to therapy noninvasively
5. Ability to use contralateral eye as in-vivo control

Methods of delivery (Figure 2)

There are two common methods being used to introduce the gene therapy product into the eye:

1. Subretinal injection- This involves a parsplana vitrectomy, followed by raising a subretinal bleb close to the macula with the viral vector with the genetic material being injected directly into the subretinal space. Although this creates a temporary retinal detachment, this has the advantage of direct delivery to the cells of interest. Procedural complications include potential retinal detachment and other complications associated with vitrectomy.
2. Intravitreal injection: This involves direct injection into the vitreous cavity, without the need for a vitrectomy. Although the procedure is much simpler and associated with lesser complications, the availability of the viral vectors to the subretinal cells is difficult. In addition, an induced humoral response to the intravitreally delivered vectors, which has not been noted in subretinal injections.

Intravitreal injection allows a more widespread distribution of the therapeutic agent over the retina than that of subretinal delivery,using a less challenging and invasive procedure. However, several physical barriers, such as the vitreous, the ILM, and the inner retina limit diffusion of the therapeutic agent to the PR and RPE after intravitreal delivery. Thus, subretinal vector delivery is currently considered to be the most efficient route for targeting PR and RPE cells in the outer retina, the target cells for the treatment of most IRDs.

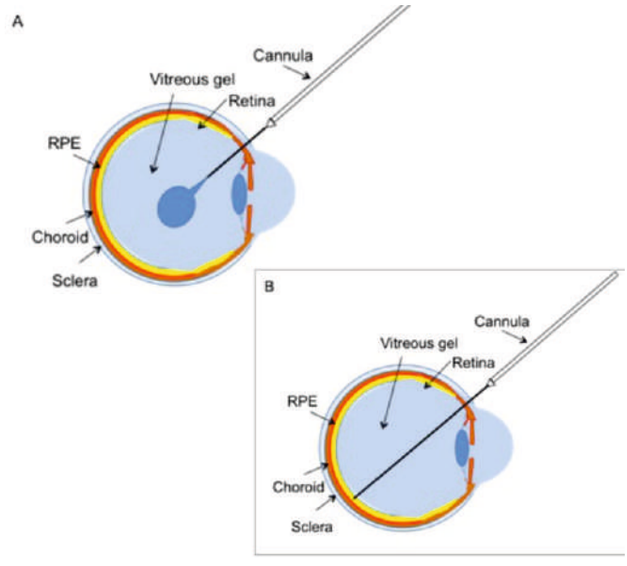

Figure. 2 Schematic diagram identifying ocular structures and location of (A) intravitreal injection and (B) subretinal injection

Challenges

1. Gene therapy requires viable cells and hence will not be effective in advanced stages of IRD with severe photoreceptor degeneration.
2. It is not definite that gene therapy can prevent progression of retinal degeneration.
3. Gene therapy is gene specific, and treatment for each gene has to go through all the steps of a drug development including animal studies, clinical trials and regulatory processes.
4. Gene therapy is very expensive. Luxturna, the RPE-65 gene therapy product currently costs about $450,000 per injection in the US.
5. The ability of delivering genes to photo receptors is limited by the cargo capacity of viral vectors.
6. The therapy is associated with the complications inherent to the method of delivery of the product, be it subretinal or intravitreal delivery.
7. Potential presence/development of anti AAV2 antibodies in the eye that may reduce the efficacy of gene therapy.
8. Mutations in genes such as Rhodopsin that cause autosomal dominant RP are associated with dominant-negative effects. Treatment of these conditions necessitates disruption of the mutated allele along with the insertion of a functional copy of the gene.

Future prospects

Science is at the cusp of being able to treat hither-to untreatable diseases. This is a major breakthrough for patients with IRDs. Future gene replacement therapy in IRDs will target patients at an early disease stage when the retinal architecture and function are still intact. Progress in retinal imaging including Adaptive optics, microperimetry and OCT-angiography should be able to identify clinical markers that identify diseases and its progression very early in the disease, so that maximum functional vision is preserved.

Stem cell science is advancing, and although early, offers unprecedented opportunities for cell replacement strategies. Although most of the early research was conducted using embryonic stem cells (ESC), induced pluripotent cells (iPSC) is making headway in current research. Obtained from peripheral blood or a skin biopsy, iPSC offers an easy approach compared to ESC. Derivation and differentiation of human iPSC into RPE, photoreceptors and retinal organoids *invitro* provides exciting opportunities for cell-replacement therapy and screening small molecules for therapeutic potential.

This has several implications for the clinician. Current counseling of patients with IRDs should include information on current results of gene replacement/stem cell trials. Furthermore, genetic testing and identification of the underlying mutation should be used to support the clinical diagnosis. In addition, it is important to establish a database of patients with confirmed genetic mutations to inform patients of forthcoming gene/cell replacement therapies and offer them the possibility of participating in future trials.

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Microincision vitreous surgery for intraocular foreign body removal

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1. In the era of MIVS, advantages of MIVS and its instruments should be given to every case of RIOFB.
2. IOFB can be removed through limbus in case of traumatic cataract with compromised posterior capsule.
3. Enlargement of one port i. e Hybrid MIVS is used to remove IOFB through pars plana.
4. In our experience, making fourth port in hybrid MIVS is a better option rather than enlarging the existing port.
5. Along with MIVS, the decision to put encircling band can vary according to situation and surgeon's preference. We prefer encircling band in cases of zone 3 injuries with or without retinal detachment

Retained intraocular foreign bodies (RIOFBs) in open globe ocular injuries are seen in 18-40% of ocular trauma cases[1,2] Conventionally, posterior segment RIOFBs were removed after enlarging one of the sclerotomy ports during 20G vitrectomy. Enlargement of sclerotomy is associated with intraoperative complications such as hypotony, vitreous hemorrhage, incarceration of the retina in the wound ,retinal detachment and late onset complications such as macular pucker, fibrovascular proliferations and proliferative vitreoretinopathy.[3,4,5] .The introduction of 25G transconjunctival vitrectomy system using micro-trocars and cannulas by Fujii et al. in 2002[6], 23G vitrectomy by Eckardt in 2005[7] and 27G vitrectomy system by Oshima in 2010[8], has enabled retina specialists to shift from conventional 20G systems to newer advanced micro incision vitreous surgery (MIVS). MIVS has considerably reduced total surgical time, minimised surgical trauma and post surgical inflammation, induces relatively less postoperative astigmatism, early postoperative recovery has better patient comfort and patient satisfaction. [9]

Various techniques of RIOFB removal using MIVS have been described.[10-15] MIVS for RIOFB with traumatic cataracts can be combined with lensectomy or cataract extraction with primary intraocular lens (IOL) implantation.[16,17] Limbal/scleral route in aphakic eyes as well as different variants of sclero-corneal incisional approaches in phakic eyes have been described for externalization of IOFB .[12,14,15]

Decision and Timing of IOFB Removal

Most of the IOFBs commands removal. IOFB of metallic and vegetative nature and the ones with associated endophthalmitis are the among that requires early surgical removal. Glass IOFBs that do not endanger retinal tissue and which are located in difficult areas can be observed. Plastic and silver IOFBs can also be observed. There is a increased risk of endophthalmitis and PVR, if IOFB removal is delayed for more than 24 hours after the primary/initial surgical procedure. The advantages of early removal of RIOFB are reduced risk of PVR and endophthalmitis. The early removal of RIOFB apart from reducing the risk of PVR and endophthalmitis, also saves additional surgical procedure required for RIOFB related complication. Primary surgical repair, removal of RIOFB and definitive treatment can also be done in one sitting. On the other hand there are also advantages of delayed surgery which include fewer chances of wound leak, reduced intraocular inflammation, clearer corneal status, resorption of hemorrhage, adequate instrumentation and operation theatre support and establishment of a posterior vitreous detachment (PVD).[5,18]

Routes of IOFB Removal

In patients with a clear crystalline lens, lensectomy should be avoided while doing IOFB removal. In these cases active sclerotomy can be enlarged with the help of a 20G MVR knife.

