The official Newsletter of the

VITREO RETINAL SOCIETY - INDIA

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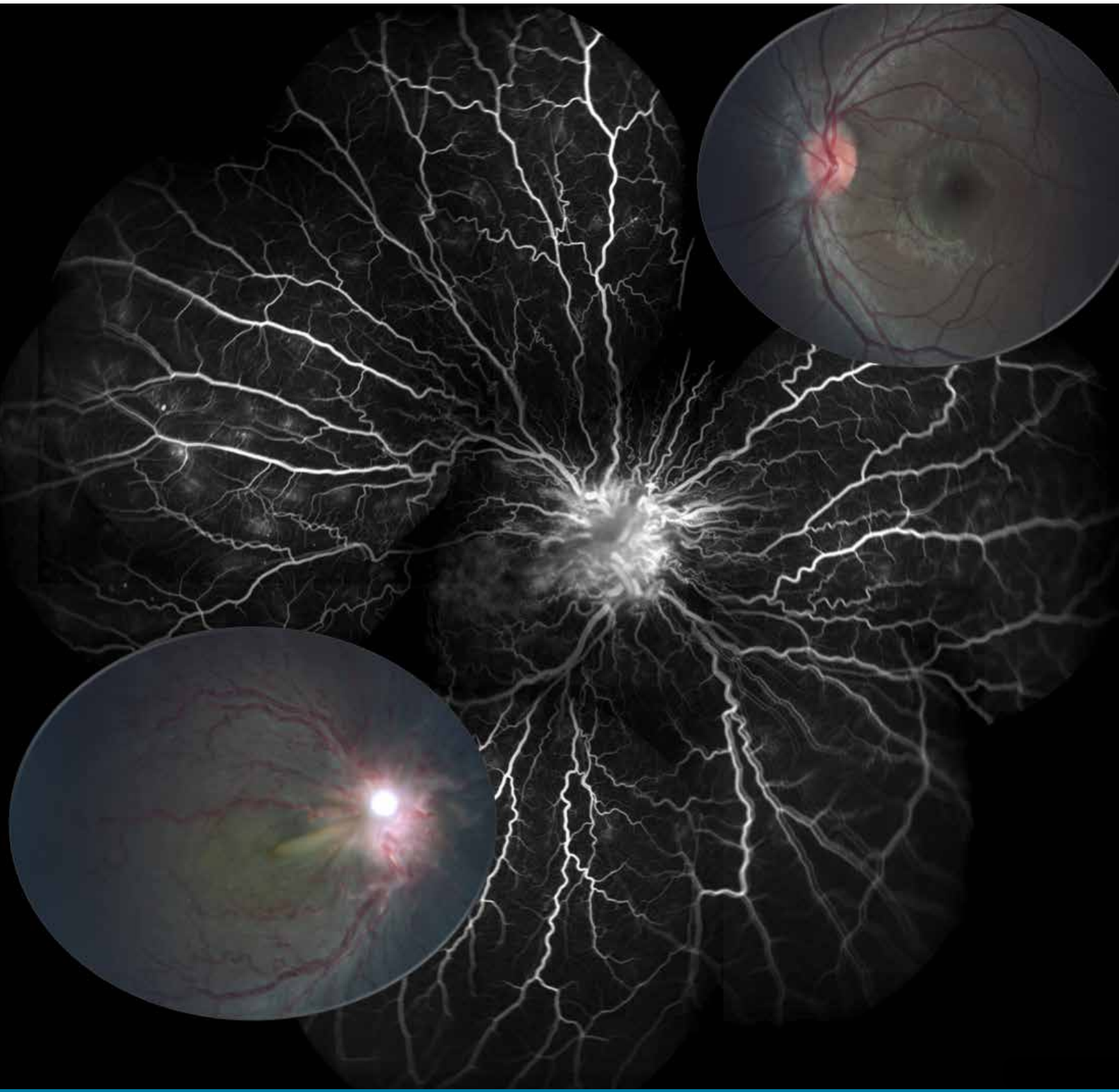

From the President's Desk

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Dear Friends,

On behalf of Vitreo-Retinal Society of India (VRS-I), I extend warm welcome to all the members to the **Silver Jubilee Annual conference of VRSI** to be held on **30 November to 4 December, 2016** at Chandigarh. I would like to thank the Local Organizing Committee headed by Dr. Sunandan Sood, and the Organizing Secretary Dr. Subhina Narang and executive team of the LOC (including Stalwarts like Prof. Amod Gupta & Dr. Mangat Dogra), who have plans to make this mega event a grand success.

Being Silver Jubilee year, we have large number of International Society participation in the VRSI annual conference. **Macula Society, Euretina, American Society of Retina Surgeons, Egyptian Vitreo-Retina Society** apart from, **Retnet India and Members of SAARC Countries** taking active part. I hope this international association will certainly take the conference to a new high.

VRSI newsletter is a regular feature of academic activity of the VRS-I. Our Convener Scientific Committee Dr. Kim Ramasamy and his team put in lot of efforts in bringing this issue. This issue features tribute to Dr. Amod Gupta, a living legend, who has contributed immensely to the scientific literature. Featured articles on OCT in Ocular tumors, Optic Nerve Head Melanocytoma certainly interest the readers. This issue of newsletter also touched upon the new therapeutic options for DME and Micropulse lasers in CSCR. Subretinal abscess and submacular hemorrhage management can be tricky and are also been chaptered. Sickle cell retinopathy needs a distinguished and effective treatment which has been described well with a case report.

This issue features long awaited VRSI/AIOS Guidelines on intravitreal Avastin. As all members know we, along with AIOS, could successfully convinced the Government to lift the ban imposed on this very essential drug. These are the days of literature bombardment. It is very essential to rationalize the available material. Unless one masters the art of analyzing the publications in a given journal, arriving at a logical conclusion is very hard. In this regard, the chapter on how to analyze a Journal article may prove handy. This newsletter features glimpses of the VRSI Conference held at Kumarakom, will refresh our memories and certainly stimulate the members who missed last conference to attend this year's Silver Jubilee Conference.

I would like to thank all the contributors of literature for this newsletter and people who helped the scientific committee to put things together. I would like to place my special thanks to Dr. Kim Ramasamy for his untiring efforts for the scientific programs of the Society. Dr. Vishali Gupta, our Hon. Secretary certainly needs appreciation for her efforts to make the society effective in day to day functionality. The executive members of VRSI have contributed through their critical reviews and positive feedbacks on all the planning for the Silver Jubilee Year.

From the Hony Secy Desk

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Dear friends,

It gives me immense pleasure to write this foreword for the newsletter that shall be released during the historical event celebrating 25th year of Vitreo-retina society of India. This year has been an eventful year for VRSI, with total membership reaching 700, thus making it one of the largest societies of Vitreoretinal surgeons. The last annual conference held in Kumarakom Kerala was a huge success with record number of attendees and on behalf of VRSI, I would like to thank the local organizing committee as well as each one of you for contributing towards the success of this meeting. We do look forward to an enthusiastic participation from all of you to celebrate the silver jubilee of our society in Chandigarh between November 30th to Dec 4th 2016. We have received an overwhelming response from several international societies and would have the participation by The Macula Society, ASRS, Euretina, Egyptian Vitreoretina society, Retnet India. This shall be a mega event and we do look forward to active participation from all our members.

During early part of this year, the DCGI issued an alert notice to ban the use of intravitreal Avastin. Our society acted promptly and our president requested All India Ophthalmological Society to join hands for acting to get the ban lifted. The VRSI is thankful to the executive committee of AIOS as well as our own members who worked tirelessly day and night and got a historical decision where the alert notice was revoked. The combined AIOS-VRSI guidelines have been prepared and circulated to all our members. The current issue for the newsletter has a copy of these guidelines for your reference. In another uphill task, VRSI worked with AIOS to get the list of official distributors of Avastin from Roche and is still working to get the Kezzler code reinstated. We request all our members to follow the guidelines and be safe.

As the society grows, it is now payback time and keeping this in mind, VRSI wishes to take up several charitable activities including public education. This shall expand the role of society to educate the public as well as comprehensive ophthalmologists. We shall keep you all updated on these activities.

In continuing the efforts of previous years, the editorial team of VRSI has worked extremely hard to bring out this newsletter. On behalf of VRSI, we would like to thank the editorial team for bringing out this amazing newsletter that I am sure all of you would enjoy reading.

Looking forward to see you all in Chandigarh

Vishali Gupta

From the Convenor Scientific Committee Desk

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We are gearing up for the **Silver Jubilee Annual conference of VRSI** to be held on **30 November to 4 December, 2016** in the City beautiful, Chandigarh.

With the special arrangements made by the local organizing committee efforts of office bearers and members of the VRSI, the annual conference at Kumarakom was a grand success. In spite of the Chennai floods, the conference was heavily attended and appreciated, setting up a new benchmark for the forthcoming annual meetings. Being the Silver Jubilee year, many International Retina Societies have been invited for participation in the planned mega event. The Macula Society, Euretina, American Society of Retinal Surgeons, Egyptian Vitreo-Retina Society and Retnet India would be taking active part in the proceedings. I hope the deliberations of our esteemed international faculty will enrich our minds with new ideas and their expertise provides worthy wisdom for our clinical and surgical practice.

The vitreoretinal consultants in India faced an unprecedented challenges this year, especially the alert notice issued by DCGI on the use of Avastin for intraocular use. All of you are aware of the efforts taken by VRSI in association with AIOS to convince the Government to lift the ban imposed on this very essential drug In this issue the important guidelines for the intravitreal Avastin designed by the VRSI/AIOS has been included along with the numerous other interesting articles.

We are bringing out the VRSI newsletter as a regular academic activity of the VRSI. Our team tries to put in their best efforts in getting good academic articles which are current and futuristic. I would like to thank all the authors for their excellent contributions for this newsletter. I urge each one of you to send in their work in form of original articles, interesting case report/series, images and review of literature; which would benefit our readers.

I would like to thank our vibrant President Dr. Ajit Babu Majji and our ever active Honorary Secretary Dr. Vishali Gupta, for their constant support and advice. I thank all the executive members of VRSI for their support and critical reviews on all the planning for the Silver Jubilee Year. A word of special appreciation goes for my team members, Dr. Anand Rajendran, who helped the scientific committee to put things together and Dr. Jatinder Singh, who helped in collecting the various articles and organizing this issue.

As the Chairman Scientific committee, I would appreciate suggestions, participation and support from you on various academic activities of VRSI to enhance the level of retinal care across the country.

Thank you
Dr. Kim Ramasamy

Whither India Retina!

Taraprasad Das
Vice Chairman, L V Prasad Eye Institute,
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The care for vitreoretinal diseases has come a long way from low products and unsure results to efficient technology and predictable outcome. Thanks to very sincere efforts of innumerable clinicians, clinician scientists, technologists and the industry. While the scientists worked to understand the basic pathobiology, the clinician scientists worked on several probable hypotheses. While the clinicians translated these new discoveries into practice, the industry matched the patient's need. Finally the randomized clinical trials formed the basis of evidence-based care. It has always been a combined effort. There are many giants and my list is not inclusive. Charles Schepens designed the modern indirect ophthalmoscope, Jules Gonin unraveled the pathobiology of retinal detachment, Robert Machemer designed the instrumentation for a closed vitreous surgery, Arnall Patz understood the blinding effects of excess oxygen in a pre-term, under-weight baby, and Judah Folkman researched with retinal angiogenesis. In recent times, Shrnya Yamanaka further researched the initial findings of John Gurdon on reversible nature of cell on reprogramming of cells and his team introduced the potential of induced pluripotent stem cell (iPSC). We all believe, this new technology with or without gene therapy, will herald an era of personalized medicine that will treat many hitherto untreatable vitreoretinal disorders.

Where does India stand in this quest? We have been beneficiary of all these new finds and have successfully applied to our patients in our daily practice. We had the benefit of some of the Indian giants such as SS Badrinath, P Namprumalsamy, PN Nagpal and Bijayananda Patnaik, who chose to return to India after their international training and work in difficult and challenging conditions to breed generations of vitreoretina specialists in India. Many who availed this new opportunity are now very accomplished leaders in the country. The current generation is better prepared than ever before, and thanks to the flattening of the world there is a free exchange of knowledge.

The early masters had a mission- shifting the traditional mass cataract surgery model of eye care to institutionalized eye care and developing exclusive vitreo retinal services within the institution. This has brought a number of advantages. Now we have retina specialists spread across the country. They meet annually through the Vitreoretinal society of India (VRSI) that started in 1992 and is celebrating the silver jubilee this year. Many fellows trained by the masters are offering very robust specialized training programs (retina fellowship). These continuing efforts have resulted in over 500 practicing retina specialists in India. The young truck today travel extensively, speak at or listen in many advanced retina courses; several of them have also worked with international stalwarts to advance their knowledge and skill. The immediate effect is that we no longer encounter very advanced retinal detachments and most of the vitreoretinal conditions are managed effectively. The Indian industry has risen proportionately to match the clinician's need and patient's demand. We have witnessed a dramatic decline in the incidence of primary vasculitis (often grouped under Eales' disease) and this is probably related to better socio economic conditions in the country and institution of early treatment. In many senses India has become a destination for advanced vitreoretinal care for many neighboring countries and Africa. While we will probably not be off the mark to boast of our clinical services, can we say the same for our research and contribution to the world of scientific knowledge?

The mission of yesteryear can't be the same today. The mission of our pioneers was to build. The mission of the generation next was to consolidate the gain. And the mission of the current generation should be to focus- focus on the problems unique to us. There is now widespread acknowledgement that the Indian researchers are best placed to ask questions that are relevant to India. In my opinion we must move away from parachuting research questions in from high-income countries to address India's problems. But how can this be done without the local capacity? It is time that we groom a generation of clinician scientists. They in turn will identify common problems and focus on every aspect- individually and collectively. It is time that we make large research consortium that will address the entire spectrum of the disease- prevention, cure, and rehabilitation. Our focus must base on the roots of public health, flower with sound evidence-based clinical care and fruit in translational research.

Let me identify two diseases that has haunted in my entire professional life- Diabetic eye disease and retinitis pigmentosa. Diabetes mellitus affects nearly all segments of the eye even though the most blinding cause is the retinopathy. Today we are home to 65.1 million diabetics (from 50.8 million in 2010); there is near equal urban-rural and gender divide. [1] The recent situational analysis by the Indian Institute of Public Health (IIPH), the Public Health Foundation of India (PHFI) identified the gaps in the Indian policy frame work. Two important gaps were the "lack of focus on building sustainable synergies" and

the “poor convergence between the national programs.” It was suggested to rely on strong operational research and bring about a “nuanced holistic perspective” with implementable goals. [2] While this policy shift will strengthen our diabetes and diabetic eye disease care, the Indian retinologists have an opportunity to put the heads together to form a clinical research platform similar to the Diabetic Retinopathy Clinical Research network (DRCR.net) in the USA. This network will address India relevant research questions in diabetic eye disease in specific and the retinal disorders in general. The DRCR.net is a National Eye Institute (NEI) sponsored program that allows public and private groups to design and research on common protocols that creates new evidences in diabetic retinopathy care. This northern American work has worldwide impact. India with a large population, disease prevalence and availability trained eye care personnel, is eminently placed for this kind of collaborative work that will define care of many eye diseases.

`Retinitis pigmentosa (RP) is an inherited, progressive rod photoreceptor degenerative disease that is partly related to consanguineous marriage. A sizeable population in India is affected and this results in loss of productivity. It is a multi-gene disorder and is perfect example where the scientists and clinicians could work together in search of a cure. Nearly two decades ago we worked on the fetal neural retinal transplant in patients with severe bilateral retinitis pigmentosa. Our study proved the safety of such transplantation, but registered a limited functional success.[3] Following this work there were similar studies in the other parts of the world, and with similar results. That brought others and us back to the laboratory to work on a different strategy of retinal cell replacement. Hopefully we will find a solution soon.

The inescapable conclusion is the need for collaborative research networks within India, and between India and the rest of the world. The researchers in India are always better equipped to address India relevant questions. This process has already begun in India, but needs a huge push. A recent analysis has illustrated the status of medical research in India. [4] With only 4.3% (n=25) institutions publishing over 100 research papers annually, and with 57.3% of medical colleges (n= 332) not publishing at all for a decade, we cannot boast of any meaningful research or expect any miraculous outcome.

Medical research cannot be done in a vacuum. For individuals to flourish they need support from mentors and colleagues, and they need help to formulate their ideas and to collaborate. Agreeably, the future medical research will depend on the work of individuals, as always has been, but it is unlikely to happen just because we build more medical services, because the Government increases the funding or because the pharmaceutical companies throw their weight behind the search of new wonder cures. The giants in Indian retina specialty has nurtured an extraordinary mission. They may have made mistakes, but learnt from them. They may have faced opposition, but were brave to believe in themselves. They all shared one passion- passion of serving people to reduce scourge of blindness, and to build a strong Indian retina fraternity. It is now imperative on us to collaborate to build a collective wisdom. I leave this challenge to all my colleagues- to individual teachers, to the professional society, and to the health policy makers. I am willing to be part of this reformative process.

May 9, 2016.

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Gaiha SM, Shukla R, Gilbert C, Anchla R, Gudlavalleti MVS. Is India’s policy framework geared for effective action on avoidable blindness from diabetes? Indian J Endocr Metab 2016; 20: 42-50.

Das T, del Cerro M, Jalali S, Rao VS, Gullapalli VK, Little C, D’Loreto DA, Sharma S, Sreedharan A, del Cerro C, Rao GN. The transplantation of human fetal neuroretinal cells in advanced retinitis pigmentosa patients: Results of a long-term safety study. Expt Neurolol 1999; 157: 58-68.

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Optical Coherence Tomography Imaging in Ocular Tumours

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B scan ultrasound, CT scan and MRI have been the gold standards to diagnose retinal and choroidal tumours. However the resolution capacity of the modern day ultrasound machines precludes the imaging of intraocular tumours smaller in size. Any intraocular mass lesion causing elevation less than 1-0.75 mm would be difficult to image with a standard 10MHz ultrasound probe used routinely. [1]MRI and CT are cross section imaging techniques that take 1-2mm thick axial and coronal sections of the intraocular tissue. They are irreplaceable in modern day practice of ocular oncology as diagnostic modalities for the intraocular tumour but they are limited in their capacity to image and characterize tumours with a size less than 2 mm.