This "hybrid MIVS" methodology allows for IOFB removal with the help of Machemer's foreign body forceps through the enlarged active port by performing a "handshake technique". (Figure 1).

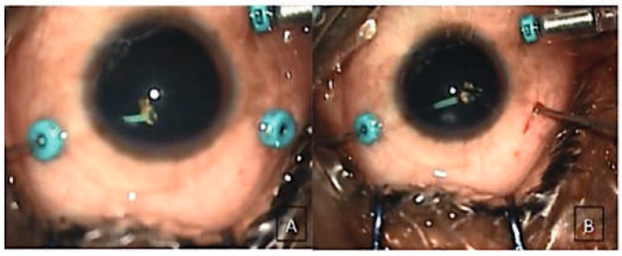

Figure 1: Intraoperative photos showing phakic eye with no cataract (A) 3 port 25 G PPV setting with iron IOFB held with suction behind the lens; (B) 10 o'clock port was converted with MVR for hybrid PPV and IOFB holding forceps was introduced and held with it before removing it.

Another variation to this practice is, to make a fourth sclerotomy port at 11 or 1 o'clock depending on the eye and to leave trocars in situ. This fourth port is used to engage the IOFB with forceps and externalize it. (Figure 2) This technique allows closed chamber dynamics during the surgical procedure. The suturing of this fourth port is done after IOFB removal. Following which one can proceed with further needed steps of vitrectomy.

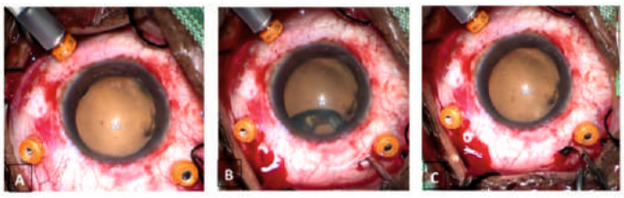

Figure 2: Intraoperative photos showing phakic eye with no cataract (A) 3 port 23 G PPV setting with preplaced 240 band for equatorial support; (B) (C) Fourth port was made with MVR to remove the IOFB, IOFB forceps was used to hold it behind the lens and later removed.

Ravani et al[15] have recently described a modification of this technique, in which chandelier assisted removal of IOFB is done through the fourth port. This minimises the chance of iatrogenic lens damage during IOFB removal by doing the "handshake technique" in the mid vitreous cavity and not in the anterior vitreous.

In patients where lensectomy is planned, limbal removal of IOFB is preferred. This decreases the chances of scleral port site vitreous incarceration and subsequent retinal detachment . It also, avoids the need for encircling band. (Figure 3) .To facilitate future visual rehabilitation it is advisable to preserve anterior capsular rim.[14]

The decision to put encircling band can vary according to situation and surgeon's preference. We prefer encircling band in cases of zone 3 injuries with or without detachment. It provides equatorial support and prevents late onset RD due to port site vitreous traction.

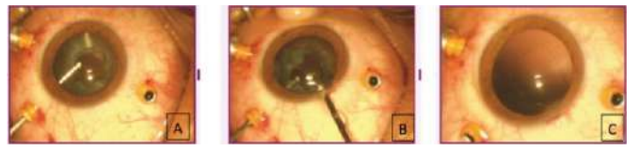

Figure 3: Intraoperative photos showing traumatic cataract (A) 3-port 23 G PPV setting with lensectomy being done and IOFB was seen at 6 o'clock: (B) iron IOFB was held with IOFB forceps and removed through limbus: (C) anterior capsule was preserved for future or same setting IOL.

RIOFB with associated Crystalline Lens injury

Posterior chamber IOFBs with ruptured lens capsule, traumatic cataract or subluxation of lens need astute pre-operative planning. In absence of RD, phacoemulsification with in the bag or sulcus implantation of IOL can be combined with MIVS assisted IOFB removal. Scleral suturing of IOL combined with IOFB removal has also been described, but is associated with increased rates of post-operative RD which is as high as 28%.[17] IOL implantation at the time of IOFB removal is fraught with a theoretical risk of post operative inflammation and endophthalmitis. Also, biometry in injured eyes is usually not feasible and is may give erroneous results.[16,17]

In most cases, lensectomy is done with the help of vitreous cutter and an anterior capsular rim is left behind to facilitate secondary IOL implantation at further follow ups. (Figure 4,5) .This approach provides time for the ocular inflammation to settle and permits accurate biometry.

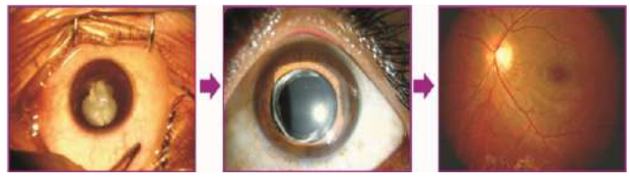

Figure 4: (A) Preoperative photo showing traumatic cataract and encapsulated iron IOFB on retinal surface; (B) 2 weeks post 25 G MIVS with adequate sulcus support ; (C) Posterior segment of the same eye showing grade 1 media with laser marks below the disc.

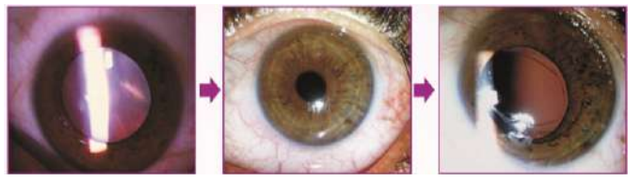

Figure 5: (A) Preoperative photo showing traumatic cataract and iron IOFB seen behind the posterior capsule of lens; (B, C) 2 weeks post 25 G MIVS quiet eye with preserved anterior capsule for visual rehabilitation.

IOFB with endophthalmitis

This is an ophthalmic emergency and requires immediate MIVS with IOFB removal, irrespective of the nature of IOFB. Lensectomy is required in majority cases. The aim of surgery is to debulk the vitreous exudates, remove the IOFB without causing damage to the retina and to inject intravitreal antibiotics. PVD induction should be avoided in these cases as it increases the chances of retinal breaks.

IOFB with endophthalmitis and retinal detachment (RD) portends a poor prognosis. Encircling scleral band, lensectomy, PVD induction, removal of IOFB, silicone oil tamponade with injection of quarter dose intravitreal antibiotics can also be attempted. MIVS helps to maintain a closed chamber during instrument exchange thereby preventing hypotony and sclerotomy site complications.[19,20]

IOFB with Retinal detachment

Trauma leading to IOFB with RD is best managed with lensectomy, encircling band, PVD induction, IOFB removal and silicone oil/gas tamponade. As described previously, MIVS is extremely useful in this situation.[19,21]

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Micropulse laser : Principles and Current Indications

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INTRODUCTION

Micropulse laser has recently started getting integrated in clinical practice and no longer remains a research tool. This article discusses the principles and practical aspects of Micropulse Laser Therapy (MPLT) and its current indications and personal experience. All patients presented here have been treated with IridexIQ 577 ™ Yellow micropulse laser.

Laser photocoagulation has been in use for several decades and its benefit has been well validated for numerous retinal conditions like Proliferative Diabetic Retinopathy (PDR), Diabetic Macular Edema (DME), Macular Edema associated with Branch Retinal Venous Occlusion (BRVO), Central Serous Chorioretinopathy (CSC), Choroidal Neovascularization, retinopexy of retinal tears and others. Conventional laser photocoagulation of the retina delivers a continuous wave (CW) laser, which normally results in a full-thickness visible lesion due to thermal damage of the retinal pigment epithelium (RPE), neurosensory retina, and the choroid. This typically results from coagulative necrosis beginning in the RPE and spreading to involve the photoreceptors and overlying retina and underlying choroid and results from elevation of local temperature by 20-30°C above the body temperature (Fig1). The resulting greyish white lesion may spread further laterally due to involvement of the zone of latent lethal damage, which is invisible during the laser treatment.[1] Retinal whitening is the optical signature of chorioretinal burn. More damage means less transparency and whiter lesion. Hemorrhages occur at roughly three times the exposure needed to produce ophthalmoscopically visible lesions. Invisible lesions that are angiographically apparent occur at approximately half the laser exposure needed for a visible lesion. Maximum permissible exposure (MPE) levels established by international laser safety standards represent roughly one-tenth the laser exposure needed to produce a retinal effect.[2]

With the advent of anti-vascular endothelial growth factor (VEGF) therapy and its success in the treatment of various retinal pathologies, the utilization of conventional laser has declined. With pharmacotherapy, Laser induced retinal damage is also avoided. Hence the role for laser therapy for these entities in the anti-VEGF era is being questioned.

Recent studies have, however, suggested that it may be possible to deliver a subthreshold laser that is above the threshold of biochemical effect but below the threshold of a visible, destructive lesion. This non-damaging retinal laser therapy, also called subthreshold laser therapy, does not cause collateral tissue damage and is not visible clinically or is documented on the OCT. It is proposed that, subthreshold laser treatment stimulates a metabolic effect whereby the retinal tissue produces mediators with anti-angiogenic and anti-edema effects, such as pigment epithelium derived factor (PEDF), beta actin, and thrombospondin 1 (TSP1). Subthreshold laser therapy is also hypothesized to improve RPE function by stimulating the upregulation of heat-shock proteins (HSPs).[3,4] Advantages of subthreshold laser therapy include the ability to apply treatment near the fovea or even transfoveally and its ability to be applied multiple times without a cumulative damage. This novel laser delivery modality, called the Micropulse laser was developed by Pankratov in 1990. His laser produced a train of millisecond laser pulses separated by variable quiet intervals, micropulsing allowed selective treatment of the retinal pigment epithelium (RPE) and sparing of the neurosensory retina.[5] This reduced the thermal retinal damage. However, being invisible, micropulse laser failed to become popular because of the belief that that no therapeutic effect is produced without a visible thermal damage to the retina.Non-destructive and thus non- inflammatory, SDML (Sub Threshold Diode Micropulse Laser) has been reported effective for a number of disorders and uniquely allows safe transfoveal treatment in eyes with good visual acuity.[7,8,9] SDML has also been uniquely shown to increase, rather than decrease, retinal sensitivity by microperimetry at the locus of laser application.[10]

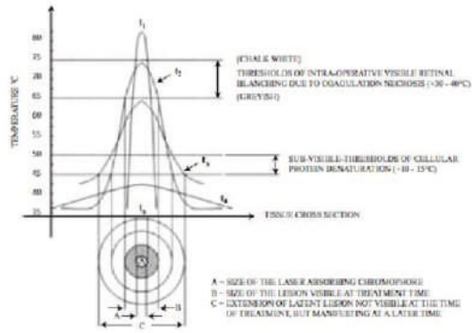


Fig 1: Temperature –Tissue interaction during CW laser photocoagulation. The laser lesion is small (A) but the visible lesion at the end of laser session is larger than the selected spot size (B); This further expands with time © [1]

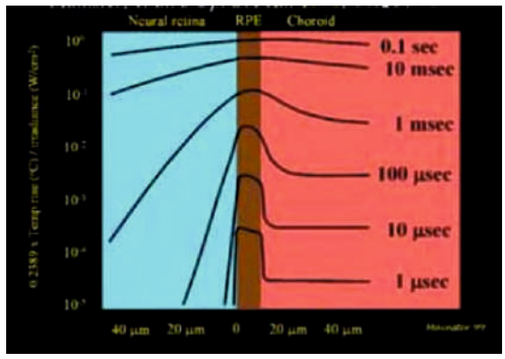


Fig2: If the laser energy is applied for 1 µsec the effect is restricted to RPE. With increasing duration of laser application for the same power there is increasing collateral damage[11]

Table 1: Thermal Diffusion distance versus Pulse duration in Water[12]

Pulse Duration µsec	Thermal Diffusion Diatance µm
1 sec or 100,0000µsec	1mm or 1000µm
0.5sec / 500,000µsec	707µm
100msec /100,000µsec	320µm
50msec/50,000µsec	225µm
10msec/10,000µsec	100µm
1msec/1000µsec	32µm
100µsec	10µm
10µsec	3.2µm
1µsec	1µm

Fig 3 : Subthreshold CW Laser: 532nm; 200 µm spot 50 mW; 30 msec; Clinical photo shows faint laser marks. FFA clearly shows the Laser induced damage (courtesy Dr. Sam Mansour)

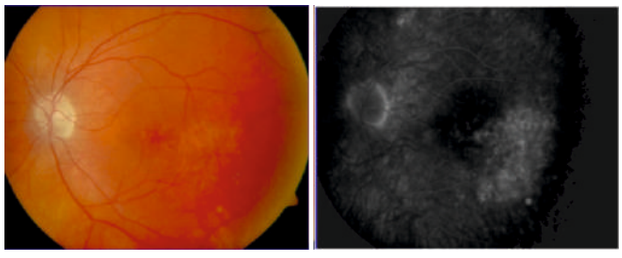
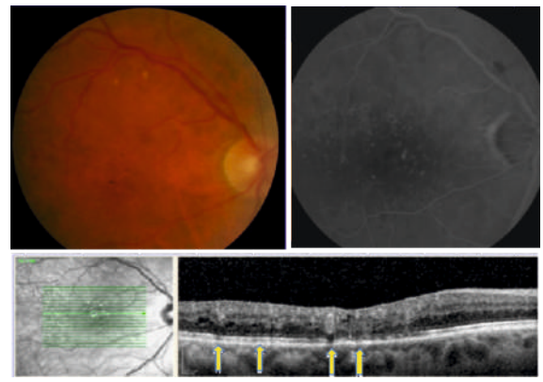


Fig 4: Subthreshold CW Laser: 532nm; 200 µm spot 50 mW; 10 msec; Clinical photo and FFA show no laser effect. OCT clearly shows the Laser induced damage (Yellow arrows)(courtesy Dr. Sam Mansour)



Continuous conventional laser can be delivered in a subthreshold fashion using lower energy, which may not produce clinical retinal whitening but will be detectable on an angiogram or OCT (Fig 3,4) demonstrate that by restricting the energy delivered to the RPE one can restrict the laser-induced damage. One hundred millisecond laser exposures at approximately half the threshold power of RPE damage induced transcription of HSP70, an indication of cellular response to sublethal thermal stress.[13] In a micropulse laser the laser energy is delivered as a pulse train interrupted energy with an "on" time when the laser is active and " off" time when the laser is off (Fig 5). The off time is the tissue relaxation time allowing the tissue to recover. The total amount of energy delivered may be the same as the CW laser delivered as single pulse, but because of on and off time the damage is restricted to the RPE alone. Hence it is not detectable either on FFA or OCT. This absence of clinical damage and hence absence of a clinical endpoint, has prevented the micropulse laser becoming acceptable.