Optical coherence tomography (OCT) was devised as a non-invasive imaging method that used low-coherence interferometry to obtain cross-sectional images of the retina. The previous time-domain (TD-OCT) technology allowed around 10microns resolution of the retina, but gave no information about the deep structures like choroid. [1,2]

The spectral domain (SD) OCT systems developed recently improved the resolution by incorporating the interferometry principle with reducing the image acquisition time and enhancing imaging of the retinal layers. The SD OCT provided axial scan with resolution till 5 microns with ability to image a larger area of the retina. SD OCT is mainly useful in detection of the secondary changes like macular changes and sub-retinal fluid due to retinal and choroidal tumours.[3] Enhanced depth imaging (EDI-OCT) was first described in 2008 using the Heidelberg Spectralis SD-OCT (Heidelberg Engineering, Heidelberg, Germany). This protocol allows enhanced resolution of the outer retinal layers and choroid. Swept source technology (SS OCT) further improved this capacity of imaging the chorioscleral interface and providing excellent resolution of the choroidal structures .[4]

This review article will discuss the OCT findings of some of the common intraocular tumors involving the posterior segment with examples of cases imaged with the Swept Source OCT (TOPCON DRI Atlantis).

Combined hamartoma of the retina and retinal pigment epithelium:

This is a benign tumour and seen as an ill-defined mass of disorganized vascular, and melanocytic lesion involving the neurosensory retina and retinal vessels as well as the RPE.[5,6]

It may cause traction over the retina leading to dragging and disorganization of the retina, retinal folds, tractional retinal detachment and foveal ectopia, .[6,7,8]

Arepalli *et al.* described EDI-OCT features combined hamartomas and noted vitreoretinal traction causing inner retinal disturbances in 100% of cases and entire retina in 38 %. [9] They described 2 patterns on the EDI OCT based on the vitreoretinal traction. The patterns of sawtooth (mini-peaks) described as sharp, pointed and hyperacute noted mostly in inner retinal layer traction and large retinal folds (maxi peaks) involving full thickness retina. They also noted clinically significant reduction in the mean choroidal thickness as compared to the unaffected eye.[9]

Fig 1 A&B. Color fundus photograph and SS OCT image of a combined hamartoma of the retina and RPE. There is a pigmented lesion adjacent to the disc with overlying glial tissue and peripheral finger like projections. The OCT shows an epiretinal membrane that is adherent to the retina. The mass is mainly low reflective and involves the full thickness of the retina. Few high reflective areas are seen within it. The retina appears disorganized in this region. The RPE shows protrusions similar to polypoidal lesions. The underlying choriocapillaris is thinned out.

Astrocytic Hamartoma:

These are benign retinal tumours that appear typically as whitish calcific masses with a mild degree of retinal vessel dilatation.[10] Serafino et al noted the OCT findings to range from subtle white flat lesions in the nerve fibre layer, mildly elevated lesions, lesions with a moth eaten appearance and those with optically empty spaces. [11]

Choroidal naevus:

The choroidal naevus is a relatively common intraocular tumour, benign in nature and with little potential for visual loss or growth into melanoma.[12-16] Earlier OCT reports showed retinal alterations overlying the nevus such as intraretinal edema, subretinal fluid, photoreceptor atrophy, and retinal pigment epithelial (RPE) detachment, as the lesion itself could not be studied. [17] EDI OCT and SS OCT with their deeper imaging capabilities provide more information on the lesion itself. On EDI OCT, the choroidal nevus appears as a gently domed smooth-surfaced choroidal mass with deep choroidal shadowing depending on the degree of pigmentation. Intra-lesional featurs as well as the chorioscleral interface are better seen in non-pigmented naevi. Other EDI-OCT features include choriocapillaris thinning, RPE changes and changes in the outer retina. Subretinal fluid overlying the nevus may be seen most often with retracted or absent photoreceptors.[18] Francis et al compared EDI with SS OCT in choroidal naevi. They noted that SS-OCT enabled visualization of intra-lesional details such as vessels (present in 100% of tumors imaged), cavities, and granularity. [19] For melanotic lesions, SS-OCT was noted to be superior in depicting certain intralesional characteristics compared to EDI-OCT. Distended bordering vessels were significantly associated with previous or persistent subretinal fluid. [20]

Choroidal Melanoma:

The recognition of small choroidal melanomas (<3mm) using characteristic clinical features is critical to early detection and can provide improved patient prognosis. [21,22] The challenge in early detection of choroidal melanoma relates to its clinical similarity to benign choroidal nevus. In the past, TD OCT described overlying retinal changes with little details on the choroidal component. [23,24]

The benefits of EDI OCT are due to its more accurate delineation of tumour boundaries especially the identification of the retinochoroidal and the chorioscleral interfaces.[20,25] Here it shows a distinct edge over ultrasonography where these details are unclear. [26] The intralesional features on EDI OCT can be similar to nevus with deep optical shadowing, and overlying choriocapillaris compression. Secondary retinal changes more commonly involve the outer retina but can involve the inner layers including the nerve fibre layer. In addition, subretinal fluid, subretinal deposits of lipofuscin, shaggy photoreceptors and intraretinal fluid may be seen.[26]

A comparison of EDI-OCT of small choroidal melanoma versus similar-size choroidal nevus revealed statistically significant differences with melanoma (compared with naevus) showing increased tumor thickness (P = 0.0001), subretinal fluid (P = 0.0001), subretinal lipofuscin deposition (P = 0.0001), RPE atrophy (P = 0.0002), intraretinal edema (P = 0.0029), photoreceptor shagginess (P = 0.0054), loss of external limiting membrane (P = 0.0082), loss of ellipsoid layer (P = 0.0233), irregularity of inner plexiform layer (P = 0.0385), and irregularity of ganglion cell layer (P = 0.0385). In that analysis, shaggy photoreceptors were found overlying choroidal melanoma (49%) but not observed overlying nevus (0%) (P = 0.0001). [20]

Limitations of imaging in even small nevi and melanomas are seen in highly pigmented tumors where the shadowing on the surface obscures the intralesional details as well as identification of the chorioscleral interface.[17,20]

Choroidal haemangioma:

Choroidal haemangiomas are benign vascular tumours of the choroid. They can be well circumscribed or diffuse depending on the extent of involvement of the choroid. On indirect ophthalmoscopy choroidal haemangiomas are seen as circumscribed orangish lesions over the posterior pole. They are generally non-pigmented and can be associated with pigmentary changes of the overlying RPE, cystic changes at the macular, exudative retinal detachment and subretinal fibrosis. The diffuse type is generally associated with systemic conditions like Sturge Weber syndrome and has extensive involvement of the choroid. [27,28]

Fig 2A-C. Fundus pictures and SS OCT images of a young boy with bilateral astrocytic hamartoma. The right eye shows subtle whitening along the upper arcade. The left eye shows a more typical white retinal lesion with a moth eaten appearance. The OCT image of the right eye through the lesion shows high reflective thickening of the nerve fiber layer. The lesion in the left eye shows an elevated lesion involving the inner retinal layers. The lesion is well-defined and shows multiple hyporeflective spaces giving the typical moth eaten appearance of an astrocytic hamartoma. The outer retinal layers and choroid are uninvolved.

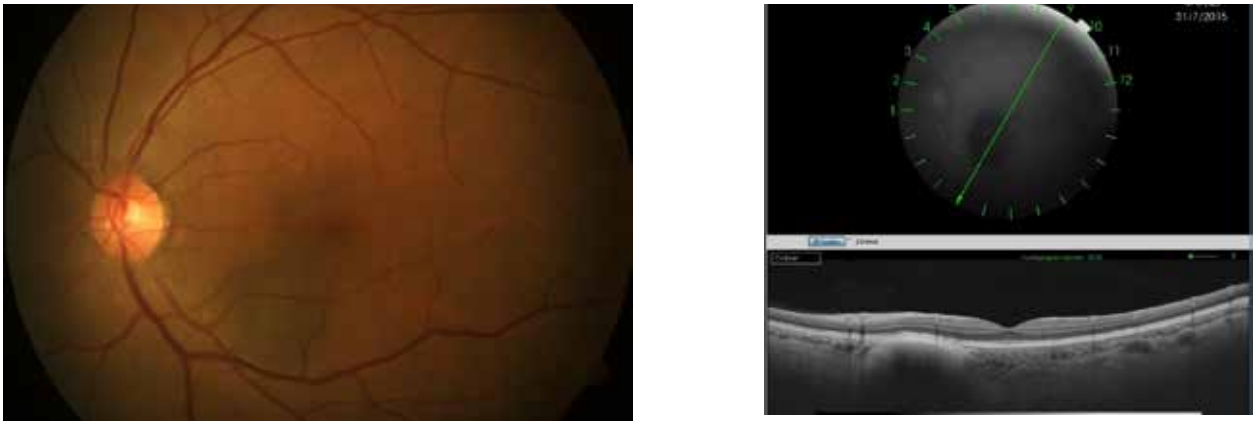
The ultrasound, FFA, auto fluorescence and ICG features are well described. [27,29] SD OCT allows visualization of the choroidal haemangioma and associated retinal changes. Subretinal fluid, retinal edema, schisis and photoreceptor loss are common retinal findings[30]. The anterior surface of a circumscribed choroidal haemangioma is generally hyporeflective with normal overlying retina.[31] The RPE shows domed shaped elevation with RPE changes like atrophy, hypertrophy and fibrosis. Acute changes include preservation of the inner segment/ outer segment photoreceptor line and the integrity of the RPE layer and chronic changes include loss of photoreceptors, cystic changes in the retina, retinoschisis and subretinal fluid.[30-32] Enhanced depth imaging and swept source imaging is particularly useful in circumscribed choroidal hemangiomas which can often be imaged in their entirety and measured accurately due to their circumscribed nature and characteristic internal features of expanded vascular interfaces involving all layers of the choroid. The choriocapillaris layer is usually compressed but not destroyed. Secondary changes such as RPE irregularity and thickening, secondary RD may be noted and can be used to monitor response to therapy. [33,34]

Choroidal osteoma:

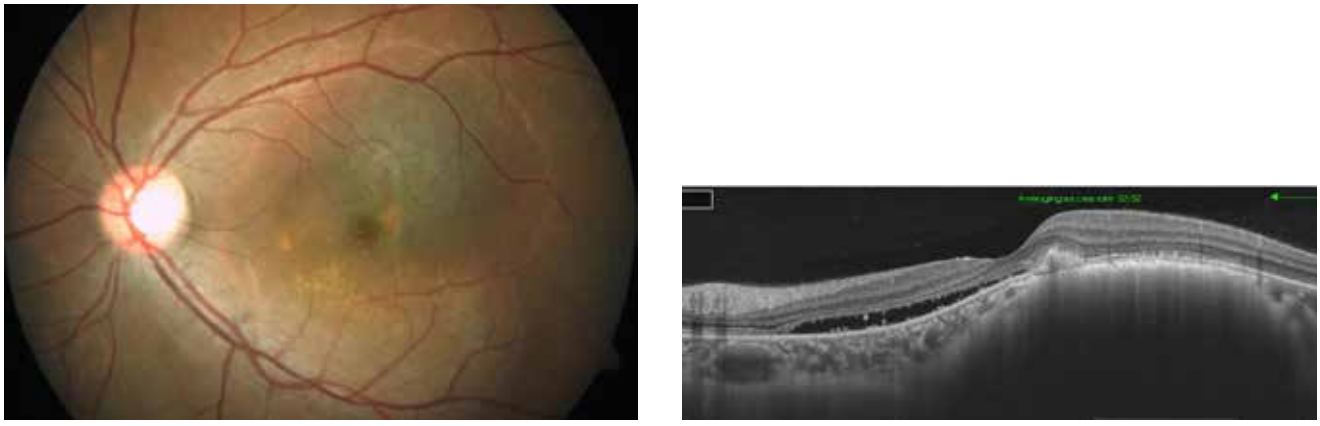
These are benign tumours appearing as orange-yellow plaques at the posterior pole with areas of calcification. The yellow orange colour is associated with RPE atrophy and areas of decalcification that can develop over time.[35,36] The tumour is autofluorescent due to the calcium content.[37] Subretinal fluid, secondary choroidal neovascularization and photorecptor loss are reasons for visual morbidity.[35,36] The tumor has a tendency to grow and the 10 year visual outcome is less than 20/200 in approximately half the cases. Shields et al described OCT features in choroidal osteoma that depended upon the calcification of the tumour. In the calcified portion, most of the retinal layers were intact with mild transmission of light. In case of decalcification the inner layers remained intact but outer retinal and RPE changes were noted in most cases.[38] The lesion itself typically shows hyper reflective horizontal lamellae, spongy appearance with speckling and horizontal and vertical tubules within the lesion. Secondary damage to the outer retinal layer including photoreceptor layer and cystic/ schitic changes of the inner retina may be seen. Choroidal neovascularization can be imaged with its characteristic findings in addition to the above mentioned changes. [38]

Choroidal metastases:

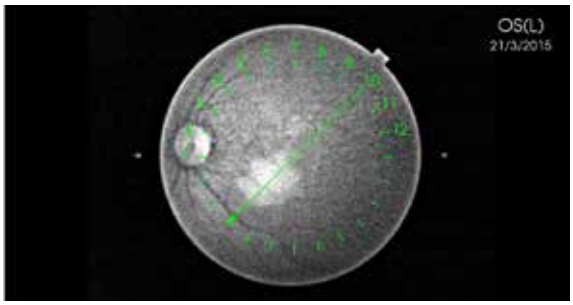
Secondary metastasis to the choroid is one of the more common intraocular malignancies.[39] Breast cancer accounts for more



Figs 3 A&B Color fundus photograph SS OCT images of an asymptomatic pigmented choroidal nevus detected on routine examination. The OCT shows a dome shaped choroidal mass with smooth surface and high reflectivity causing shadowing. The borders of the lesion are less highly reflective and show small hyporeflective areas suggestive of vessels. No overlying changes are noted in the retina. Choriocapillaris compression is seen overlying the lesion.



Figs 4 A&B. Color fundus photograph and SS OCT image of a choroidal nevus with secondary changes that are suspicious of a melanoma. There is a pigmented mass at the posterior pole with orange pigment and subretinal fluid. OCT shows a smooth dome shaped mass with high reflectivity causing shadowing. Overlying RPE changes and high reflective lipofuscin deposits are seen with subretinal fluid and elongated photoreceptor segments. The lateral margins are easily measured as the lesion is well defined, but the shadowing by the pigmentation precludes measurement of the height and visualization of the chorioscleral interface.



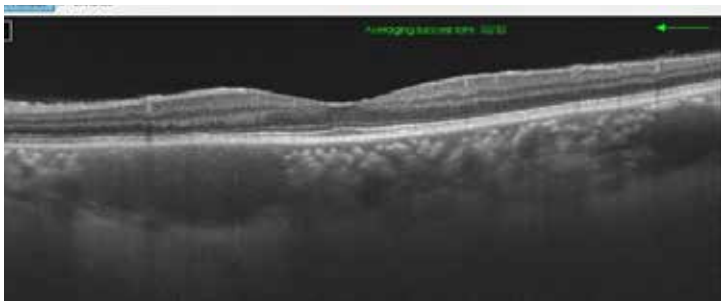
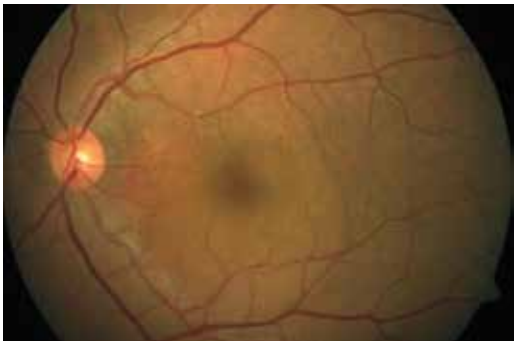
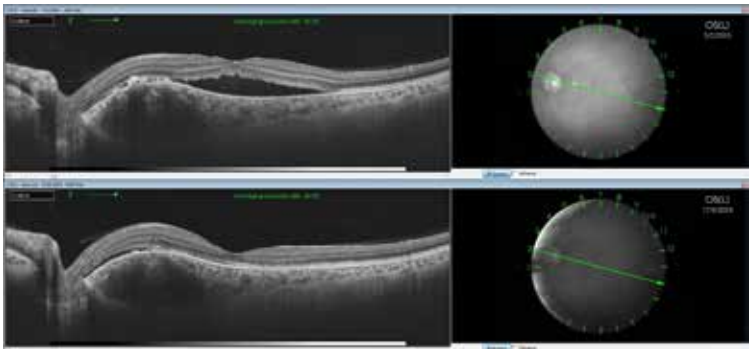


Fig 5. Fundus and SS OCT image of an amelanotic nevus. The lesion has a smooth plateau like surface with no overlying retinal changes. The lesion is uniformly low reflective and the chorioscleral interface is well delineated.

Figs 6 A&B. Fundus photograph and SS OCT images of a small choroidal hemangioma adjacent to the disc with subretinal fluid. The OCT shows a well-defined choroidal mass which is hyporeflective and shows distended vascular spaces. The chorioscleral interface and the border adjacent to the disc are well delineated. The choriocapillaris appears compressed. There are overlying RPE changes with thickening and irregularity. A sensory retinal detachment with elongated photoreceptors is seen. The lower image post PDT shows a reduction in the sensory retinal detachment as well as RPE changes. The hemangioma itself does not show a change in size.

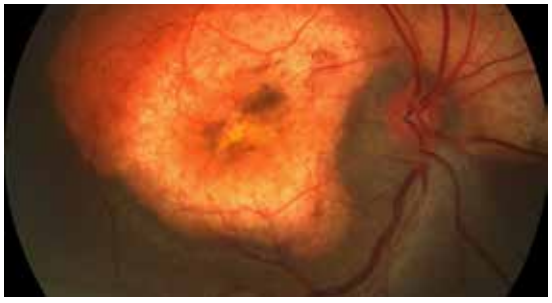
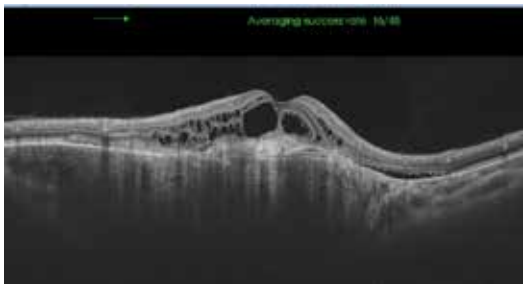



Fig 7 A&B. Color fundus photo and SS OCT of a choroidal osteoma with calcification and secondary changes. OCT image shows cystic retinal changes and subretinal fluid overlying a choroidal neovascular membrane. The osteoma consists of horizontal closely packed lamellae with shadowing suggestive of calcification. The choriocapillaris cannot be identified and the Bruch's membrane shows loss of continuity with CNV formation.

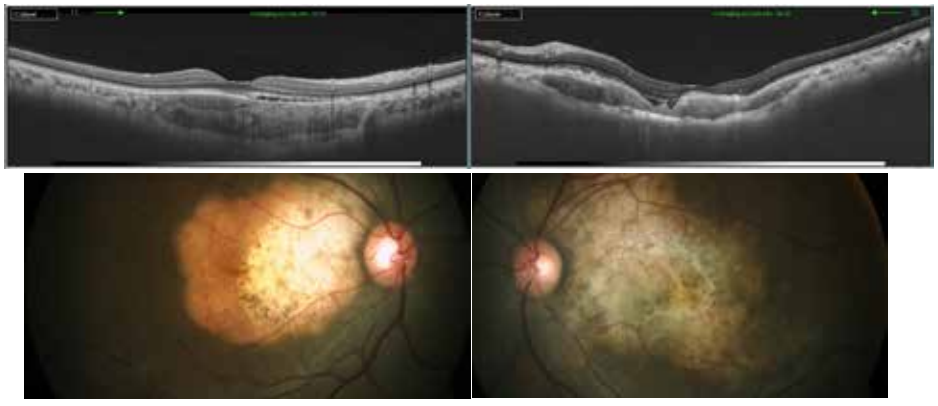
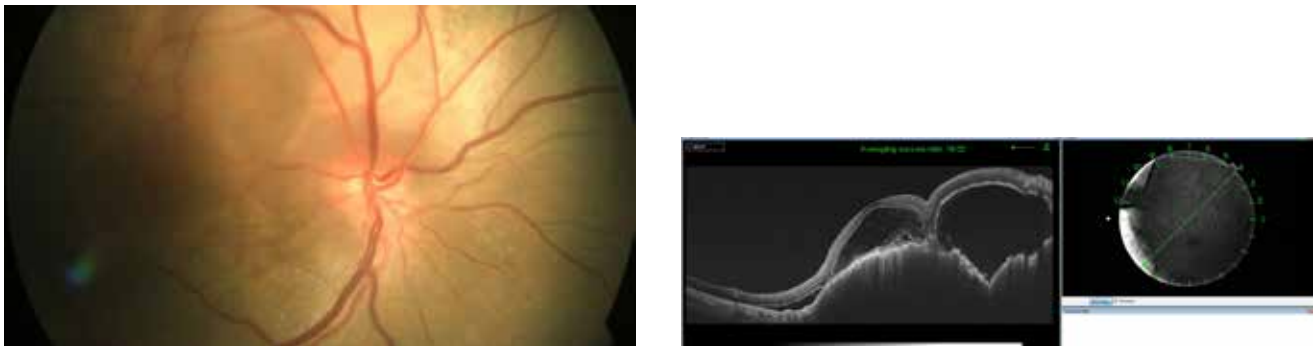


Fig 8 A, B & C. Color fundus photographs and SS OCT images of bilateral choroidal osteoma with decalcification. The OCT image of the right eye shows a smooth tumor surface with subretinal fluid and photoreceptor elongation. The lesion shows areas of hyporeflectivity suggestive of the Haversian system or vascular channels. The chorioscleral interface is well seen due to the absence of shadowing. The left eye shows a more irregular surface with the intralesional echoes appearing more compact and spongy. The overlying RPE changes are more marked. The chorioscleral interface is irregular but well defined. The inner retinal layers in both eyes are undisturbed.



Figs 9A&B. Color fundus and SS OCT images of a patient with choroidal metastases from small cell carcinoma of the lung. The fundus photograph shows a choroidal mass above the disc with secondary retinal detachment. The OCT shows a large bumpy choroidal mass with loss of the choriocapillaris layer. The retinal pigment epithelium shows irregularity. Overlying retinal detachment with dot like subretinal echoes and septae are noted. The inner retinal layers are intact.

Figs 10 A& B. Color fundus photograph and SS OCT images of the right eye of a patient with treated primary vitreoretinal lymphoma. The yellow vitelliform like deposits at the posterior pole are seen as focal elevation of the RPE with moderate reflective deposits in the sub RPE space. The underlying choroid appears normal. The temporal edge of the image shows a rip of the RPE with underlying moderate reflective material.

than half of all patients with choroid metastases, followed by lung cancer. Choroidal metastases are usually 3mm or smaller in thickness and therefore ideal for imaging with OCT.[39,40] They usually appear as a hyporeflective band in the deeper choroid causing enlargement of the suprachoroidal space. Overlying retinal changes can show changes like intraretinal oedema and subretinal fluid with domed shaped elevation in choroid and RPE atrophy of the overlying retina. Subretinal lipofuscin and debris may also be seen.[40,41]

Al Dahmash et al imaged 31 eyes with choroidal metastasis using EDI-OCT.Characteristic EDI-OCT features of metastasis included an irregular “lumpy bumpy” appearance, anterior compression of the overlying choriocapillaris in 93% and posterior shadowing in 86%. [42]

Lymphoma:

Uveal infiltration of malignant , B Cell lymphoma can manifest as solitary or multiple lesions either as a primary tumour or secondary to systemic lymphoma.[43] Primary vitreoretinal lymphomas usually present with homogenous large vitreous cells and irregular infiltrates in the retina that may be either subretinal or sub RPE.[44] In additional paraneoplastic feature of paraneoplastic cloudy vitelliform submaculopathy has been described by Pang et al in eyes with primary vitreoretinal lymphoma.[45]

OCT findings include subretinal and sub RPE hyper reflective infiltrates. In the paraneoplastic presentation, hyper reflective subretinal debris with irregular RPE thickening resembling vitelliform degeneration can be seen .[46,47] In case of choroidal lymphomas, depending on the thickness the surface of the tumour on OCT has been described by Shields et al as either placid, rippled or stormy. [48]

Summary:

With the advent of enhanced depth and swept source OCT imaging techniques, it is possible to accurately image intraocular tumours of the posterior segment where the size is too small (<1mm) to be characterized by ultrasound, CT or MRI. In addition to overlying retinal changes that are secondary to the tumour, the surface as well as intralesional characteristics of most of the common choroidal tumours are better understood. Along with fundus photography and autofluorescence imaging, OCT is now one of the important non invasive diagnostic tools in posterior segment ocular oncology. The current limitations are the limited depth penetration (max 2.6 mm) that is a disadvantage in larger tumours, the inability to image more peripherally located tumours accurately as well as the inability to overcome the shadowing artefacts caused by highly pigmented tumours.

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Management of subretinal abscess in metastatic endophthalmitis

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Subretinal abscess is reported to occur is about 5% of patients with metastatic endophthalmitis.[1] The presence of subretinal abscess indicates a more severe form of infection. The usual management approach in these patients is similar to that for metastatic endophthalmitis without subretinal abscess and revolves around systemic pharmacotherapy, intravitreal pharmacotherapy and vitreous surgery.[2] The results however are less than satisfactory. Patients who undergo surgery seem to do well in the early postoperative period but tend to develop secondary tractional retinal detachment sooner or later. This is more likely to occur in patients with subretinal abscess.

Recently we encountered a young lady who was immunocompetent but had a history of intravenous drug abuse for several months. She presented with features typical of metastatic endophthalmitis in the left eye and through the hazy media a subretinal abscess could be visualized. Using standard treatment protocol she was initially managed with systemic and intravitreal vancomycin and ceftazidime. Seeing no response she was subjected to early vitreous surgery using 25G MIVS. After core vitrectomy a large subretinal abscess was noted. Since it had responded poorly to earlier treatment, a decision was made to deliver antibiotics directly into the abscess. Intralesional injection of antibiotic (vancomycin) was successfully delivered using 41G needle (figure 1a). Postoperatively the abscess showed signs of resolution within the first week and good anatomical (figure 1b) and visual recovery was seen at follow up. Intralesional pharmacotherapy has not been described earlier for the management of subretinal abscess.

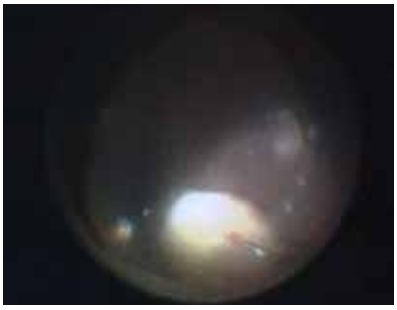

Figure 1a

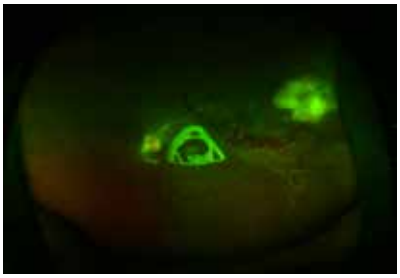

Figure 1b

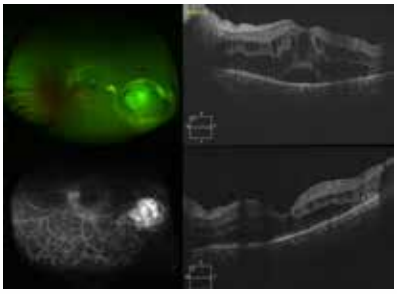

Figure 1c

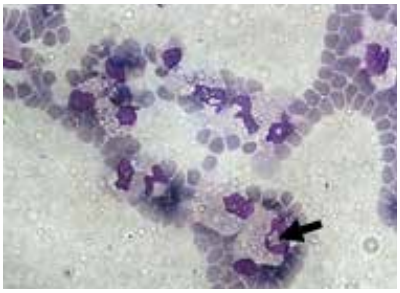

Figure 1d

FNAC of intraocular mass lesions

FNAC (Fine needle aspiration cytology) is still a widely debated topic due to the risks involved. However it has a well established role in clinching the diagnosis when faced with atypical lesions. Moreover, FNAC is likely to become a more commonly offered surgery with advances in genetic and molecular diagnosis and prognostication of intraocular tumors such as choroidal melanoma.

For FNAC of intraocular tumors, two routes can be used, transcleral and transvitreal. For tumor localization, the still widely used approach is transillumination and indirect ophthalmoscopy.[3, 4] A few years ago we for the first time reported the use of endoillumination and wide angle viewing for the management of rhegmatogenous retinal detachment and subsequently reported

our two year results.[5,6] This approach has now been replicated by other surgeons and has been found to have safety and efficacy comparable to that of conventional scleral buckling surgery.[7]

We have now started performing FNAC of intraocular mass lesions using two port MIVS, endoillumination (chandelier) and wide angle viewing under the surgical microscope. Endoillumination assisted FNAC has helped us obtain adequate tissue sampling and clinch the diagnosis of an intraocular mass that was reported as melanoma on MRI. This, on FNAC turned out be an inflammatory mass (figure 2a, 2b) and not a tumor. In another patient with granulomas in the lung and liver, a successful diagnosis of amelanotic melanoma was made following FNAC with this technique.

Endoillumination assisted FNAC has the ability to replace other modes of tissue biopsy of intraocular mass lesions because there is minimal learning curve (most retinal surgeons are already familiar with using endoillumination and wide angle viewing), localization is precise and hence there is greater safety. Also, the risk of tumor dissemination into the needle track is almost nil as the procedure is carried out through the MIVS cannula system.

Removal of Hyperoleon

Silicone oil is used frequently as a long term tamponade in the management of complex retinal detachments. With increasing duration of intraocular retention of the oil, there is progressively greater emulsification. This emulsification often remains confined to the posterior segment and there is minimal spill over into the anterior chamber. Sometimes however, there is massive emulsification seen within the anterior chamber (hyperoleon). Severe forms of hyperoleon is more likely to be seen in emerging countries and poorer nations as patient follow up is often delayed for several years.

The commonly used method for removal of all grades of emulsified silicone oil in the anterior chamber is irrigation-washout using a syringe. This approach is adequate when there is minimal emulsification. However in the presence of significant hyperoleon, irrigation alone is less than the ideal approach. This is because, in the washout approach there is a dispersive force being used. During this dispersive movement of the emulsified oil, some of them egress through the incision site but most keep moving randomly within the anterior chamber. Hence, to obtain a complete removal of the hyperoleon relatively prolonged washout needs to be performed.

Removal of the hyperoleon using the vitrectomy system is also possible but this may not be available with all surgeons and more importantly this approach is likely to clog the tubing and add to the cost of replacement and maintenance of the equipment.

A simpler, safer and cost effective approach to removal of significant hyperoleon would be removal using the Simcoe or Daljit Singh irrigation- aspiration cannula. These cannulas have been routinely used for extracapsular cataract surgery. The advantage of using these cannulas is that centripetal aspiration force can be applied while preventing collapse of the anterior chamber. As there is no dispersive force, all the emulsified globules are easily and quickly removed from the anterior chamber. A small disadvantage is that one may have to slightly enlarge the entry wound; but this is self-sealing by stromal hydration.

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Newer agents for treatment of Diabetic Macular Edema

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Introduction

Ever since the recognition of vascular endothelial growth factor (VEGF) as a critical component in pathogenesis of diabetic macular edema (DME), anti-VEGF agents constitute the main stay of treatment of DME.[1] The beneficial effects of these anti-VEGF injections require repeated injections over a prolonged period of time.[2] Several studies have recognized the role of multiple growth factors and pro-inflammatory cytokines in the pathogenesis of DME.[3] Newer drugs specifically targeting these pathways have been extensively studied (Table 1)

Newer agents – systemic administration

These systemic agents have potential beneficial effects of possible better glucose control and HbA1c levels as well as simultaneous effect of both eyes. Also, these agents would avoid possible complications of repeated intravitreal injections such as endophthalmitis, retinal detachment, vitreous hemorrhage, cataract etc.

Insulin-Like Growth Factor (IGF) Inhibitors:

Elevated vitreous levels of IGF-1 were found in proliferative diabetic retinopathy.[4] IGF-1 has been linked to breakdown of blood-retinal barrier and increased vascular permeability.[5] The progression of diabetic retinopathy in pregnant women has been associated with pregnancy-induced increase in IGF-1.[6] Teprotumumab is a fully human antibody which targets the Insulin-like Growth Factor-1 receptor (IGF-1R). Currently, this drug administered intravenously in the dose of 20mg/kg is being investigated in a phase I, open label study.[7]

Angiopoietin Pathway inhibitors:

Angiopoietin binds with their physiologic receptors, i.e. tyrosine kinase with immunoglobulin-like and EGF-like domains (TIE2) and enhance VEGF-mediated vascular permeability.[8] Intravitreal injection of tyrosine phosphatase that downregulates TIE2 activity suppresses ocular angiogenesis. AKB9778 is a small-molecule competitive inhibitor of vascular endothelial-protein tyrosine phosphatase (VE-PTP) that promotes TIE2 activation. In an open-label, dose escalation, clinical trial, AKB 9778 was found to be safe. Doses of 15 mg or more injected subcutaneously twice-daily reduced macular edema and improved vision in some patients.[9]

Interleukin Inhibitors:

Increased vitreal cytokines such as interleukin (IL) such as IL-1 and IL-6 have been observed with proliferative DR.[10] Interleukin contribute towards the breakdown of blood-retinal barrier and accelerate apoptosis of retinal capillary and endothelial cells. In preclinical trials, IL-6 antibody demonstrated reduction in pathological ocular angiogenesis.[11]

Chemokine Inhibitors:

Chemokines such as monocyte chemoattractant protein (MCP-1) may also play an important role in development of DME and may contribute to formation of subretinal fluid in patients with DME.[12] A phase II, multicenter study to compare efficacy and safety of a chemokine CCR2/5 receptor antagonist with ranibizumab for treatment of DME has been initiated in 2013. The drug is administered orally in a dose of 200mg once daily. This study is currently recruiting patients.[13]

Vascular Adhesion Protein (VAP) inhibitors:

Retinal endothelial cells when stimulated by high glucose or other inflammatory cytokines such as TNF-α and IL-1β release VAP.[14] As the name suggest VAP serves as leukocyte endothelial adhesion molecule and is essential for leucocyte transmigration.[15] Leukostasis and inflammation have been linked to development of ocular neovascularization. In preclinical studies on streptozotocin-induced diabetic rats, oral administration of synthetic novel VAP-1 inhibitor resulted in reduction of vascular permeability.[16] A multicenter phase II, double masked, randomized controlled study has been initiated to evaluate the safety and efficacy of ASP8232 (VAP-1 inhibitor) in reducing the central retinal thickness in subjects with DME.[17]

Newer agents – local ocular therapies:

Designed Ankyrin Repeat Proteins (DARPin):

Designed Ankyrin Repeat Proteins (DARpin) are genetically engineered binding proteins derived from natural ankyrin repeat proteins with high affinity and specificity for binding to specific proteins. These acts as versatile building blocks with characteristic feature – small size (good tissue penetration), high potency (active at low concentrations), high stability (long shelf-life), high solubility (ideal drug properties).[18] Abicipar Pegol (MP0112) is a

specifically designed DARPin that binds and inhibits VEGF. It has small molecular weight (34kDa) and is a highly potent blocker of VEGF-A isoform.[19] An intravitreal doses of 0.4mg inhibited VEGF for 8-12 weeks and achieved reduction of edema for a longer duration of time. A phase II, double-masked randomized control trial studying the safety and efficacy of Abicipar Pegol (MP0112) in DME has completed enrolment of patients and results of this study are awaited.