Principles of Operation and Terminology : Recent advances in the understanding of laser photocoagulation indicate that tissue or cellular events occur at far lower laser exposure levels than needed to produce a clinically visible lesion. These may occur at a half to a fourth of the exposure needed to produce ophthalmoscopically obvious lesions. Additionally, VEGF down regulation has been noted to occur at even lower laser exposures. Therapeutic effects may thus be produced with milder retinal irradiances causing lower temperature rises associated with less or no significant retinal damage.[3,6,7,14]

Also, direct photocoagulation of the microvascular abnormalities is not required for resorption of the associated macular edema.[7] In fact, the RPE plays a significant role in the repair of the outer and inner blood–retinal barrier, regardless of the type or location of the laser application [15]. Laser photocoagulation decreases the intraocular concentrations of vascular endothelial growth factor and RPE derived

transforming growth factor beta II (TGF-βII), thereby inhibiting active retinal neovascularization. On the contrary, pigment epithelium-derived factor is upregulated after laser photocoagulation.[13]

In continuous wave mode, the laser energy is delivered as a single pulse, with a "width" typically in the range of 0.1–0.5 sec that constitutes the exposure duration. In micropulse mode, the laser energy is delivered with a train of repetitive short pulses (typically 100–300 µsec in duration each) within an "envelope" whose width is typically in the range of 0.1–0.5 sec, and this envelope duration constitutes the exposure duration. The "ON" time is the duration of each micropulse. The "OFF" time between successive micropulses reduces heat in the tissues and regulates the thermal isolation of each pulse contribution. The period T is the sum of the "ON" and "OFF" times and its reciprocal, 1/T, is the repetition rate in pulses per second (pps), also referred to as frequency f in hertz (Hz). The ratio between the "ON" time and the period T is the duty cycle in percent. (Figure 5) Repetition rate and duty cycle determine "isolation" of the increase in temperature produced by each single micropulse. Isolation of thermal rises requires a relatively long "OFF" cooling time and this implies a relatively low repetition rate. Dorin noted that the period T should not be shorter than 2 millisecond (1/500 sec), the "OFF" time should not be shorter than 1.7 millisecond, and the duty cycle should not exceed 15%. (23)

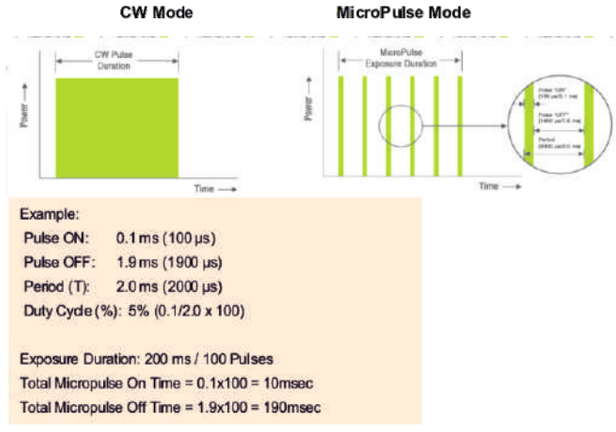


Fig 5: Duty Cycle Concept: In CW laser when a single pulse is fired the laser is on for the total duration of the pulse. In Micropulse laser with 5% Duty Cycle and exposure of 200ms,the laser is on for only 10msec (100 repetitive pulses each of 100usec is on time) and is off for 190msec (1900usec after each pulse of 100usec is the off time)

Kim et al found that micropulse power as low as 10–25% of the visible threshold power was sufficient to show consistent RPE-confined damage with sparing of the neurosensory retina with light and electron microscopy[16]. In Dutch belted Rabbits, Lavinsky et al have shown that laser power less than 30% did not produce any damage on the RPE. The correlation between the power of the laser needed for a visible threshold retinal burn and for histologically RPE-confined damage at various duty cycles can be used for determining the laser power for micropulse subthreshold treatments, in the absence of a visible endpoint.[17]

BIOPHYSICAL BASIS OF MICROPULSE LASER

Subthreshold micropulse laser intends to minimize the laser-induced chorioretinal damage and spare the neurosensory retina; and thus produce only sub-lethal thermal elevations, with effects that are invisible during treatment and remain so thereafter. It adheres to the following biophysical criteria:

Axial confinement of the thermal gradient at RPE

In retinal photocoagulation, the temperature first increases at the RPE. From the RPE, it spreads by conduction to re-equilibrate with adjacent cooler tissues. With the 100-msec exposure duration that is normally used in traditional photocoagulation, the heat production time is longer than the heat diffusion time and heat production is continuously fueled while heat diffuses. Therefore the RPE temperature equilibrates in the inner retina blemishing its transparency with the appearance of the "grayish" endpoint. Roider et al showed that for exposures in the microsecond rather than in the usual millisecond range, tissue damage is limited to subcellular molecular structures not detectable by electron microscopy, as the heat production ends before heat diffusion can occur[18]. (Figure 2 and Table 1)

Control of the thermal gradient at the RPE (avoiding excessive temperatures)

Even when the rise in temperature is confined around the RPE during laser exposure, unavoidable thermal equilibration could still damage the neurosensory retina. This can occur when the temperature at the RPE creates a heat wave that reaches the inner retina at lethal temperature levels. This post-operative inner retinal damage must be avoided by limiting the temperature rise at the RPE by adjusting the laser "irradiance" (power density in W/cm2). Micropulse laser damages only a small percentage of target tissue molecules with each micropulse, and repetitive micropulses combine to produce sub visible effects according to the semi empirical damage additivity or $N^{-1/4}$ law. The $N^{-1/4}$ law says that the same damage-threshold that can be achieved with one pulse of duration t and energy E, can be accomplished by using N repetitive pulses, each with the same duration t, but only a fraction (N−1/4) of the energy E, provided that all pulses are delivered in a brief time, shorter than any possible biological repair. For example, if a given damage-threshold can be achieved with a single laser pulse with E = 100 mJ, the same can be accomplished with 100 repetitive pulses, each having only E = 100 mJ × 100−1/4 = 31.6 mJ. Lower energy per pulse

reduces peak power, lowers the risk of hemorrhage, decreases the increase in temperature per pulse and, ultimately, results in improved confinement[19]. Micropulse laser works by producing sublethal cellular injury that causes production of **Heat Shock proteins (HSP70**), which has antiangiogenic and tissue restorative abilities. There is upregulation of **PEDF (Pigment Epithelium Derived Factor: (**plays a role in inhibiting neovascularization by its anti-angiogenic activity); TSP1 **(Thrombospondin1:** one of the most potent anti-angiogenic factors); SDF1 **(Stromal Cell Derived Factor1:** plays a key role in recruitment of bone marrow-derived reparative cells) and ß**-actin (**protein that is involved in cell motility, structure and integrity), HSPs have activity against apoptotic pathways and inflammation. Multiple studies demonstrate that HSPs interfere with both caspase-dependent and caspase-independent apoptotic cascades in various tissue types, including, brain, spinal cord, and retinal ganglion cells[20-23]. HSP70 upregulates the anti-apoptotic protein Bcl-2 and may also prevent mitochondrial cytochrome c release. In addition, HSP70 prevents formation of the complex central to caspase-dependent apoptosis, the apoptosome, while also inhibiting activation of caspase-3. HSP70 also interferes with the caspase-independent apoptosis-inducing factor[21-24]. HSP reduces the presence of inflammatory mediators such as TNFα, possibly through interaction with NFκB (a nuclear transcription factor for multiple genes associated with inflammation) and its inhibitor, IκB

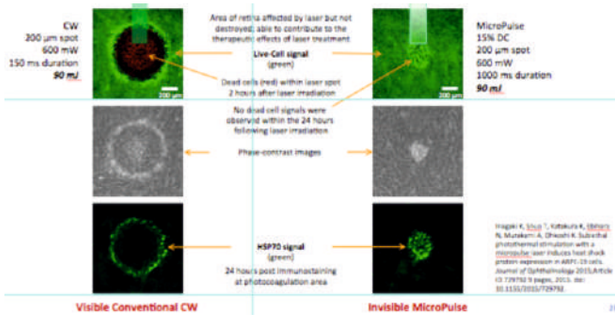


Fig6: Induction of HSP70 in ARP-19 cells recoded on phase contrast microscopy. With CW laser there is an umbra around the destroyed cells that show HSP70production. In a micropulse laser with same energy there is production of HSP70 at the site of laser burn[25]

Micropulse Laser was earlier delivered as low intensity and low density. This has now changed to low intensity, high density (no inter burn space). Macular treatment is done with 5% Duty Cycle while Micropulse PRP is done with 5% 0r 10% duty cycle.

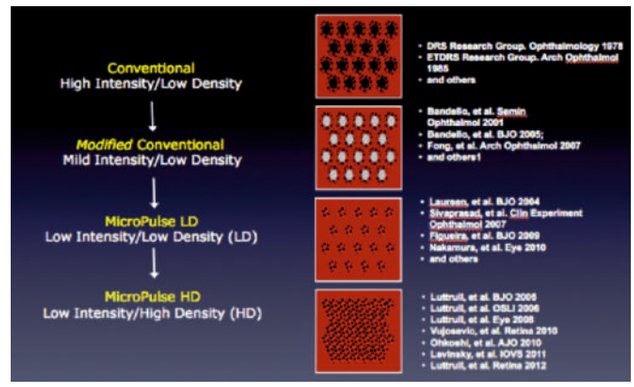


Fig 7: Evolution of Laser application from micropulse laser delivered with low intensity with low density and recently low intensity and High Density

CLINICAL APPLICATIONS OF MICROPULSE LASER IN RETINAL DISORDERS

Subthreshold micropulse diode-laser (MPD) protocols using a micropulse 810 nm diode laser were originally pioneered by Freiberg and Hamilton and are now gaining the interest of retinal surgeons worldwide.[26,27] It has been found to be equally efficacious and less destructive than conventional laser in a number of diseases. Shorter wavelength lasers (below 550 nm) have been found to produce photochemical damage to the neurosensory retina without improving outcomes. Thus, the therapeutic effects of retinal laser treatment appeared to be entirely thermal in origin. Recently, the 577nm Yellow Micropulse laser, has become the preferred wavelength for micropulse laser. This being a visible wavelength, can also work as conventional CW laser where necessary. It produces less pain than 810nm diode laser.

TITRATION OF LASER POWER

The main problem with Micropulse laser has been to decide appropriate laser parameters, as the endpoint is invisible. There is always a worry that we may be undertreating. This fact is compounded by case reports using same machine showing MPLT to be effective at widely varying power. Following are suggested option of titrating the laser power.

1) **Standard parameters as recommended by the Laser Manufacturer (Iridex)**: No Test Burn, 400mW power, 200msec duration, 5% Duty cycle and 200um spot size.

2) **Test Burn in the CW mode:** Laser test burn is given nasal to the optic disc in CW mode. The parameters used are 200msec, 200um spot size. The power at which a faint whitening is seen is recoded, say x. The laser is now shifted to Micropulse mode at 5%Duty cycle. The power is now tripled/quadrupled i.e 3x or 4x, keeping the spot size as 200um and duration 200msec.

3) Test Burn in Micropulse Mode: Laser is turned to micropulse mode 5%Duty cycle. Power is raised to 1200mW, duration 200msec and spot size 200um. Laser test burn is attempted nasal to the optic disc. till a faint whitening is observed. This may happen anywhere between 1200 to 2000mW.The power so determined is then reduced to 30% and this is used for treatment purpose.

Other Methods: Some Micropulse Laser machines use End Point Management system. Numerous authors have reduced the spot size to 150um.

CHOICE OF DUTY CYCLE

Duty cycle (the frequency of the train of micropulses) decides the duration of on and off time and the frequency with which the laser gets on. The lower the duty cycle, longer the off time between pulses (lower repetition rate) and lesser the heat buildup. If the off time exceeds the thermal relaxation time of RPE melanin (the target molecule), the average tissue temperature rise in the RPE during micro pulsed laser application can be maintained below levels lethal to the cell.

From the available evidence most studies use 5% duty cycle for the treatment of macular diseases. There have been studies that have used 10% or 15% DC. Present Clinical data and computer modeling has demonstrated that treatment safety is maximized by the use of 5% or lower duty cycles. Higher duty cycles rapidly take on the clinical characteristics of CW lasers.

Lutrull et al in a long term retrospective review of 274 consecutive eyes with Macular Edema due to DME/BRVO who were treated with Heavy density MPLT at various duty cycles (DC): 5%, 10% and 15% and followed up 10 years found 8% of eyes (7/84) showed laser induced retinal damage when treated with DC10-15% while no eye treated with 5% DC (0/168) showed any Retinal Damage.