Table 1

Newer agents for treatment of diabetic macular edema

Systemic therapies	Local Ocular Therapies
Insulin-Like Growth Factor (IGF) Inhibitors	Designed Ankyrin Repeat Proteins (DARPin)
Angiopoietin pathway inhibitors	Squalamine Lactate
Interleukin inhibitors	Integrin antagonists
Chemokine Inhibitors	Sirolimus
Vascular Adhesion Protein (VAP) inhibitors	

Squalamine Lactate:

Squalamine is an synthetic, small molecule aminosterol that binds to phospholipid membranes at physiological pH and inhibits plasma membrane ion channels with downstream effects on VEGF.[20] This VEGF inhibition results in endothelial cell inactivation and in certain cases, apoptosis leading to cessation of angiogenesis. A phase II study is evaluating the role of squalamine lactate 0.2% eye drops in combination with ranibizumab for the treatment of DME.[21]

Integrin antagonists:

Integrins are cellular proteins that serve as transmembrane receptors and help in signal transduction for cell growth, division and survival.[22] Leucocyte function-associated antigen (LFA-1) is a unique leucocyte integrin which is found on all T and B cells and serves as a chronic inflammatory target for increasing retinal vascular permeability and retinal angiogenesis.[23] ALG-1001 is an integrin inhibitor that blocks integrin a-b. This drug is being investigated in a phase II, multicenter, double masked, randomized controlled trial. This trial is designed to evaluate the safety and efficacy of ALF-1001 as compared to bevacizumab and focal retinal laser treatment for treatment of diabetic macular edema (LUMINATE study).[24]

Sirolimus:

Sirolimus is a macrolide antibiotic isolated from actinomycete, *Streptomyces hygroscopocus.*[25] It is known to inhibit the secretion of various pro-inflammatory cytokines such as IL-2, IL-4, IL-15 and also down regulates hypoxia inducible factor mediated VEGF expression.[26] In a phase I study, repeated subconjunctival sirolimus injection produces no significant drug-related adverse effects in five patients with centre-involving DME.[27] In another phase I study, subconjunctival and intravitreal sirolimus injections was well tolerated with minimal systemic drug exposure.[28]

Conclusion

AntiVEGF agents have revolutionized the treatment of diabetic macular edema. However, many DME patients do not show complete resolution of macular edema despite multiple intravitreal injections. These agents have a more robust effect on retinal neovascularization compared to DME, probably indicating that DME is a disease involving more than VEGF. There is more and more scientific data hinting towards an inflammatory process in DME. New pharmacotherapies targeting these inflammatory mediators are being developed. In future, there is a high likelihood that eyes which poorly respond to antiVEGF, may require these newer agents to achieve better visual and anatomic outcomes.

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Sickle Cell Proliferative Retinopathy

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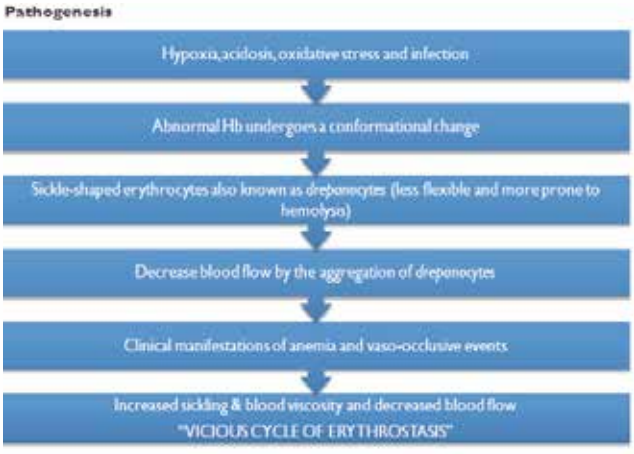
Sickle Cell Disease

Hemoglobinopathies are a group of hereditary disorders characterized by abnormal hemoglobin (Hb) formation. The Hb molecule is composed of two alpha and two beta polypeptide chains. In sickle cell disease, an amino acid substitution occurs at position 6 of the beta chain. In HbS, glutamic acid is replaced by valine, while in HbC it is replaced by lysine. [1]

The diagnosis of sickle cell haemoglobinopathy can be performed by sickling test, solubility test, peripheral blood smear method and hemoglobin electrophoresis. Sickling and solubility tests have sensitivities of 65.0 % and 45.0% respectively and peripheral film has 35.0% sensitivity. Sickling, solubility and peripheral film have specificities of 95.6%, 90.0% and 96.7% respectively compared to Hb electrophoresis method.[2] Hence the gold standard method for detection of haemoglobinopathies is hemoglobin electrophoresis. About 8% of Individuals with African Caribbean descent and 10% Brazilian population manifest sickle cell trait.[3] Majority of clinical manifestations leading to hemolysis and sickling crisis are associated with Hb SS genotype. Most severe retinal manifestations are associated with Hb SC genotype.[4]

Pathogenesis of sickle cell haemoglobinopathy is presented in the graphic below.



Retinal manifestations in sickle cell retinopathy can be broadly classified as nonproliferative and proliferative.

Goldberg Staging of Proliferative sickle cell retinopathy [5]

Case report : A 43 year old male patient, tailor by occupation hailing from Ghana reported to us with painless loss of vision in the right eye of over three months and in the left eye of over one year duration. His best corrected visual acuity in the right eye was 20/800 and in the left eye was CF 1M. Both eyes anterior segment and intraocular pressures were with in normal limits.

Both fundi showed combined tractional retinal detachment with incomplete posterior vitreous detachment and thickened taut posterior hyaloid over the posterior pole and proliferative vitreoretinopathy changes more marked in the left eye (Figure 1 and Figure 2). Fluorescein angiogram revealed characteristic active peripheral sea fan neovascularization (Figure 3 and 4)

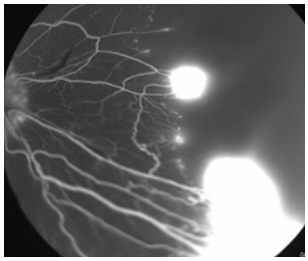
Figure 1 and 2 shows combined retinal detachment in both fundi

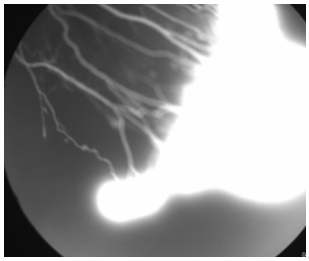
Figure 3 and 4 showing active sea fan neovascularization on FFA

In view of African race and characteristic proliferative

Stage 1	• Peripheral vascular occlusion • "Silver wire" appearance
Stage 2	• Tortuous elongation of the arteriole • Dilation of capillaries between vascular and ischemic retina
Stage 3	• Sea Fan Neovascularisation (derived from the venous side of the arterio-venous circulation)
Stage 4	• Vitreous hemorrhage
Stage 5	• Retinal detachment

vitreoretinopathy changes like typical sea fan retinal





neovascularization, we did initially sickling test to diagnose sickle

cell hemoglobinopathy. The sickling test results were negative. Hence, gold standard technique of Hb electrophoresis was done which confirmed the diagnosis of sickle cell disease in our patient. The genotype was Hb SC genotype. This shows the importance of confirming the diagnosis with Hb electrophoresis in cases where in the sickling test is negative and clinical suspicion is high.

Management of sickle cell proliferative retinopathy depends on the stage of presentation. Laser photocoagulation/ cryotherapy can be done if patient presents with only sea fan neovascularization without signs of tractional /combinedretinal detachment. Our case presented with advanced proliferative sickle cell retinopathy with bilateral combined retinal detachment which can be only be managed by vitreoretinal surgery. We performed parsplana vitrectomy with belt buckle, endolaser and silicone oil injection in both eyes (Right followed by left) at one month interval. During surgery, care was taken to keep the infusion at low pressures by constantly monitoring optic nerve head perfusion. We used brilliant membrane blue staining to remove the tractional membranes at the posterior pole. The negative staining facilitated clear demarcation and complete removal of preretinal membranes. Intraoperatively, incomplete PVD was noted upto the arcades and two small retinal breaks were noted in the superotemporal quadrant in the peripheral retina at the edges of peripheral retinal vascularization in the right eye. Care was taken to gently strip the cortical vitreous with forceps and cutter from posterior pole to periphery in order to avoid hemorrhage from peripheral neovascularization areas. Excessive shaving of vitreous was avoided in the periphery and a belt buckle was put to support the vitreous base.

Postoperatively at 3 months follow-up his visual acuity improved to 20/40 in the right eye and maintained at CF 1mt in the left eye with attached retina (Figure 5) and stable Intraocular pressures in both eyes.

Important preoperative, postoperative considerations[1] in the management of proliferative sickle cell retinopathy are presented below.

Conclusion: A high index of clinical suspicion is necessary for accurate detection of systemic and ocular manifestations of sickle cell proliferative retinopathy. We can achieve satisfactory anatomical and functional results with appropriate precautions and surgical intervention in these challenging cases.

Figure 5 Right eye montage fundus photo shows attached retina with complete relief of tractional membranes

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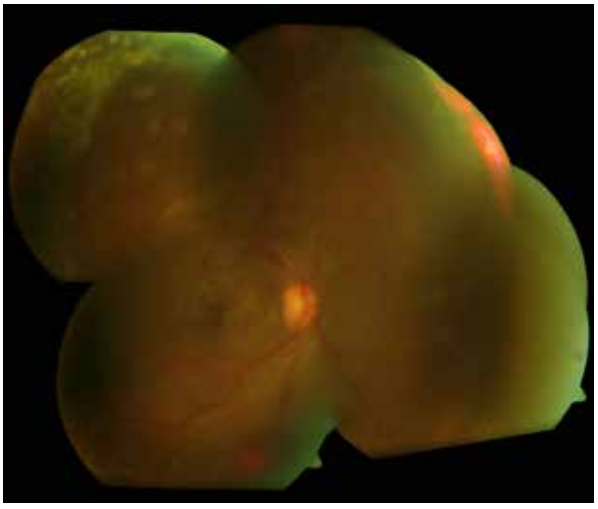

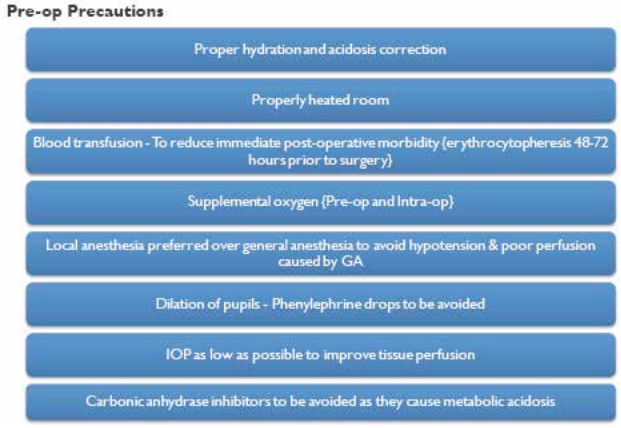

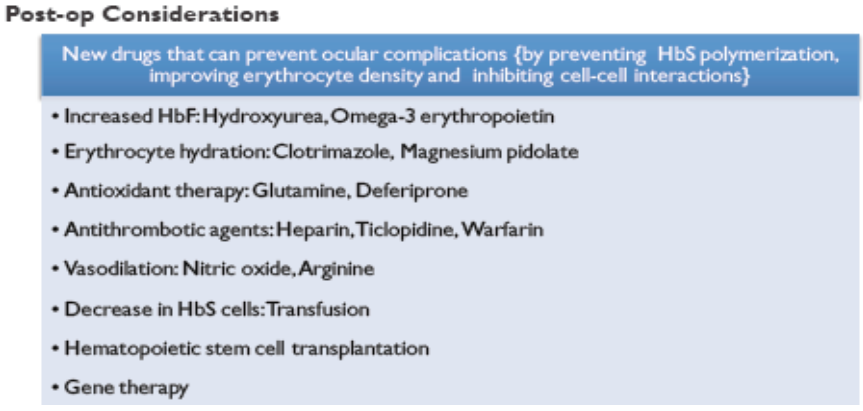

Changing paradigms in treatment of CSCR

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Introduction

The incidence of central serous chorioretinopathy (CSCR) is

The incidence of central serous chorioretinopathy (CSCR) is estimated to be about 1 in 10,000 individuals1 and about six times higher in men than in women.2 Visual acuity at presentation can range from 20/20 to 20/200 with 50% having vision lower than 20/30.2 Treatment options include observation, life style modifications like decreasing stress and cessation of smoking, focal laser, photodynamic therapy (PDT), Intravitreal bevacizumab or micropulse laser.3 With a high incidence of spontaneous resolution, acute CSCR is treated with lifestyle modifications or close observation. Treatments like focal laser or PDT can cause collateral damage and hence are reserved for recurrent or chronic cases. Chronic CSCR represents only about 5% of the total number of cases.2

Separation of the neural retinal from the retinal pigment epithelium (RPE) initiates a complex series of cellular and molecular changes.4 Untreated detachment can lead to permanent visual loss, however when treated these molecular changes can be arrested.5

A cascade of changes are observed in the acute and chronic phase in the RPE, photoreceptors and second order neurons in response to detachment. A large number of photoreceptors are lost by 1 month with 80% of outer nuclear cells lost by 3 months.6 Hence observation of a subject of acute CSCR for a period of 3 months for spontaneous resolution may result in loss of important and key cells in the visual pathway.

Eyes with CSCR also show electrophysiological derangements.7 Untreated eyes experienced long term compromise in macular function.8 Our role should be to ensure prompt and safe resolution of sub retinal fluid with reattachment.

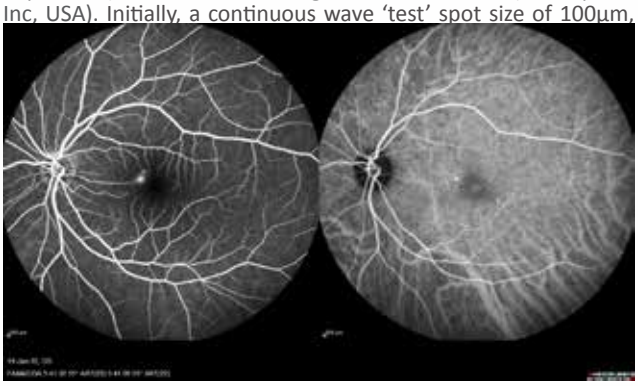
With previous mainstays of treatment like focal laser or PDT, observation was probably justified as risks of treatment were significant. In our previous study, we demonstrated the efficacy and safety of micropulse yellow laser(MPY) in chronic CSCR.3 Keeping these results in mind the question arise if we are right in observing the patient or prompt treatment would be a better option.

The study

Patients with neurosensory detachment involving the fovea on spectral domain optical coherence tomography (SDOCT) and with an active leak on FFA (Fig 1). All patients underwent Indocyanine angiography (ICGA) also. The patients were divided into two groups – acute and chronic. Patients with persistent sub-retinal fluid who had been observed for a minimum period of three months for spontaneous resolution and then given MPY laser treatment were included in the chronic group; patients treated earlier were included in the acute group. Exclusion criteria included use of exogenous corticosteroids, diabetic retinopathy, uveitis, any hereditary retinal or macular disease and history of previous retinal treatment for the CSCR.

Fig1. The FFA showing an ink blot pattern of leakage nasal to the fovea. The corresponding ICGA showing an area of hyperpermeability.

The focal leaking points and areas of hyperpermeability formed a guide for laser therapy. A 577 nm yellow laser (Quantel Medical, Supra Scan) was delivered through the PDT laser lens (Volk Optical Inc, USA). Initially, a continuous wave 'test' spot size of 100µm,



0.2 seconds exposure time and using enough power to cause mild retinal whitening was placed superonasally. Using similar settings but with half the power, a duty cycle of 10% (200µs on and 1800µs off) and the micropulse emission mode, multiple overlapping spots were placed over areas identified on ICGA.

We have presented the results at an early (within one month) visit to describe the immediate effect seen with treatment. Findings at a late (after one month) visit have also been studied to evaluate the long term efficacy and recurrence with the treatment.

Outcome measures

The primary objective was to study the change in the sub retinal fluid volume (PSV). Using SD-OCT scans we measured the number of section of horizontal scans involved, the horizontal distance (in mm) of detachment and the height of the detachment (maximal height of detachment seen taking into account all the scans). The product of these 3 parameters gave a measure of the volume of detachment. (Fig 2)

The secondary objective was to assess the change in the best corrected visual acuity (BCVA).

Results

A total of 11 eyes with an average final follow up of 126 days in

the acute group and 14 eyes with an average final follow up of 98 days in the chronic group were analysed.

The average age in the acute group was 48.6 years and in the chronic group was 47.6 years. The male female ratio was 7:4 and 14:0 in the acute and chronic groups respectively. The median BCVA in the acute group was 6/9 (range 6/6 – 6/18) and in the chronic group was 6/9 (range 6/6 – 3/60). The demographics and pre laser parameters have been summarized in the Table 1.

Follow up visits

In the early visit (defined as follow up within one month) 15 eyes were evaluated and 21 eyes were evaluated in the late visit (defined as follow up after one month).

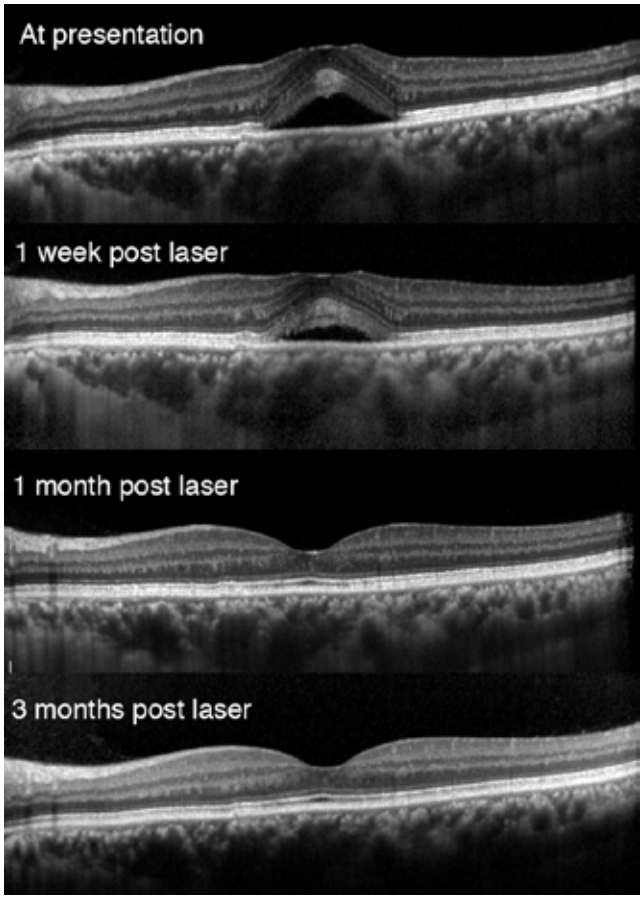
Treatment outcome

Since no statistical difference was seen between acute and chronic groups, we have provided follow up data for all 25 eyes together in an attempt to simplify the data presentation.

In the early visit, the average number of lines of improvement was 0.33 (5 eyes showed 1 line improvement and 10 eyes remained stable). The PSV also showed a statistically significant reduction.

In the late visit, the average duration after laser was 133.8 days and the average number of lines of improvement was 0.44 (1 eye showed 2 lines improvement, 8 eyes showed 1 line improvement, 11 eyes remained stable and one eye decreased by one line). The PSV also showed a statistically significant reduction.