CURRENT INDICATIONS FOR MICROPULSE LASER AND PERSONAL EXPERIENCE (1-6)

1. Central Serous Chorioretinopathy
2. Diabetic Macular Edema
3. Proliferative Diabetic Retinopathy
4. Macular edema due to BRVO
5. Macular edema due to non-ischemic CRVO
6. Post ERM peel Macular Edema
7. CNVM not responsive to antiVEGF therapy
8. Inherited Macular Degenerations

1) CENTRAL SEROUS CHORIORETINOPATHY

Most cases of central serous chorioretinopathy (CSR) have a self-limiting course, but patients who need rapid recovery of visual acuity or those with a chronic course threatening visual recovery may benefit from continuous-wave laser photocoagulation. (37) Traditional laser treatment in CSR, however, has several drawbacks, including symptomatic scotomas, choroidal neovascularization, foveal distortion, and subretinal fibrosis, especially in cases with juxtafoveal leaking points. Enlargement of the laser spot may also threaten central vision. Bandello et al first proposed MPLT for the treatment of CSR in 2003. In their study, five out of five eyes showed complete resorption within 1 month of MPLT and maintained through 4 months of follow-up. No evidence of retinal changes resulting from laser treatment was discernible with fluorescein angiography or fundus biomicroscopy.[39]

All studies in which MPD laser treatment was used for CSR have supported the hypothesis that MPD produces therapeutic benefits comparable to those of conventional photocoagulation with no detectable signs of laser-induced iatrogenic damage. [39,40] The absence of a visible endpoint, however, represents a challenge for the surgeon. To overcome this problem, some investigators performed MPD treatment over ICG-stained RPE cells to enhance the selectivity of the treatment for the active leaking sites while sparing the neurosensory retina. This also aided in the documentation of the placement of laser applications seen as dark spots in the ICG background fluorescence.[41]

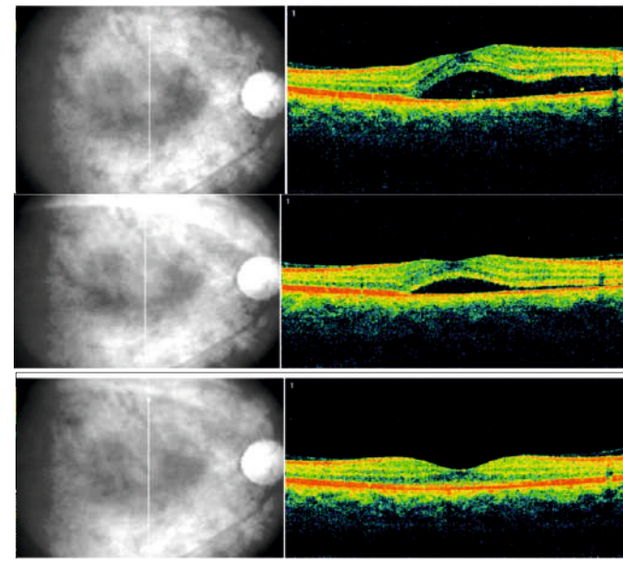


Fig 8: (Top) 8 weeks after onset;(Middle) 7 days after MPLT; (Bottom) 3 weeks after MPLT

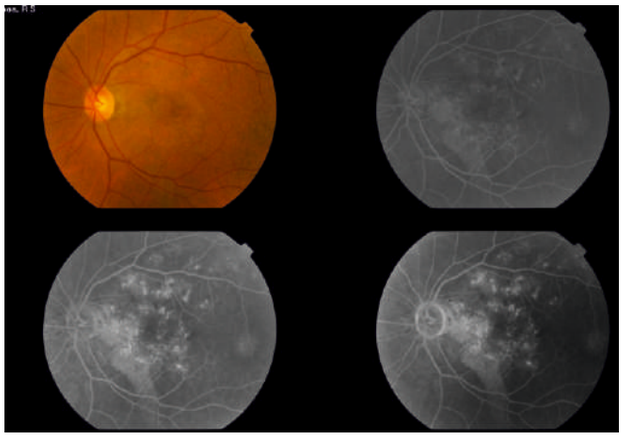


Fig 9a *58 years male Chronic CSR for 14 months : Fundus Photo and FFA*

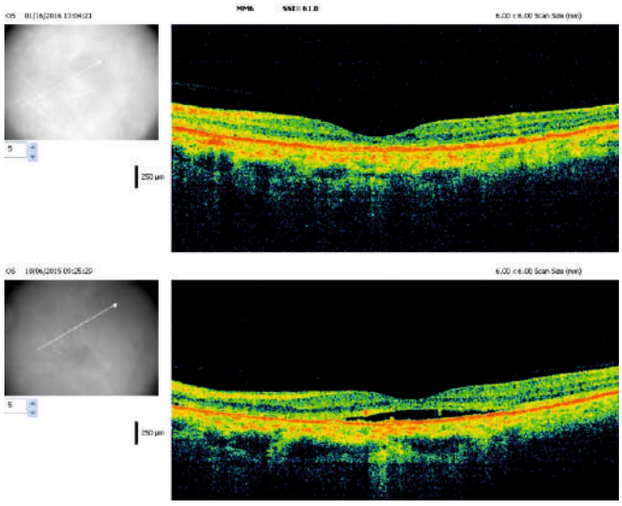


Fig 9 b: 58 years male Chronic CSR 14 months; Foveal flattening after single MPLT

Over 30 studies for Micropulse Laser have been published including retrospective and randomized controlled studies of various sizes employing a variety of different laser wave-lengths, treatment parameters, treatment protocols, and patient populations. Despite such heterogeneity, in all studies MPLT for CSR has been found to be effective: comparable to half-fluence photodynamic therapy. Nearing completion is the PLACE (Prospective Randomized Controlled Treatment Trial for Chronic Central Serous Chorioretinopathy) trial (clinicaltrials.gov: NCT01797861), a randomized prospective clinical trial in the Netherlands comparing half-dose verteporfin photodynamic therapy with MPL for CSR. Initial data from this indicates that MPLT is as good as half fluence PDT, if not better[42].

2) DIABETIC MACULAR EDEMA

Diabetic macular edema (DME) is the leading cause of visual impairment in patients with Diabetic Retinopathy. Before the advent of antiVEGF therapy ETDRS laser treatment had become the standard for DME, with focal photocoagulation being done for localized areas of leakage and a grid pattern being applied to areas of diffuse macular edema. The ETDRS showed that increased treatment intensity was associated with more adverse treatment effects, increased treatment density improved clinical results, grid treatment was as effective as focal treatment; and the location and extent of macular angiographic leakage did not correlate with clinical outcomes. This information provoked use of higher density with lower intensity laser photocoagulation. However, laser induced retinal damage was still the end point for most ophthalmologists. In 1997, Freiberg and Karatza first reported clinical application of MP 810-nm diode laser therapy for DME They however used 15%DC. Lutrull et al with their report on clinically significant macular edema set the benchmark of using 5% Duty cycle for macular treatment. They showed that benefit could be achieved without visible/invisible retinal damage. This also supported contiguous treatment with no interburn spacing. This new approach, called “low-intensity/high-density subthreshold diode micropulse laser” (HD-SDM), allowed effective and reliable sublethal retinal laser treatment without any retinal damage or adverse effects. This SDM strategy of sublethal retinal laser application defines modern retinal laser treatment.

Levinski et al in their prospective, randomized, clinical trial in previously untreated DME patients showed that at 1 year, the clinical performance of HD-SDM was superior to that of the mETDRS (modified ETDRS) photocoagulation technique, both anatomically and functionally. They suggested that, as experience grows, HD-SDM might become the preferred treatment approach in these cases.

Today, in the antiVEGF era, pharmacotherapy is commonly employed for Centre involving DME and laser is used for non-Centre involving DME as per ETDRS protocol. Steroids are added in pseudophakics and those who do not respond to antiVEGF. This strategy involves multiple Intravitreal injections and carries with it the risks associated with Intravitreal injections. It is believed that MPLT will support pharmacotherapy, reduce the intraocular procedures and hence the complications associated with Intravitreal injections. I personally use MPLT after the central macular thickness has reduced to less than 450µm. (Table 2)

Table 2: Central Foveal thickness based Interventions Algorithm

Central Foveal Thickness	Algorithm
< 250 µm	a. Observe
250 – 450 µm	a. anti-VEGF injection) or /and b. HD-SDM (Contiguous MPLT)
> 450 µm	a. Pre treat with anti-VEGF injections b. HD-SDM, after CFT is reduced to around 450µm

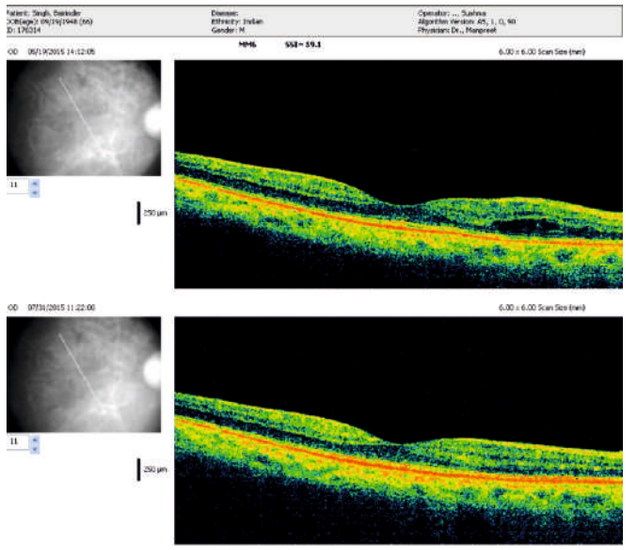


Fig 10: Non Centre Involving Diabetic Macular Edema treated with 5%DC MPLT and followed up after 10 weeks with cataract surgery

3) PROLIFERATIVE DIABETIC RETINOPATHY

Untreated PDR is the leading cause of blindness in PDR cases. Protocol S has demonstrated that Intravitreal injection of Ranibizumab is non inferior to PRP and at the end of two years 40-45% eyes treated in both groups (Ranibizumab and PRP) had active Neovascularization.

Moorman and Hamilton using high duty cycle of MPL were able to deliver minimal intensity MP PRP without causing clinical retinal damage and avoid any other adverse events. In 10 of the 13 eyes treated, they noted regression of Neovascularisation[27]. Lutrull et al used 15% DC of sublethal panretinal micropulse laser (SDM PRP) in 99 eyes (61 with PDR and 38 severe nonproliferative DR) of 69 consecutive patients treated between 2000 and 2003, and followed for a median of 12 months.[35] Overall VA remained unchanged, but the proportion of eyes with excellent VA (20/30 or better) increased from 39% to 48%. SDM PRP was performed in a single session with topical anesthesia, and no patient reported postoperative pain or loss of visual acuity, accommodation, night vision, or visual field. No eye progressed to a surgical traction retinal detachment or neovascular glaucoma. Only 3 of 38 eyes with severe non-PDR (7.9%) progressed to PDR. Compared to the expected annual rate of 50%, this reduction in DR progression was significant (P = 0.0001).

Till we have larger studies available, it may be best to explain the available options to the patient. He must understand the pros and cons of using antiVEGF agents or MPLT versus the time tested CW laser PRP.

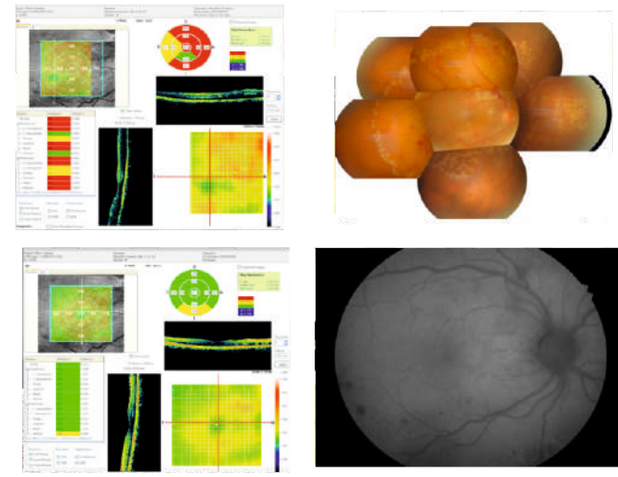


Fig 11: Forty-three years male Diabetic for 10 years, non-hypertensive: PDR with CIDME, good metabolic control, underwent CW Laser demarcation of the area to be treated, Focal Laser with CW laser over the areas of NVE. Remaining areas were treated with 10% DC MPLT. He has been on follow-up for 2 years. Underwent Follow-up with multimodal imaging and received supplementation of MPLT supplementation at 18 months. His VA is maintained at 6/6 and his fields are normal.

4) MACULAR EDEMA SECONDARY TO BRVO

Limited studies have described the use of MPD laser in the treatment of macular edema secondary to branch retinal vein occlusion. [43,44] Parodi et al have shown that MPD laser treatment is as effective as conventional grid laser photocoagulation in reducing macular edema (ME) and improving the VA, even though the MPD acted more slowly. Lutrull et al have demonstrated that 5%DC is ideal for treating Macular edema due to BRVO. Since macular edema in BRVO waxes and wanes, MPLT may actually be beneficial in these cases as it can be repeated whenever indicated.

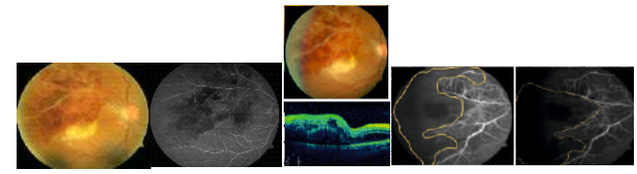


Fig 12a

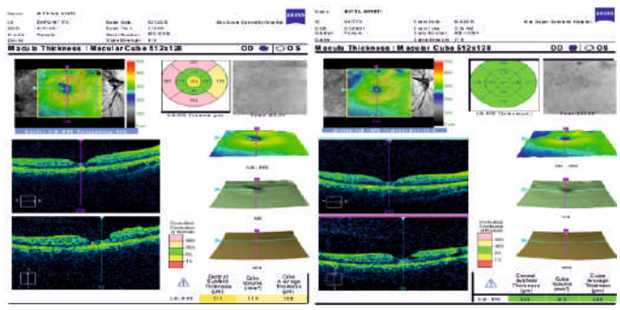


Fig 12 a and b: 23 years female, Inflammatory BRVO with Macular edema, VA 6/60; treated with systemic steroids and later with two Intravitreal injections of Bevacizumab. VA improved after first injection to 6/12 and later 6/36.Underwent third injection of Avastin followed by Sectorial MPLT (area marked out on Fundus photo) with 10%DC. VA improved to 6/9 with clearance of retinal hemorrhages. Underwent repeat Sectorial MPLT after 14 months and has maintained dry macula with VA of 6/6p for 36 months.

5) MACULAR EDEMA DUE TO NON-ISCHEMIC CRVO

There are no documented reports of MPLT for CRVO. Ischemic CRVOs may not respond to a MPLT intervention. I have treated Non Ischemic CRVO with initial VA 6/60 with MPLT 5%DC to the macula and 5% DC to extra macular areas.