Fig 2- Showing the resolution of the subretinal fluid in a case of acute CSCR after treatment with micropulse yellow laser.



Discussion

We saw a significant reduction in SRF and a gain in visual acuity in acute and chronic groups alike. Importantly no significant adverse effects were noted.

Earlier due to harmful effects of focal laser and inability to treat sub foveal leaks, treatment was deferred. Our observations tell us that we no longer need to worry about the above factors with micropulse laser.

The above facts offer compelling reason for the use of micropulse laser as a first line therapy.

We feel that this treatment modality could in the future be mainstay in treatment of macular edemas and CSCR due to its enhanced safety profile and effective therapeutic outcomes.

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Tables

Parameter	Acute (range)	Chronic (range)	P value
Age (years)	48.6 (36-63)	47.6 (27-63)	0.979
Sex	7:4	14:0	0.026
Follow up (days)	125.6 (11-438)	97.6 (14-194)	0.979
Vision pre (Snellen)	6/9 (6/6 – 6/18)	6/9 (6/6 – 3/60)	0.727
PSV pre (µm)	18914 (459 – 72000)	11032 (800 – 31688)	0.344

Table 1: Summary of demographics and outcome measures

Should I change treatment based on this article?

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In continuation to the last article, which ended a little abruptly, we continue on a journey to analyzing an article. This time let's focus on analyzing the methodology of an article where it's the small things that matter.

Basically, the question we are asking is --Why Should I believe Him/Her? (In other words, was the author rigorous and honest enough in the conduct of the study?)

This is the part we usually skip and this is the part that we actually need to read most carefully. The devil is in the details.

Also this is where we need to read laterally to evaluate the validity of each technique used. For example, how was visual acuity taken, how was OCT done, which machine, what protocol etc. It's some of these small things that can change the entire interpretation of the study. Consider this: If we tried to detect a difference between groups of 10 microns in OCT thickness and the variability of the machine in measuring CMT is 20 microns, then what we are measuring could be just due to the variability in machine measurement and not a true difference. This would lead one to disregard the study findings.

Questions we should ask about methodology:

- **What was the primary outcome measure?** This is a critical question, which is more important to us as clinicians and patients. The primary endpoint should be clinically relevant and should not be a surrogate measure for our actual endpoint. This may not always be possible but is desirable. For example, visual acuity is always our desired endpoint, however macular thickness on OCT is sometimes used as a surrogate to add objectivity. When this is done, we need to be aware that a lower thickness does not always mean better vision. The primary endpoint is also important for the reason that it must be used for sample size calculation.

  The duration of the study and time at which the endpoint data is collected is important so that the full effects of the intervention as well as natural history are felt, the classical example being interventions in BRVO

- **Secondary analysis**

  Beware of secondary analysis. Studies are statistically powered to deliver information about the primary endpoint, however the temptation to draw conclusions about other variables that can readily be studied is very strong. While it is useful to look at the trends, drawing therapeutic decisions about these secondary variables may be dangerous since the degree of certainty about our conclusions would be low

- **Multiple comparisons**

  Also beware of multiple comparisons. If we compare multiple variables, then the level of significance or the p value needs to be adjusted (typically by dividing 0.5 by the number of comparisons) to a lower number to be considered significant. There are many techniques to cater for this, the commonest technique is a Bonferroni adjustment of the p value

- **How were the patients assigned** into groups? Randomization and masking; Stratification by visual acuity? Were groups comparable at onset? Look at entry data. Were investigators blinded? The effect of bias can be most keenly felt by conducting any simple study in the OPD with a favored hypothesis. The temptation to peek into the treatment assignments and the visual acuity measurements in your own operated patients are easy to experience.

- **Statistical testing**

- Parametric / Non-parametric tests to be applied appropriately– This requires a bit of study. Parametric tests are best applied when data is normally distributed while non-parametric tests are applied when data is not normally distributed. How do we quickly assess if a data set is normally distributed? If the original data is available, then it can be plotted to see the distribution. There are tests for this too but beyond the scope for most of us. Does it matter? In large samples sizes, even if a parametric test is used for non parametric data, it does not affect the results to a large extent. However with small sample sizes, the effects on the results can be significant.
- Obscure tests –Look for obscure tests you have not heard of before. The usual tests are seen in most articles and most analyses are done using seven to eight common statistical tests. If obscure statistical tests are found, some hanky panky may be afoot! At this point, reading laterally would be worth to see why the obscure test is used.
- How has the data been reported? – RCTs will have measures of central tendency like mean, median and mode reported. They will also have measures of dispersion like standard deviation mentioned. A word on the p value- most studies will report this. However just because p is less than 0.05 does not mean much. It merely means that for the effect size studied, it is unlikely that the difference observed is due to chance. In other words, the two groups are different in some way. It is up to the reader to decide how clinically relevant this difference is. If the effect size studied (that is the difference we are trying to detect) is not clinically relevant, then whatever the p value, the study would have no clinical relevance.

There are other parameters to assess how different these groups are and whether this difference is likely to be replicated in other studies. One such measure is the Confidence Interval, for example the confidence interval of a mean. In any study, the mean is the average value of that particular sample, the standard deviation is the difference of various values in the sample from the mean, or in other words it indicates how the data is spread in the sample. This data is just part of the population and may or may not accurately depict the actual TRUTH in the population data

The confidence interval on the other hand tells us that if we replicated this study multiple times in the entire population then the mean would be found within the values of the 95% confidence intervals, 95% of the times that the study is done. Since we obviously can not test the entire population, this is a valuable statistical technique that tells us that the value of the mean in our study may be X but the value of the mean of the entire population (or the absolute truth) is likely to lie between Y and Z. If the 95% confidence intervals of two populations have values that overlap, then the difference between those populations may not be great, whatever the p value. It tells us that our particular sample shows a difference but this may not necessarily be the truth when applied to the entire population. So, beware of wide confidence intervals.

This brings us to the end of Part 2 of this three part series. Next… interpreting results and integrating them into your practice.

Optic Nerve Head Melanocytoma

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Introduction

Melanocytoma of the optic disc is an ophthalmic tumor that arises from melanocytes and is a variant of the melanocytic nevus. This pigmented lesion occurs on the optic disc,often extends into the peripapillary retina and choroid, obscuring part or whole of the disc.

Melanocytoma of the optic disc was previously called melanosarcoma.[1] It was once believed to be a malignant neoplasm with lethal potential for which, enucleation was routinely performed for the concern of it to be a possible choroidal melanoma. [2-3]

This was until 1962, when Zimmerman and Garron[4] coined the term 'optic disc melanocytoma.' They described it as a darkly pigmented mass of the optic disc, characterized histopathologically as an uniform accumulation of heavily pigmented cells with abundant cytoplasm, small nuclei, inconspicuous nucleoli, which are benign cellular characteristics which resemble ocular melanosis.

Shields et al[2] proposed the name hyperpigmented magnocellular nevus of the optic disc (HMNOD) as this would describe the histopathological features more correctly. The term melanocytoma however, is very widely and uniformly used, all over the world.

Presentation

The mean age at diagnosis of melanocytoma is 50 years[5] with slight higher predilection in females. [6] Most melanocytomas are probably, present since birth and are found coincidentally on routine ocular examination.

Optic disc melanocytoma is usually unilateral which can rarely have multifocal presentation along with uveal melanoma.

Afferent pupillary defect is seen in one third of the patients which could be present due to mechanical pressure of the melanocytoma cells over the optic disc fibres.[7]

Visual loss caused by the tumor can occur in about 26% of the presenting patients,[2] due to mild retinal exudation involving the fovea or neuroretinitis which arises from tumor necrosis, central retinal vein obstruction, spontaneous tumor necrosis and malignant transformation. Acute ischemic necrosis can lead to abrupt and severe visual loss with signs of unilateral optic neuritis, secondary retinal vein obstruction, and vitreous seeding. Focal necrosis in the tumor is also believed to account for seeding of tumor cells into the vitreous and anterior chamber.

Clinical features

Ophthalmoscopically it is characteristically a dark brown to black lesion that is located partly or entirely in the optic disc which can involve the adjacent choroid or the adjacent sensory retina. Retinal involvement usually appears darker than the choroidal component, and has feathery margins because of extensions into the nerve fiber layer.

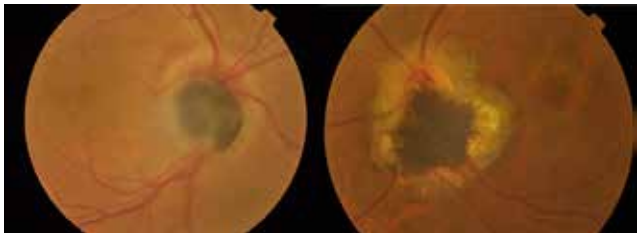

Fig 1 Brown to black lesion over the optic disc partially obscuring it with adjacent involvement of the retina and choroid

Associated conditions

Bilateral optic disc melanocytoma has also been associated with intracranial meningioma, neurofibromatosis type II, basal cell carcinoma and vitiligo.

The common embryological origin in neural crest cells is proposed to be the cause of coincidental diseases.[8]

Complications

Disc edema is the most common complication associated. Intraretinal edema, subretinal fluid, yellow intraretinal exudation, focal haemorrhage, vitreous seeds and retinal vein obstruction are the other complications seen due to extension of the lesion and needs evaluation for malignant transformation.

Malignant change is estimated to occur in about 1--2% of cases.[5]

The characteristic features of malignant transformation are, initial lesion originating exclusively from optic nerve without juxtapapillary choroidal involvement, progressive growth, visual loss and intrinsic circulation on fundus fluorescein angiography.

Diagnosis

The diagnosis of a melanocytoma of the optic disc usually is made by its typical ophthalmoscopic presentation. Fundus photography, fluorescein angiography, B-Scan ultrasonography, optical coherence tomography and visual field examination can facilitate the diagnosis and are helpful in following up the patient and assessing the severity in subsequent visits of follow up.

Malignant transformation can be easily picked up with the help of these ancillary investigations.

Visual field defects are seen in 90 % patients which include minimal to large enlargement of the blind spot, concomitant nerve fiber bundle defects including nasal step, relative nerve fiber bundle defect, quadrantal defect, nasal step, or paracentral scotoma and absolute arcuate defect, representing impaired axonal flow secondary to mechanical compression. [7] The amount of tumor extension beyond the disc margin corresponds to blind spot enlargement and compression of axons in optic disc corresponds to arcuate defects. This extension causes a shadowing effect on the peripapillary retina and subsequent blind spot enlargement.

Fluorescein angiography of melanocytoma of the optic disc demonstrates hypofluorescence which remains throughout the angiogram. Close compact architecture of the cells with deep pigmentation with very little vascularity explains the persistent hypofluorescence.[9]

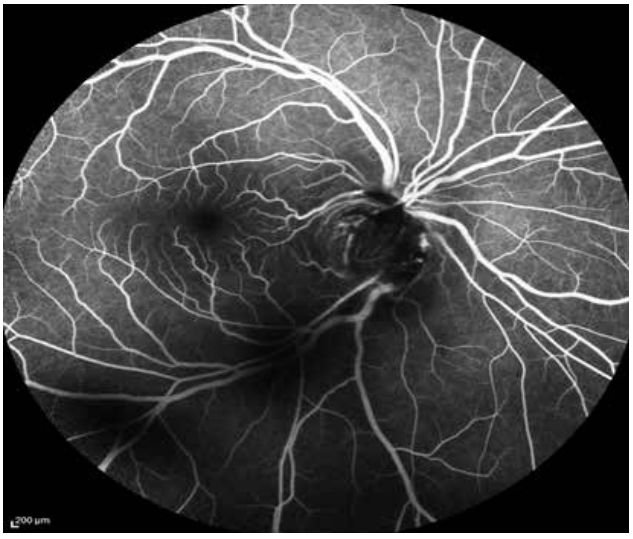

Fig 2 : FFA of optic disc melanocytoma in mid venous phase showing hypofluorescence of lesion

B-scan can delineate acoustically solid optic disc mass with high initial spike in larger lesions, but cannot detect microscopic extension of the tumor into the retrolaminar portion of the optic nerve.

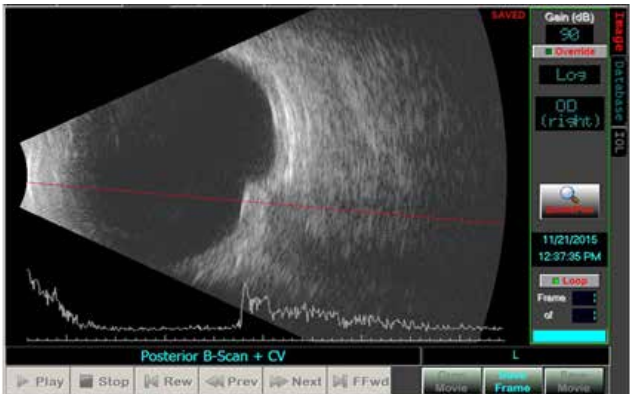

Fig 3 B scan showing acoustically solid optic disc mass with high initial spike, as shown

The characteristic features on *optical coherence tomography* include,gradual transition from normal retina into nodular tumor,bright anterior border layer and dense shadowing associated with no internal detail.

OCT in optic disc melanocytoma is specifically helpful in identifying subretinal fluid associated with the lesion its extent, shape and depth involvement[10].It can be used both to document the extent of the lesion at diagnosis and to track any progression that may not be apparent with ophthalmoscopy alone

On *histopathological examination*, the melanocytoma cells are unique and have characteristics like intense cytoplasmic pigmentation, low nuclear cytoplasmic ratio, uniform size of the cells and nuclei.

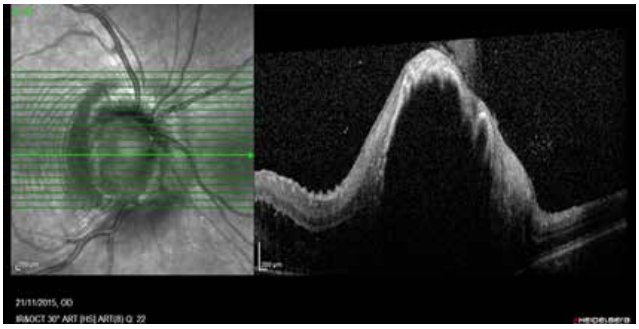

Fig 4 OCT picture showing bright anterior border layer and dense shadowing associated with no internal detail

The plump round cells seen on light microscopy contained giant round cytoplasmic melanosomes with relative sparse distribution of other cytoplasmic organelles. *Ultrastructural studies* of optic disc melanocytoma show, plump round cells seen by light microscopy containing giant round cytoplasmic melanosomes with relative sparsity of other cytoplasmic organelles.[11]

Differential diagnosis

The differential diagnosis of optic nerve melanocytoma are juxtapapillary choroidal melanoma, choroidal nevus, hyperplasia of the RPE, combined hamartoma of the retina and RPE, adenoma of the RPE, metastatic melanoma to optic disc, epipapillary vitreous haemorrhage.

Management

An unknown and incidental pigmented lesion of the optic disc and peripapillary area is a cause for concern. However, keeping in mind the main characteristics of a melanocytoma of the optical disc can help diagnosing this lesion and differentiating it from choroidal melanoma and preventing any radical treatment.

Frequent follow up in initial few months looking for features of malignant transformation is mandatory. If the lesion is proven to be stationary regular follow up every six to twelve months can be advised.

Periodic follow-up to assess changes in size, shape, collateral extension and consistency of the lesion is important.

Macular edema due to the tumor has been tried with corticosteroids treatment and long term study and large cohort though is awaited.

A large involvement of the optic disc and/or progressive growth of pigmented lesion with loss of vision with characteristics of malignant transformation as mentioned is suggestive of malignancy.[12]

In cases of malignant transformation enucleation is considered.

Conclusion

Optic disc melanocytoma is a benign condition with a malignant potential. Hence the need of clinical diagnosis with serial follow up with the help of ancillary diagnostic modalities wherever needed, is indicated. Surgical intervention is indicated in cases where features of malignant transformation are seen.

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Traumatic Sub-macular Haemorrhage

Dr Raju Sampangi,

Dr Hemalatha B C

Blunt trauma has a potential to cause vision threatening injury to the macula. These injuries affect mostly the younger population as trauma happens either at work or while participating in a sport. In all these types of trauma, minor injuries may cause little or no permanent damage. The more severe cases can have sight threatening complications.

Blunt trauma to the macula can result in a variety of clinical presentations like Berlins edema, Macular hole, Sub-macular haemorrhage, Choroidal rupture. It is important for the treating ophthalmologist to identify conditions which require active intervention from whose which require conservative observation.

Traumatic Maculopathy can present in the following ways, usually a combination of features is found in many cases

- Acute Traumatic Maculopathy
    1. Berlins edema
    2. Traumatic sub macular haemorrhage
    3. Traumatic macular hole
    4. Choroidal Rupture
    5. Hypotonic maculopathy
- Late Traumatic Maculopathy
    1. Choroidal Neovascular membrane
    2. Macular scarring
    3. Retinal Thinning
    4. Late Traumatic Macular hole

Of the above presentations most commonly misdiagnosis or missed diagnosis happens in relation to traumatic sub-macular haemorrhage. Many a time these cases are initially treated conservatively as Berlin's edema. Sub-macular haemorrhage however is a vision-threatening condition requiring immediate and appropriate management. Visual prognosis depends on the cause of haemorrhage, the duration of sub-macular haemorrhage prior to treatment, and the location, and thickness of the sub-retinal bleed.

Although delayed treatment may result in poor visual recovery but it is important to also note two important points with respect to traumatic sub-macular haemorrhage

Not all sub-macular haemorrhages need active pneumatic displacement.

Traumatic sub-macular haemorrhage patients have better prognosis if treated early compared to other etiologies.

Source of sub-macular bleed following trauma is usually from a choroidal rupture. ***The first step in the management of sub-macular bleed is to determine the exact location of the sub-retinal bleed.*** The anatomical location of the sub-macular haemorrhage may be between the neurosensory retina and retinal pigment epithelium (RPE) or below the RPE i.e. between the RPE and Choroid. In acute stages, both types of sub-macular haemorrhage may present with significant reduction in vision. However, both behave differently, their prognosis and management would differ significantly. It is often difficult to differentiate the types of sub-macular haemorrhage based only on a clinical examination. Fluorescein angiography is not useful as they both appear similar.

The current high definition spectral-domain optical coherence tomography (SD-OCT) technology allows us to differentiate the two types of sub-retinal haemorrhages using the automatic three-dimensional segmentation of layers in patients with sub-macular haemorrhage.

We would like to share our experience in treating patients with traumatic sub-macular haemorrhage. In this article we will try to highlight the utility of SD-OCT in the treatment decision making with these case examples.

In our initial published case report, two of our patients presented with traumatic submacular haemorrhage following injury while playing cricket with tennis ball. Based on the SD-OCT we diagnosed that the first case had subRPE and while the 2nd patient had subphotoreceptor bleed that was initially misdiagnosed as Berlin's edema at a different centre. Pneumatic displacement was carried out only in the 2nd case.

Even though, we did not initiate any measures to displace the submacular bleed in the first case, visual recovery started as early as 3 days after injury and continued to improve, which correlated with a decrease in the thickness of the subRPE bleed. The first case had a higher foveal elevation on raster scan (353 µ) compared with the 2nd case (104µ), and therefore, should have had a poorer prognosis without therapeutic measures to displace the blood. Both the patients recovered to a BCVA of 6/6 once their sub-macular haemorrhages cleared and have maintained the same for 5 years. So far, we have treated 18 patients with traumatic sub-macular haemorrhage (subphotoreceptor [n = 8] and subRPE [n = 10] bleed) using the same analogy and all patients with subRPE bleed in the foveal region have recovered

≥6/9 vision (minimum followup of 6 months) with conservative management.

In patients with haemorrhage between the RPE and neurosensory retina, immediate management either a gas injection or surgical evacuation to displace the blood away from the fovea needs to be initiated. In patients with a sub-RPE bleed, it may be difficult to displace the blood because it is a closed space. Furthermore, sub-RPE blood cannot be removed with surgery without creating iatrogenic damage to the RPE with resultant poor vision. Hence, observation would be prudent in such cases.

Apart from establishing the anatomical location of the bleed, we can utilise the SD- OCT to visualize retino-choroidal interface using a RPE-fitted slab. Using this feature allowed en face visualization (C-scan) of the choroidal rupture in both cases that was hidden to clinical evaluation due to haemorrhage (Fig. 8A,B). The area of the choriodal rupture detected at first visit by en face visualisation co-related with the area of choroidal rupture seen much later clinically after resolution of the bleed. Identifying the location of choroidal rupture even before initiating the treatment helps to prognosticate the visual recovery; Patients with choridal rupture not involving the foveal centre will have better visual recovery with appropriate management. Patients can be counselled better regarding the visual recovery with this information.

A blanket interventional treatment of traumatic submacular haemorrhage which is commonly practiced would put all patients at risk of complications secondary to pneumatic displacement/ surgery. Importance of the decision of "need for intervention" is exemplified in cases with concurrent retinal tears or retinal dialysis that can sometimes be seen in these patients with trauma.

One of our patients had a combined sub-Photoreceptor and sub-RPE bleed with a retinal dialysis this patient was subjected to a pneumatic displacement. (Figure 9) Another case of sub-macular bleed had an associated retinal tear with vitreous hemorrhage. As the blood was sub-RPE he underwent just a prophylactic laser for the retinal tear without any pneumatic displacement (Figure 10) there by avoiding risks associated with gas injection.

Based on this experience we would recommend the use of SD – OCT in all patients with traumatic submacular haemorrhage to identify the exact location of the bleed and one should consider pneumatic displacement only in patients with subphotoreceptor bleed and patients with subRPE bleed can be observed. However, there is a need to interpret the OCT images correctly as there can be a combination of bleed in some cases. In these cases one may need to intervene early to displace the sub-photoreceptor blood if it involves the foveal centre.

References/ suggested Reading:

1. SD-OCT to differentiate traumatic submacular hemorrhage types using automatic three-dimensional segmentation analysis. Sampangi R, Chandrakumar HV, Somashekar SE, Joshi GR, Ganesh S. Ophthalmic Surg Lasers Imaging. 2011 Mar 3;42
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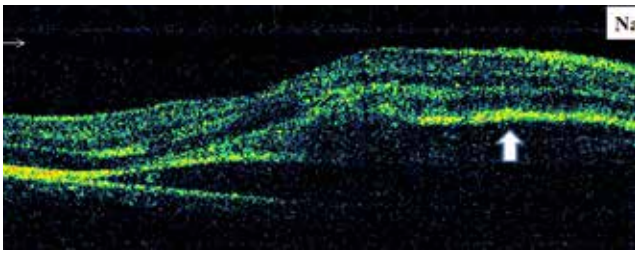


Figure 1: SD-OCT Raster scan shows sub-macular elevation involving the fovea. High back scattering of the RPE is clearly seen nasal to fovea with preservation of retinal architecture

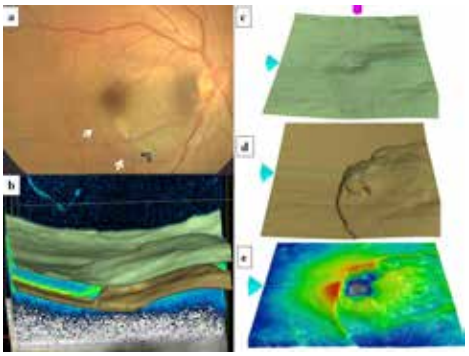


Figure 2:

Case 1 (A) Fundus photograph 3 days after trauma showing the extent of the submacular hemorrhage. The temporal edge of the hemorrhage appeared to be clearing, indicating the previous extent of the hemorrhage (white arrows), whereas the arrow head shows the new edge. (B) Advanced three-dimensional segmentation analysis of the 512 3 128 macular cube scan shows elevation of both the internal limiting membrane (ILM) and retinal pigment epithelium (RPE) due to the submacular hemorrhage. (C) ILM segmentation map. (D) RPE segmentation map. (E) ILM–RPE thickness map shows normal retinal thickness in the area corresponding to the submacular bleed.

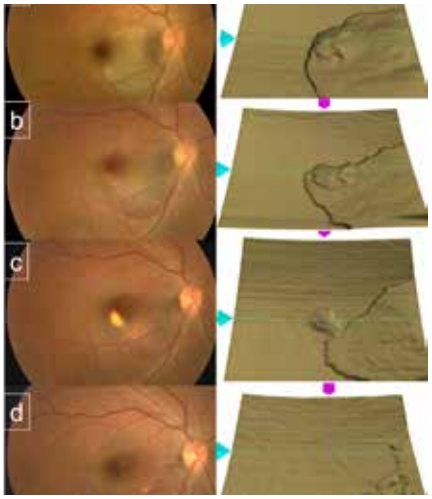


Figure 3: Sequential fundus photographs and corresponding three-dimensional retinal pigment epithelium segmentation maps show the reducing height of the submacular bleed in the first case. (A) Three days after trauma. (B) Seven days after trauma. (C) Seventeen days after trauma. (D) Thirty-five days after trauma.

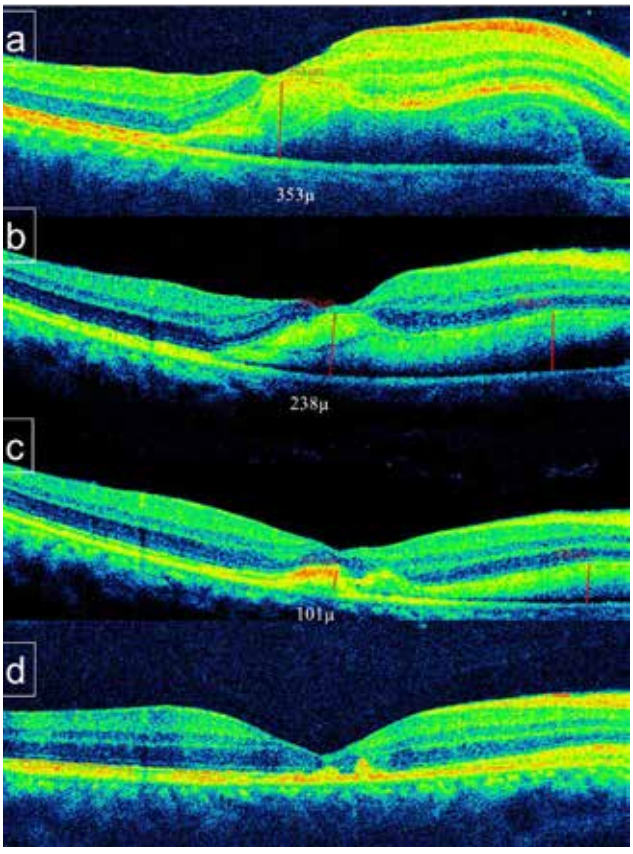


Figure 4:

Sequential high-definition raster scans show the decreasing height of the submacular bleed at each follow-up. (A) Three days after trauma (height = 353 µm). (B) Seven days after trauma (height = 238 µm). (C) Seventeen days after trauma (height =101 µm). (D) Thirty-five days after trauma (height = 36 µm).

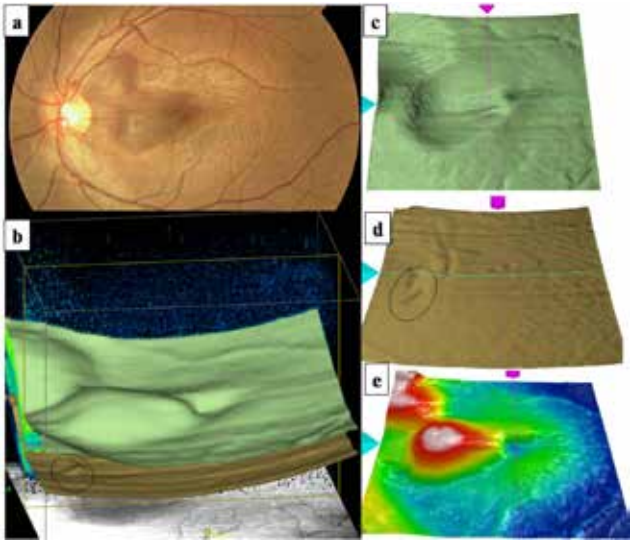


Figure 5.

Case 2. (A) Fundus photograph 7 days after trauma showing the extent of the submacular hemorrhage. (B) Advanced three-dimensional segmentation analysis of the 512 3 128 macular cube scan shows elevation of the internal limiting membrane (ILM), whereas the retinal pigment epithelium (RPE) is flat except for small elevation (oval dashed line). (C) ILM segmentation map. (D) RPE segmentation map showing small elevation (oval dashed line) that corresponded to choroidal rupture detected later. (E) ILM–RPE thickness map shows increased retinal thickness in the area corresponding to the submacular bleed.

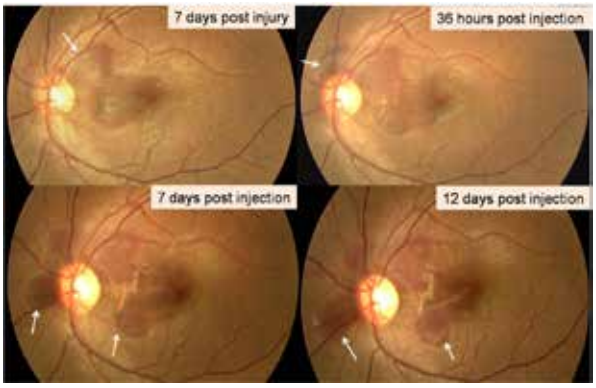


Figure 6.

Sequential fundus photographs show displacement of submacular bleed following gas injection. Progressive displaced edge of the bleed at each visit (white arrows) and unmasking of choroidal rupture are clearly seen. (A) Seven days after injury. (B) Thirty-six hours after gas injection. (C) Seven days after gas injection. (D) Twelve days after gas injection.

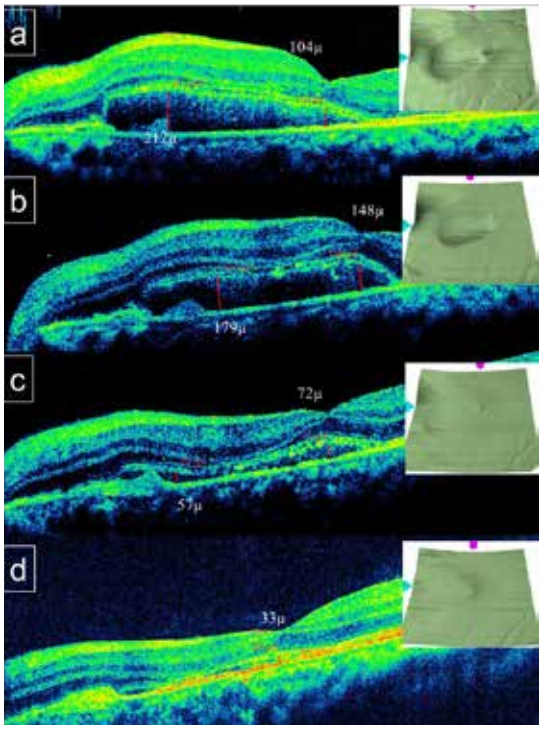


Figure 7:

Sequential HD-Raster scans show the decreasing height of the submacular bleed at each follow-up. Corresponding ILM segmentation maps are shown in the insert on the right side. a) Seven days post trauma; Ht-104µ b) Six hours post gas injection; Ht-148µ c) Thirty six hours post gas injection; Ht-72µ d) Twelve days post gas injection; Ht-33µ

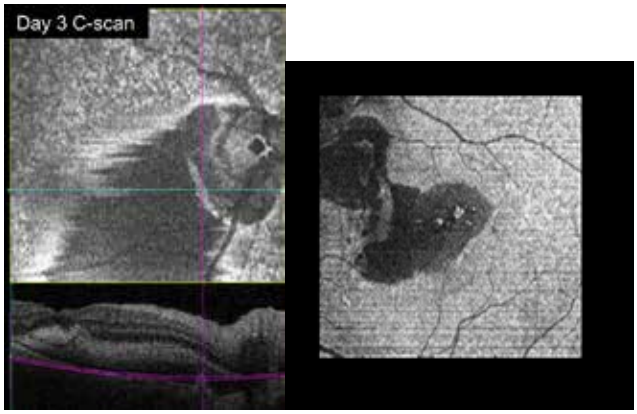


Figure 8:

Advanced 3-dimensional en face visualization showing Choroidal rupture seen as a hyper reflective area on a 20 micron RPE fitted slab placed just below the RPE

Case 1:3 days post injury;

Case 2: 7 days post injury

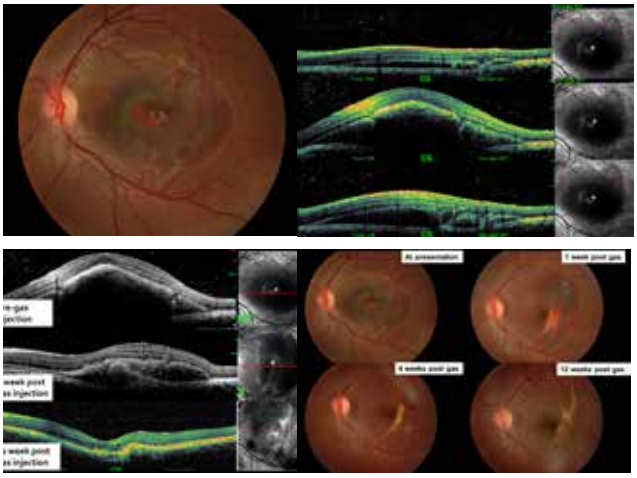
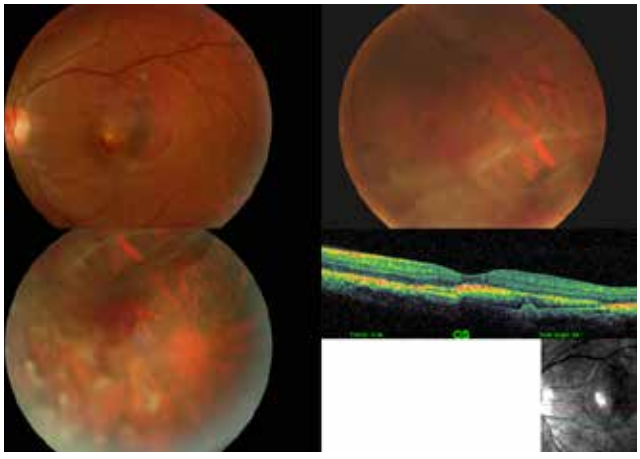
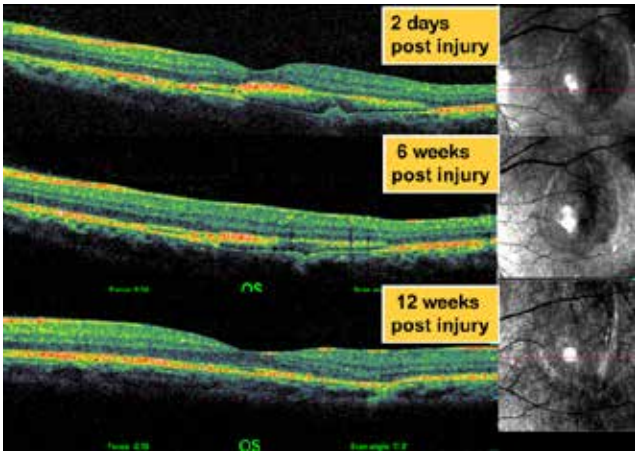
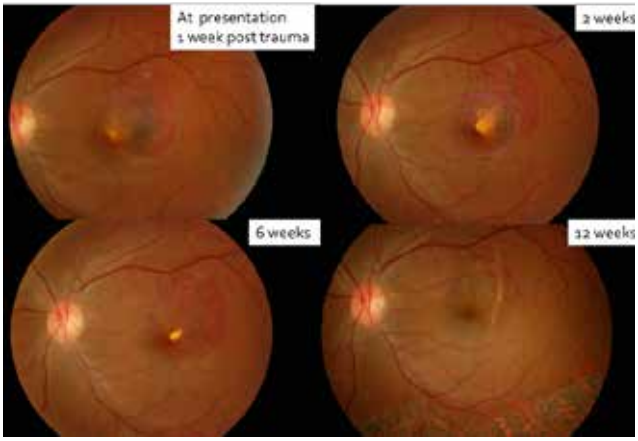


Figure 9:

Fundus image at presentation of patient with sub-macular haemorrhage with associated retinal dialysis







OCT line scan images showing the presence of combination of sub-photoreceptor (upper and lower images) , sub RPE bleed(centre image),

d) serial OCT and Fundus images showing the resolution of haemorrhage post gas injection

Figure 10:

Fundus image at presentation of patient with sub-macular haemorrhage with associated retinal tear, OCT image shows the sub-RPE location of the bleed,

c) serial OCT and Fundus images showing the spontaneous resolution of haemorrhage with conservative management.