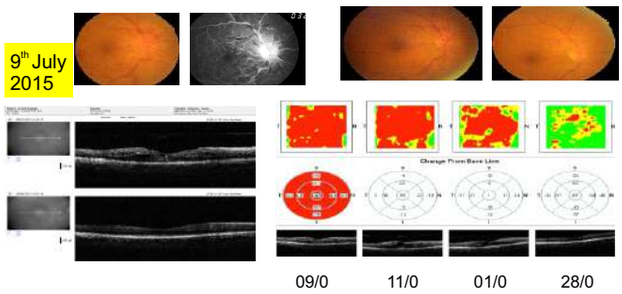


Fig 13: Case 1: 76 years male, operated CA rectum, Hypertensive for 20 years, diabetic 8 years, Non Ischemic CRVO with VA of 6/60. Refused Intravitreal injection of antiVEGF and was treated with 5%DC of MPLT to the macula and 5%DC MPLT to extra macular areas of capillary non-perfusion. VA improved to 6/12 in 6 weeks with reduction of CMT on sequential OCT.

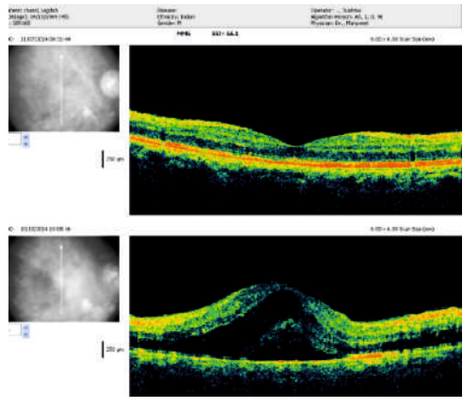
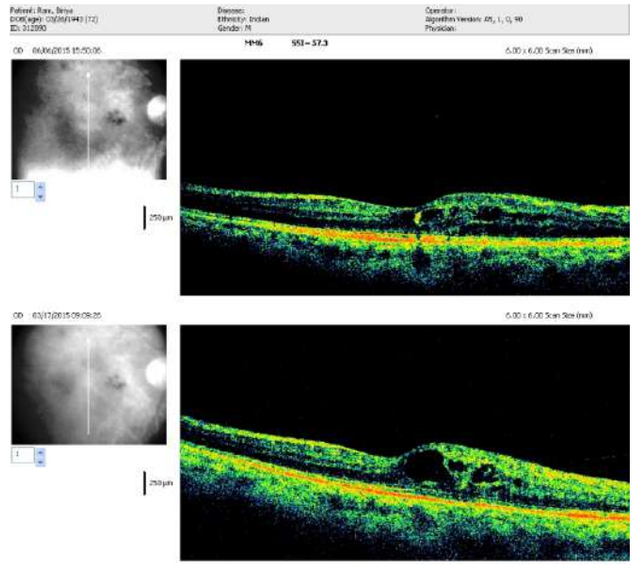


Fig 14: Case 2: Non Ischemic CRVO: 46 years male, 8 years Hypertensive, non-diabetic, VA 6/60. Received two injections of Intravitreal Avastin with minimal response. Macula treated with 5%DC MPLT. Responded with macular flattening and improvement of VA to 6/9

6. POST ERM PEEL MACULAR EDEMA

Fig 15: 72 year's male, Operated Vitreous Hemorrhage for BRVO, developed macular pucker. Underwent Re PPV with ERM peel and two Intravitreal injections Avastin and later IVTA without any improvement. Subsequently underwent MPLT at 5%DC .VA improved from 6/24 to 6/18 with reduction in macular edema (15a is before and 15b after treatment)



7. CNVM NOT RESPONSIVE TO ANTIVEGF THERAPY

In 2000 York and colleagues used indocyanine green angiography guided micropulse laser to close choroidal feeder vessels in neovascular age-related macular degeneration (AMD).[45] In 2015, Lutrull et al reported reversal of tolerance to anti-VEGF drugs in neovascular AMD using SDM.[46] Thirteen eyes, 73-97 years old, having received 16-67 antiVEGF injections and unresponsive to all anti-VEGF medications for at least 6 months and 4 consecutive injections of aflibercept were treated by MPL. One month later anti-VEGF therapy was resumed. After rechallenge and resumption of aflibercept, there was improvement in 12 of the 13 eyes and complete resolution of macular exudation in 9 of 13 eyes. They believe the reversal of drug tolerance in wet AMD by MPL was predicted by "Reset to Default" theory, which describes the clinical effects of RPE HSP activation. As the first report of drug tolerance reversal in medicine, these findings lend support to the reset postulate. In 2016, Lutrull and Margolis reported, "functionally guided panmacular micropulse laser" as "retinal protective therapy" in high-risk dry AMD and inherited retinopathies.[47] Patients were evaluated before and after SDM retinal protective therapy by pattern electroretinography (PERG) and visual function tests. After SDM retinal protective therapy, 139 of 158 eyes were improved by PERG (P = 0.0001). VA was unchanged, but macular sensitivity by microperimetry (40 eyes) and mesoptic contrast visual acuity (73 eyes) improved (P = 0.0439, and P = 0.006, respectively). However,

there was no change in retinal morphology, such as drusen number, size, or distribution. Eyes with the worst preoperative status improved the most by all indices (P = 0.0001). This included eyes with extensive geographic atrophy (GA). By maintaining improved retinal function guided by early and periodic electrophysiological signals, rather than late-imaging signals, the authors hope to reduce the long-term risk of vision loss. In a subsequent retrospective study of 454 consecutive eyes of 296 patients in the Age-Related Eye Disease Study treated with panmacular SDM for high-risk dry AMD and followed a minimum of 1 year (range: 1 to 7 years, average: 2 years), the incidence of new choroidal neovascularization was found to be less than 1% per year.[48] This was despite an average patient age of 83 years and high independent risk factors including fellow eye choroidal neovascularization (26%), reticular pseudodrusen (38%), and AMD severity (78% Age-Related Eye Disease Study categories 3 and 4), all significantly exceeding the Age-Related Eye Disease Study. These findings suggest that panmacular SDM may reduce the incidence of choroidal neovascularization in dry AMD more than vitamin therapy alone. In addition, in 409 of these same eyes, best-corrected logMAR mesopic visual acuity (P < 0.0001) and visual fields (P = 0.0007) were also improved following pan- macular SDM. There were no adverse treatment effects or retinal damage. These findings suggest that retinal and visual function testing may be useful surrogate indicators of longer-term treatment benefits .[47]

8. INHERITED MACULAR DEGENERATIONS

In a small group of inherited retinal diseases (IRD) Luttrull and Margolis [50] reported PERGs improvement after SDM in 10 eyes of 8 patients (retinitis pigmentosa (4 eyes), cone degeneration (3 eyes), and Stargardt disease 3 eyes). While eyes with AMD improved most by a low-contrast PERG, IRD eyes improved most by the widest-field (24 °) high-contrast PERG protocols. In both AMD and IRD, measures of signal latency improved most significantly. The authors note that both the functional improvements and the distinct PERG responses in AMD versus IRD were predicted by the reset theory of retinal laser action.[50]

CONCLUSIONS

Subthreshold micropulse laser is a relatively novel laser modality that has good clinical efficacy and minimal risk of iatrogenic side effects. The greatest limitation of MPLT is the difficulty of titrating the treatment without the feedback of an ophthalmoscopically visible endpoint. This is more of a mind set issue. The available literature with multiple randomized trials and the evidence of production of HSPs after MPLT should be enough to convince the fence sitters. Also considering a broad range in which MPLT is safely effective should make it easier for clinicians to accept it as a reliable modality in the treatment of selected cases.

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Notes

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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. 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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. 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