Guidelines For Intravitreal Injections

Acknowledgement to the VRSI sub-committee for preparing the base document :Dr Raja Narayanan,Dr Ajay Aurora,Dr Vishali Gupta and Dr A Giridhar & Dr Ajit Babu)

The incidence of post-injection endophthalmitis though low, is of great concern as there is a dramatic increase in the number of injections performed annually in India.

The risk of cluster endophthalmitis is high as multiple patients may receive injections from the same vial in a single session.

Cluster Endophthalmitis occurs due to:

Contaminated surgical supplies, Sterilization failure or Improperly performed technique. Commonest cause of contaminated surgical supplies is a Counterfeit Bevacizumab vial.

Following draft has been developed jointly by AIOS and VRSI under the guidance of Prof Atul Kumar.

We understand that there may be techniques, other than the ones enunciated in this draft, and working well in hands of some retina surgeons in India. However the recommendations made in this draft are based on the Best Practices followed and published worldwide. Our aim is to allow each one of us in India to achieve safe intravitreal injection of Bevacizumab (Bevacizumab) for our patients with an endpoint of zero infection.

{Please remember, this is only a Best Practice Guidelines Document and has no legal binding}

Background of this Document:

Based on the recent meeting held on 8th February 2016 between Dr V G Somani Joint DCGI, a panel of experts from all over India, representatives of the All India Ophthalmological Society (AIOS),Vitreoretinal Society of India (VRSI) and representatives from the Roche Products (India) Pvt. Ltd it was decided that Ophthalmologists in India can use Bevacizumab as an off label drug for Intravitreal injection. This should be done after taking an informed consent from the patient who should be informed about the options available. The injection should be performed in a sterile environment and should be done by Ophthalmologists, who have the knowledge and training of performing safe intravitreal injections and have the ability and the facilities to manage any adverse events that may arise after such an injection.

ROCHE COMPANY, who is the manufacturer and supplier of Bevacizumab in India, will be responsible for delivering pure and sterile Bevacizumab Vials with a documented cold chain to its distributor.

Once procured from the distributor it is the duty of the Ophthalmologist to maintain the sterility and cold chain of the Bevacizumab vial and to deliver it safely in a sterile environment to his/her patients.

Following document discusses the recommended way Bevacizumab should move from the Distributor into doctor's clinic/hospital and further used as an intravitreal injection. It will help you achieve the goal of safe delivery of sterile Bevacizumab.

- Procuring and Storing Bevacizumab Vial
- How to Use Bevacizumab Vial
- Bevacizumab Intravitreal Injection Procedure
- Post Injection Patient Monitoring and reporting of Adverse Events

A. Procuring & Storing The Bevacizumab Vial

1. Purchase drug from a ROCHE authorized distributor (List will become available on www.rocheindia.com or the dcgi website) only on a proper bill that documents the lot number and matches with the lot number on the carton.

Please ensure he/she is an authorized Roche Distributor. It is best to avoid switching dealers for the sole purpose of discounted price. Check the authorization letter of the dealer.

We can inspect the authorization and bills from Roche periodically. We are working to get the label modified so that the drug can be purchased on the prescription of an Ophthalmologist or an oncologist.

2. Check the Cold chain log record (from Roche to the Final Distributor). This may not be possible for each vial but should be asked for and checked periodically.

3. Bevacizumab carton may preferably be stored in an airtight (screwable) clean plastic container to prevent wetting of the carton at 2–8°C. Once purchased, transport the drug in a dry ice pack.

4. It should be stored at the hospital in an exclusive refrigerator at 2–8°C with temperature display, power backup, and a temperature log. Do not store any non-drug related items, such as food and beverages, microbiology or pathology samples, blood and blood products, in the same refrigerator. Electronic data loggers are available in the market to monitor the temperature. The refrigerator should ideally be lockable and access to this

should be possible only to few certified people.

5. A separate register should be kept to keep record of Bevacizumab usage. This should have following information

   a) Name of the Person who transferred the vial to the refrigerator

   b) Record of Utilization of the vial with the lot number, aliquot preparation date and samples sent for culture and their reporting.

   c) In case the culture comes positive, report to the distributor and inform on the national registry with the lot number (this registry is being developed)

Fractionation procedure guidelines (For a complete understanding, please refer to the video on the VRSI website www.vrsi.in/ Bevacizumab. This video will soon become available,

B. HOW TO USE THE BEVACIZUMAB VIAL

There are options to ensure safe injections of Bevacizumab into the vitreous which are listed below.The person (paramedical staff/doctor) who removes the vial from the refrigerator should enter his /her name in the Bevacizumab register

To ensure authenticity of the Bevacizumab vial please check that the carton has not been tempered with and then use the Kezzler code on the carton. This is an alphanumeric code that needs to be sent as an sms to the number indicated on the vial. You will get an instantaneous reply from ROCHE about the authenticity of the vial. Use the vial only after authenticating it. If the code is not correct do not open the carton and use the vial. Return it with the proof of the message you have got to the distributor.

Once the authenticity is confirmed, carefully open the vial and check that the lot number and expiration daye on the vial matches that on the carton. Also ensure the vial does not look tampered and look at the contents of the vial for anything unusual.

Options For Preparing Bevacizumab

Option 1:

Prepare aliquots in class 1000 environment under a class 10 laminar flow hood and thermosealed.

Option 2:

Fractionation and Aliquoting:

Place of Fractionation

We suggest opening a vial and preparing the required number of injections in 1ml syringes under sterile conditions (ideally under ISO class 5 conditions):

- Clean Room with Laminar flow Hood
- Compounding Isolator
- Sterile Operation Theatre with HEPA filter or Laminar flow with filter.

Steps of Aliquoting

- Open the cap of the vial. Clean the Rubber Stopper with Sterilium/ 70% Isopropyl Alcohol. The swab used for cleaning also must be sterile. A 20/23 G needle / mini spike device is inserted in the rubber stopper of the vial by a scrubbed paramedical staff / ophthalmologist in the operation theatre with mask and cap. The scrubbing and gowning should be as for any intra-ocular surgery. The vial must be held upside down by non-scrubbed personnel in the operation theater wearing a cap and mask.
- Do not talk while the procedure is being done.
- The scrubbed staff should withdraw 0.2 ml of Bevacizumab in a 1 ml disposable syringe without injecting any air in the vial.All other alliquots are similarly prepared.
- Cap it with a 30 G needle. Ensure there is no remnant air in the syringe. The needle could be optionally bent/ capped by a sterile cap.
- Do not withdraw less than 0.2 ml per syringe. All syringes should be prepared by withdrawing drug from a single puncture of 20/23 G needle.
- The prepared capped syringes with the drug must be stored in ETO sterilized sealed pouches and then placed in a sterile autoclavable container. Each sterile box should have a label with name of the drug, batch number, date of preparation of the syringe and date of expiry, (which is 2 weeks from the date of preparation) . Each sealed cover of the syringe must have an individual label of the batch number and date of expiry of the syringe. The sterile autoclavable box is to be kept at 2-8°C.On the day of consumption the required number of syringes can be taken out in the OT , in sterile environment and the rest transferred to another sterile autoclavable box and restored.
- Even if all the injections are to be consumed the same day by different surgeons in the same hospital, they should be maintained between 2-8°C.
- Two of the aliqotted syringes should be sent on day 1 for microbiological culture.
- All the boxes be kept at 2-8 C
- A freshly opened 29/30/31 G needle should be used at the time of performing the Intravitreal injection.

A separate register for maintaining a log of usage of Bevacizumab must be maintained in the operation theater. This includes medical record number, name of the patient, name of surgeon, and indication for use, and the batch number with expiry of the syringe. Two syringe must be sent for culture and sensitivity testing. If there is no growth on culture after 48 hours, the batch of syringes can be released for use in patients.

It is preferable to keep the vial for a month before destroying it. The vial should be destroyed rather than just discarded to prevent its misuse. Destroy the labeling sticker on the vial with a permanent marker or remove it physically before discarding the vial.

Option 3:

Withdraw Bevacizumab directly from the vial using a 30G needle by strict aseptic technique (after having cleaned the rubber stopper with Sterilium or 70% Isopropyl alcohol) in a sterile

OT and inject. Ensure that before you start injecting the first aliquot, send a sample for culture and sensitivity , wait 48 hrs to obtain a negative culture . The injection can be done only if

the culture is clear. This technique has limited published data and hence has to be followed with caution and at the discretion of the ophthalmologist under very strict asceptic conditions. The vial should always remain stored after use in its carton and in anairtight plastic container at 2-8°C.

It is recommended that both for technique 2 and 3, a culture is to be sent on day 1, wait for 48 hours for culture report before using the aliquots or the vial . The 30G needle used for injection should be a new one and not the one with which the aliquot was stored.The vial or the aliquots can be stored ,kept and used for a maximum duration of two weeks.

- Discard the empty vial after one month– it is NOT to be re-used

C. Intravitreal injection guidelines (Please see video at www.vrsi.in/ Intravitreal injection (This will be soon uploaded)

1. Pre-op preparation and precautions:

- **Patient screening & precautions:**
  - The need and choice of Intravitreal injection should be tailored to the individual patient according to the best clinical judgment of the attending/injecting eye specialist.
  - All patients should be screened to ensure a patent nasolacrimal duct and negative regurgitation test.
  - Patients with active infection of the ocular adnexa (blepharitis, meibomitis) or a blocked nasolacrimal duct/positive regurgitation test are at high risk for endophthalmitis and should be treated for the active infection first. Injection should be scheduled after the active infection is treated.
  - Surgical/procedural time-out to verify the patient's name, Intravitreal agent and laterality should be practiced before injection for each patient.
  - Bilateral injections are NOT recommended and injection for the other eye should be planned at least one week later.
  - Patients with uncontrolled systemic conditions like uncontrolled diabetes should first be treated for it.
  - Antibiotics: Routine use of topical antibiotics for a day prior and three days post injection may be of help.
- **Patient preparation:**
  - **Consent:** An informed written consent should be taken from all patients undergoing the injection after explaining the procedure and the risks involved. Off label use of Bevacizumab should be included in the consent and explained to the patient.
  - Each patient should be given a cleaned OT gown, protective cap and booties before entering the preoperative holding area/operating room.

Time of Using the Alliquoted Bevacizumab

- While the Aliquots are waiting to be used they should be maintained in sterile, packed pouches in a sterile container at 2-8 C. Local logistics need to be worked out by the injecting surgeons
- The drug is not to be stored for more than 15 days.

2. Steps of Injection

1. **It is recommended to do the injection procedure in an operation theater or a sterile room designated for such procedures taking all precautions as are taken for any intraocular surgery. We do not recommend Intravitreal injection Bevacizumab in an office setting.**
2. Evidence suggests that prophylactic antibiotics are not better than the use of povidone iodine 5% drops. We recommend mandatory cleaning and draping. Use 10% povidoneiodine to clean the skin and periocular adnexa and 5% povidone iodine drops to be instilled in the conjunctival sac for a contact period of 3 minutes
3. Please instill one drop of proparacaine eye drops in the eye before instilling povidoneiodine drop.
4. Patients with known povidone allergy can have fluroquinolone eye drop instilled 3 times in the eye starting 30 minutes prior to the injection.
5. The surgical area should be draped using sterile linen and a separate plastic sticking eyedrape for each patient to isolate the field.
   - A sterile speculum should be used to prevent contact of the eyelashes and eyelid margins with the injection site and needle.
   - Topical anesthetic drops should be preferred over anesthetic gel as the latter may interfere with povidone-iodine contact with the conjunctiva/injection site.
   - Reapply povidone-iodine after anesthetic drop use. Before the injection, povidone-iodine (5%) should have been the last agent applied to the intended injection site.
   - Routine anterior chamber paracentesis is NOT recommended.
6. The injecting physician must scrub, and wear cap and mask. Talking should be minimal during the injection procedure.
7. Draping should be done after a minimum of 2-3 minutes of povidone iodine painting. This is to provide adequate exposure time for the povidone iodine to act against pathogens.
8. During the waiting time of 2 minutes, one can prepare the caliper marking, and make the final adjustment of volume of Bevacizumab with a fresh 29/30 G needle.
9. Do not hesitate to re-drape if eyelashes have not been completely tucked under the drape.
10. Take a final time-out to confirm the name of the patient and the correct eye to be injected.
11. It is preferable to inject under an operating microscope.
12. Any quadrant can be chosen for injection. Sterile calipers should be used to mark 3– 4 mm from limbus (depending on lens status) to mark the injection site.
13. Post injection the cul de sac can again be flushed with

povidone iodine or the injection site dabbed with a povidone iodine soaked sterile swab.

14. The eye can be patched with povidone iodine 5% drops for 2 hours after injection.

15. Post-injection antibiotic and its use is left to the discretion of the Ophthalmologist treating the case. However, in patients with poor lid hygiene, or debilitating systemic status, topical antibiotic eye drops for 5 days are recommended.

3. Post-operative precautions:

- Proper lid hygiene should be maintained in the post-op period
- Post-injection IOP should be monitored and topical antiglaucoma may be prescribed for post-injection IOP spike as and when warranted.
- All patients should be given a discharge card mentioning the injection details, postoperative instructions, symptoms of infection (pain, redness, dimness of vision, swelling, discharge, etc.) and 24-hour emergency contact information.
- Patients should instructed to avoid washing of eyes foe 24 hours
- After each day, all the instruments and linen after thorough cleaning and drying should be autoclaved for the next day.
- Follow-up of each patient should be tailored as per the indication for the Intravitreal injections.

D. Postoperative Management

1. Patients may be examined within 3 days after injection. If the patient is unable to come forany reason, the patient must be asked to report to the nearest ophthalmologist immediately if there is unusual pain, redness, or drop in vision at any time. These instructions must be given in writing to the patient and it must be ensured that they, or the accompanying attendant have understood it.

2. We suggest a good examination of anterior segment using slit lamp for any cells in the anterior chamber or anterior vitreous. Fundus should be examined using indirect ophthalmoscopy for any exudates, floaters, or new onset peripheral retinal hemorrhages or vasculitis.

3. Please check the intra-ocular pressure at each visit.

4. Patients should be instructed to avoid head bath for 1 day post injection and swimming for 3 days post injection. Practice pate

5. In case the patient is due for injection in both eyes, it should be done at an interval of 3 days.

Cautions

- Injections for ROP are not covered in these guidelines.
- Anti-VEGF injections should be deferred in pregnant women.
- Caution should be exercised in patients with increased risk of thromboembolic phenomenon or recent history of stroke or myocardial infarction, as for any other intra-ocular surgery.
- Injections should be deferred in patients with uncontrolled blood sugar levels as it may increase the chances of endophthalmitis. However, there is no evidence-based guideline for a cut-off of blood sugar or HbA1c level.
- Patient should be informed about higher risk of endophthalmitis in uncontrolled diabetes. If the patient wishes to proceed with the injection due to unavoidable circumstances, the above discussion should be documented in the consent prior to the injection. Such patients may be given pre and post-injection topical antibiotics as an additional precaution.

Don’ts

Do not buy Bevacizumab from a Non Roche Distributor

Do not use the Bevacizumab Vial if not Authenticated by Kezzler Code

Do not inject Bevacizumab in Office.Considering the varied circumstances in India we have taken a conscious decision of injecting Bevacizumab in sterile setting of an operating room or similar area.

Do not transport partially used vials in ice packs. Do not transport Alliquoted syringes of Bevacizumab. If a surgeon is practicing at multiple centers, it is recommended that each center be equipped to fractionate Bevacizumab. If this is not feasible, it is recommended that the patient be taken to the nearest center where Bevacizumab is available.

Do not store an Bevacizumab vial for re-use once it’s seal is broken

Do not re-use the Bevacizumab vial by puncturing it multiple times.

These guidelines may be updated as and when new evidence is gathered by us or any

other Indian / Western scientific body.Visit www.vrsi.in for any updatesand to report adverse events.

Tribute to a Living Legend

Amod Gupta retired as a professor of Ophthalmology and the Dean at the Post Graduate Institute of Medical Education and Research, Chandigarh (India). He has been at the forefront of clinical research in Ophthalmology and especially in the field of retinal and uveal diseases. He raised the Advanced Eye Centre in 2006, one of the most advanced ophthalmic centres for patient care, training and research in India.

In the last nearly 25 years, he has discovered new diseases, their clinical manifestations and new management strategies, which have brought about paradigm shift in the management of several blinding diseases. His researches have been recognized internationally. He has published more than 308 original research papers in national and international journals, which have been extensively cited **(Scopus 3067,) with an H index of 28**. His coauthored books on 'Optical Coherence Tomography', 'Diabetic Retinopathy' and "Uveitis: Text and Imaging" are read all over the world.

In the early 1990's, he first introduced the use of high technology in eye care in North India and was **the first person to start Vitreo-retinal surgery in the entire North India for hitherto incurable retinal diseases.**

He pioneered the setting up of the subspecialty of Uveitis and Intraocular inflammations in India and was the founder President of the Uveitis Society of India. He is an acknowledged international leader in Ocular tuberculosis and was elected to the most prestigious the International Uveitis Study Group. He described a new disease entity, 'Tubercular Serpiginouslike Choroiditis' now recognized world over and successfully treated thereby preventing blindness from this hitherto incurable disease. **With a competitive research grant of Rs 5.00 crore by the DBT, he set up a Centre of excellence for study of intraocular inflammations at the Advanced Eye Centre, PGI, Chandigarh.**

He discovered contaminated glucose infusions in the rural settings as a previously unknown risk factor for developing fungal endophthalmitis in otherwise healthy young individuals.

His work on the use of atorvastatin in management of diabetic maculopathy is extensively cited in the contemporary literature and provided initial evidence for recommending statins in patients with diabetic retinopathy.

On the editorial board of several journals, he is reviewer for Retina- journal of retinal and vitreous diseases, Retinal cases and brief reports, Archives of Ophthalmology, British Journal of Ophthalmology, Ocular Immunology Inflammation, International Ophthalmology, Current Eye Research, Indian J Ophthalmology, Plos one, Ophthalmology and several others.

He has been recognized by his peer group for his outstanding contributions in Ophthalmology and was made the founder president of the Uveitis Society of India and the President of the Vitreo-Retinal society of India.

In view of his outstanding contributions in Ophthalmology, he was awarded the first **R N Mathur award(1996)** and **Dr P Siva Reddy International Award (2008)** by the All India Ophthalmological Society, Chandigarh Ophthalmological society **(A D Grover Memorial oration,1999)** Gold Medals by the All Assam Ophthalmological Society (1996), Haryana Ophthalmology Academy(2004), Bombay Ophthalmological Association(2011), Bangalore Ophthalmological Society (Life time achievement award,2013), Punjab Ophthalmological Society (Dr Daljit Singh oration,2005) Jharkhand Ophthalmological Society, (B P Kashyap memorial oration,2006), Andhra Pradesh Ophthalmological Society **(P Siva Reddy Award-2011)**, Asia Pacific Academy of Ophthalmology(Distinguished Service Award 2007) American Academy of Ophthalmology (Achievement Award-2009) , Ranbaxy Research Foundation (Ranbaxy Research award- clinical research 2008), Cochin Ophthalmic Club (Prof T Gopinatha Menon memorial oration and Gold medal 2011), RK Seth Memorial oration (Delhi-2011), First B Patnaik memorial oration **(Vitreo-retinal society of India-2011)**, TNC Vedantham memorial oration **(Radhatri Netralaya, Chennai,2013)** and "Teacher of Teachers Award-2012" by LVP Eye Institute, Hyderabad. He was also elected Fellow of National Academy of Medical Sciences (FAMS-2006) and delivered the prestigious VR Khanolkar oration (2007-08).

He was awarded "Padma Shri' by the President of India in 2014.

Receiving 1st B Patnaik award from Mrs Kalsi Patnaik

Last day in office

Receiving 1st B Patnaik award from Mrs Kalsi Patnaik

Delivering 1st B Patnaik award lecture 2011

Being installed Founder President of Uveits Society of India by Dr Narsing Rao 2004

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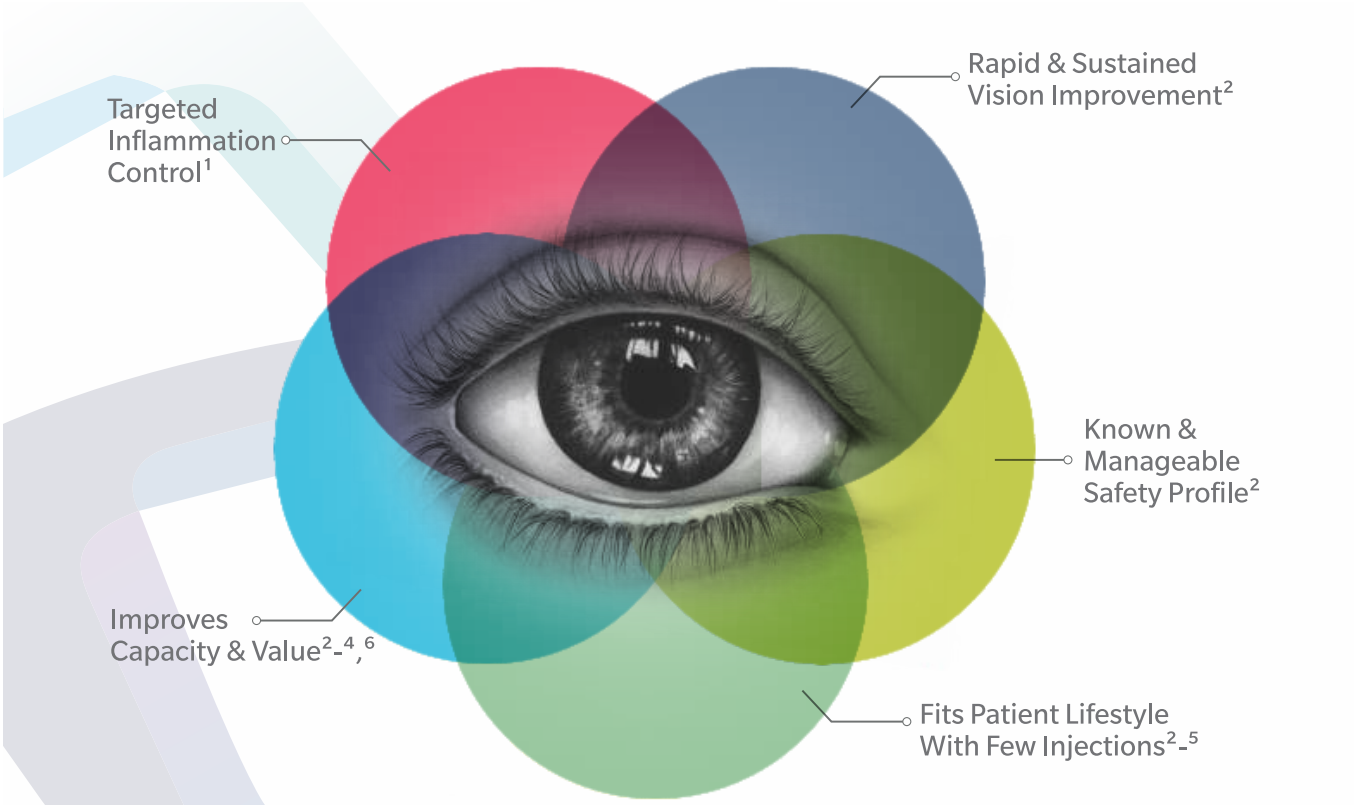
1. Abulon, et al. Porcine Vitreous Flow Behavior During High Speed Vitrectomy up to 7500 Cuts Per Minute. ARVO Poster, 2012. 2. Riemann C, et al. Prevention of intraoperative hypotony during vitreoretinal surgery: an instrument comparison. ASRS Poster Presentation, 2010.* 3. Buboltz, DC. New method for evaluating flow rates and intraocular pressures during simulated vitreoretinal surgeries. ARVO Congress Poster Presentations, 2010. Fort Lauderdale, FL.* 4. Nagpal M, et al. Comparison of clinical outcomes and wound dynamics of sclerotomy ports of 20, 25, and 23 gauge vitrectomy. Retina. 2009;29(2):225-231. 5. Davison JA, Cumulative tip travel and implied follow ability of longitudinal and torsional phacoemulsification J Cataract Refract Surg 2008; 34:986–990 6. Alcon data on file 954-0000-004. 7. Fernández de Castro, L. E. et al. (2010). Bead-flow pattern: Quantization of fluid movement during torsional and longitudinal phacoemulsification. J Cataract Refract Surg 36(6): 1018-1023.
*Based on bench lab testing.

The CONSTELLATION® Vision System is an ophthalmic microsurgical system that is indicated for both anterior segment (i.e., phacoemulsification and removal of cataracts) and posterior segment (i.e., vitreoretinal) ophthalmic surgery. The ULTRAVIT® Vitrectomy Probe is indicated for vitreous cutting and aspiration,membrane cutting and aspiration, dissection of tissue and lens removal. The valved entry system is indicated for scleral incision, cannulae for posterior instrument access and venting of valved cannulae.The infusion cannula is indicated for posterior segment infusion of liquid or gas. **Warnings and Precautions:** The infusion cannula is contraindicated for use of oil infusion. Use of disposables and handpieces other than those manufactured by Alcon may affect system performance and create potential hazards. Attach only ALCON® supplied consumables to console and cassette luer fittings. Do not connect consumables to the patient's intravenous connections. Mismatch of consumable components and use of settings not specifically adjusted for a particular combination of consumable components may create a patient hazard. Vitreous traction has been known to create retinal tears and retinal detachments. The closed loop system of the CONSTELLATION® Vision System that adjusts IOP cannot replace the standard of care in judging IOP intraoperatively. If the surgeon believes that the IOP is not responding to the system settings and is dangerously high or low, this may represent a system failure. To ensure proper IOP Compensation calibration, place infusion tubing and infusion cannula on a sterile draped tray at mid-cassette level during the priming cycle. Leaking sclerotomy may lead to post-operative hypotony. Refer to the CONSTELLATION® Vision System Operators Manual for a complete listing of indications, warnings, and precautions.



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References: **1.** Nehme A, Edelman J. Dexamethasone inhibits high glucose-, TNF-alpha-, and IL-1beta-induced secretion of inflammatory and angiogenic mediators from retinal microvascular pericytes. Invest Ophthalmol Vis Sci. 2008;49(5)2030-38. **2.** Boyer DS et al. Three-Year, Randomized, Sham-Controlled Trial of Dexamethasone Intravitreal Implant in Patients with Diabetic Macular Edema. Ophthalmology. 2014; 121(10):1904-14. **3.** Haller JA, Bandello F, Belfort R Jr, et al. Dexamethasone intravitreal implant in patients with macular edema related to branch or central retinal vein occlusion twelve-month study results. Ophthalmology. 2011; 118:2453-60. **4.** Lowder C, Belfort R, Jr, Lightman S, et al. Dexamethasone intravitreal implant for noninfectious intermediate or posterior uveitis. Arch Ophthalmol. 2011; 129:545-53. **5.** Kuppermann BD, Haller JA, Bandello, F, et al. Efficacy of Dexamethasone Intravitreal Implant for Best Corrected Visual Acuity in Patients With Retinal Vein Occlusion After 7 Days. Invest Ophthalmol Vis Sci 2011;52:E-abstract 3966. Presented at ARVO 2011, May 1-5; Fort Lauderdale, USA. **6.** National Institute for Health and Clinical Excellence. NICE technology appraisal guidance 229; July 2011. Available at www.nice.org.uk [accessed August 2015].

OZURDEX® is an intravitreal implant containing 0.7 mg (700 μg) dexamethasone in the NOVADUR® solid polymer drug delivery system. OZURDEX® is preloaded into a single-use, specially designed DDS applicator to facilitate injection of the rod-shaped implant directly into the vitreous. Indications and Usage: Retinal Vein Occlusion: OZURDEX® is indicated for the treatment of macular edema following branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO). Posterior Segment Uveitis: OZURDEX® is indicated for the treatment of noninfectious Uveitis affecting the posterior segment of the eye. Dosage and Administration: The tip of the needle is advanced within the sclera for about 1 mm (parallel to the limbus), then re-directed toward the center of the eye and advanced until penetration of the sclera is completed and the vitreous cavity is entered. Slowly depress the actuator button until an audible click is noted. Contraindications: OZURDEX® is contraindicated in patients with active or suspected ocular or periocular infections including most viral diseases of the cornea and conjunctiva and fungal diseases, in advanced glaucoma and in patients with known hypersensitivity to any components of this product. Ozurdex should not be used when there is gap in posterior capsule. Adverse Events: Adverse reactions include elevated intraocular pressure, posterior sub capsular cataract formation, secondary ocular infection from pathogens including herpes simplex, and perforation of the globe where there is thinning of the cornea or sclera. Warning and Precautions: May enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses. Caution should be exercised when corticosteroids are administered to a nursing woman. It is a Pregnancy Category C drug. Safety and effectiveness of OZURDEX® in pediatric patients has not been established. Clinical Pharmacology: Mechanism of Action: Dexamethasone, a potent corticosteroid has been shown to suppress inflammation by inhibiting multiple inflammatory cytokines. Pharmacokinetics: The majority of plasma dexamethasone concentrations were below the lower limit of quantitation (LLOQ = 50 pg/mL). Carcinogenesis, Mutagenesis, Impairment of Fertility: No adequate studies in animals have been conducted to determine whether OZURDEX® has the potential for carcinogenesis. Supply: OZURDEX® is supplied in a foil pouch with 1 single-use plastic Applicator. Storage: Store at 15°-30°C.

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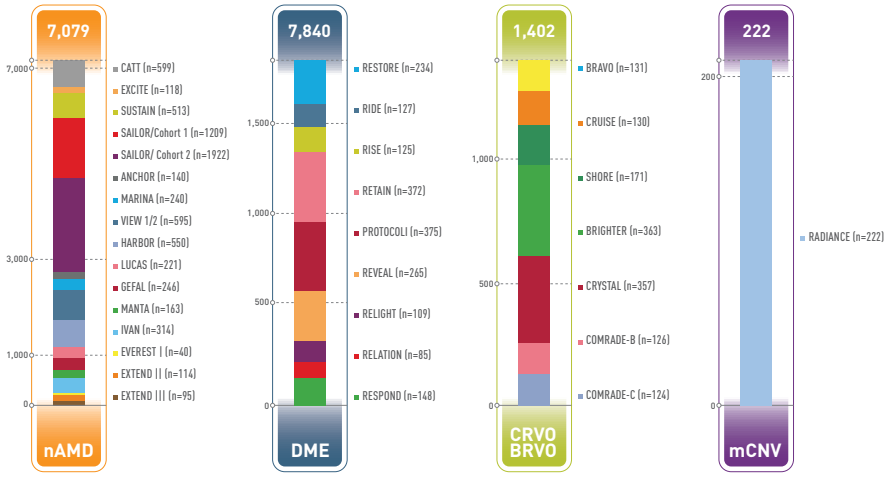

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Presentation: Vial: Ranibizumab. Each vial contains 2.3 mg of ranibizumab in 0.23 mL solution.
Indications: • improvement and maintenance of visual acuity and function and for reduction of vascular leakage and retinal oedema, in patients with neovascular age-related macular degeneration (AMD), • the treatment of visual impairment due to diabetic macular edema (DME),• the treatment of macular edema following retinal vein occlusion (RVO) • the treatment of visual impairment due to choroidal neovascularization (CNV) secondary to pathologic myopia (PM).
Dosage and administration: • The recommended dose is 0.5 mg (0.05 mL) given as a single intravitreal injection. The interval between two doses injected into the same eye should not be shorter than 1 month. Wet AMD, DME, RVO, PM: • Treatment is initiated with one injection per month until maximum visual acuity is achieved and/or there are no signs of disease activity. • Thereafter, monitoring and treatment intervals should be determined by the physician and should be based on disease activity as assessed by visual acuity and/or anatomic parameters. • Monitoring for disease activity may include clinical examination, functional testing or imaging techniques (e.g. optical coherence tomography or fluorescein angiography). • While applying the treat-and-extend regimen, the treatment interval should be extended by two weeks at a time for wet AMD and central RVO, or by one month at a time for DME and branch RVO. • Accentrix and laser photocoagulation in DME or in branch RVO: Accentrix has been used concomitantly with laser photocoagulation in clinical studies. When given on the same day, Accentrix should be administered at least 30 minutes after laser photocoagulation. Accentrix can be administered in patients who have received previous laser photocoagulation. • Accentrix must be administered by a qualified ophthalmologist using aseptic techniques. Broad-spectrum topical microbicide and anesthetic should be administered prior to the injection. • Not recommended in children and adolescents.
Contraindications: Hypersensitivity to ranibizumab or to any of the excipients, patients with active or suspected ocular or periocular infections, patients with active intraocular inflammation. Warnings and precautions: • Intravitreal injections have been associated with endophthalmitis, intraocular inflammation, rhegmatogenous retinal detachment, retinal tear and iatrogenic traumatic cataract. Therefore proper aseptic injection techniques must be used. Patients should be monitored during the week following the injection to permit early treatment if an infection occurs. • Transient increases in intraocular pressure (IOP) have been seen within 60 minutes of injection of Accentrix. Sustained IOP increases have also been reported. Intraocular pressure and the perfusion of the optic nerve head must be monitored and managed appropriately. • There is a potential risk of arterial thromboembolic events following intravitreal use of VEGF inhibitors. A numerically higher stroke rate was observed in patients treated with ranibizumab 0.5 mg compared to ranibizumab 0.3 mg or control; however, the differences were not statistically significant. Patients with known risk factors for stroke, including history of prior stroke or transient ischemic attack should be carefully evaluated by their physicians as to whether Accentrix treatment is appropriate and the benefit outweighs the potential risk. • Available data do not suggest an increased risk of systemic adverse events with bilateral treatment. • As with all therapeutic proteins, there is a potential for immunogenicity with Accentrix. • Accentrix has not been studied in patients with active systemic infections or in patients with concurrent eye conditions such as retinal detachment or macular hole. • There is limited experience with treatment of patients with prior episodes of RVO and of patients with ischemic branch RVO (BRVO) and central RVO (CRVO). In patients with RVO presenting with clinical signs of irreversible ischemic visual function loss, treatment is not recommended. • Should not be used during pregnancy unless the expected benefit outweighs the potential risk to the fetus. For women who wish to become pregnant and have been treated with ranibizumab, it is recommended to wait at least 3 months after the last dose of ranibizumab before conceiving a child; use of effective contraception is recommended for women of child-bearing potential; breast-feeding is not recommended. • Following treatment patients may develop transient visual disturbances that may interfere with their ability to drive or use machines. Patients should not drive or use machines as long as these symptoms persist.
Interactions: No formal interaction studies have been performed.
Adverse drug reactions: • Very common (≥10%): intraocular inflammation, vitritis, vitreous detachment, retinal hemorrhage, visual disturbance, eye pain, vitreous floaters, conjunctival hemorrhage, eye irritation, foreign body sensation in eyes, lacrimation increased, blepharitis, dry eye, ocular hyperemia, eye pruritus, intraocular pressure increased, nasopharyngitis, headache, arthralgia. • Common (1 to 10%): retinal degeneration, retinal disorder, retinal detachment, retinal tear, detachment of the retinal pigment epithelium, retinal pigment epithelium tear, visual acuity reduced, vitreous hemorrhage, vitreous disorder, uveitis, iritis, iridocyclitis, cataract, cataract subcapsular, posterior capsule opacification, punctuate keratitis, corneal abrasion, anterior chamber flare, vision blurred, injection site hemorrhage, eye hemorrhage, conjunctivitis, conjunctivitis allergic, eye discharge, photopsia, photophobia, ocular discomfort, eyelid edema, eyelid pain, conjunctival hyperemia, stroke, influenza, urinary tract infection*, anemia, anxiety, cough, nausea, allergic reactions (rash, pruritus, urticaria, erythema). • Uncommon (0.1 to 1%) : blindness, endophthalmitis, hypopyon, hyphema, keratopathy, iris adhesions, corneal deposits, corneal edema, corneal striae, injection site pain, injection site irritation, abnormal sensation in eye, eyelid irritation. • Serious adverse events related to intravitreal injections include endophthalmitis, rhegmatogenous retinal detachment, retinal tear and iatrogenic traumatic cataract.
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India BSS dated 27 Apr 15 based on international BSS dtd 28 Oct 2014 effective from 16 Feb 2016
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