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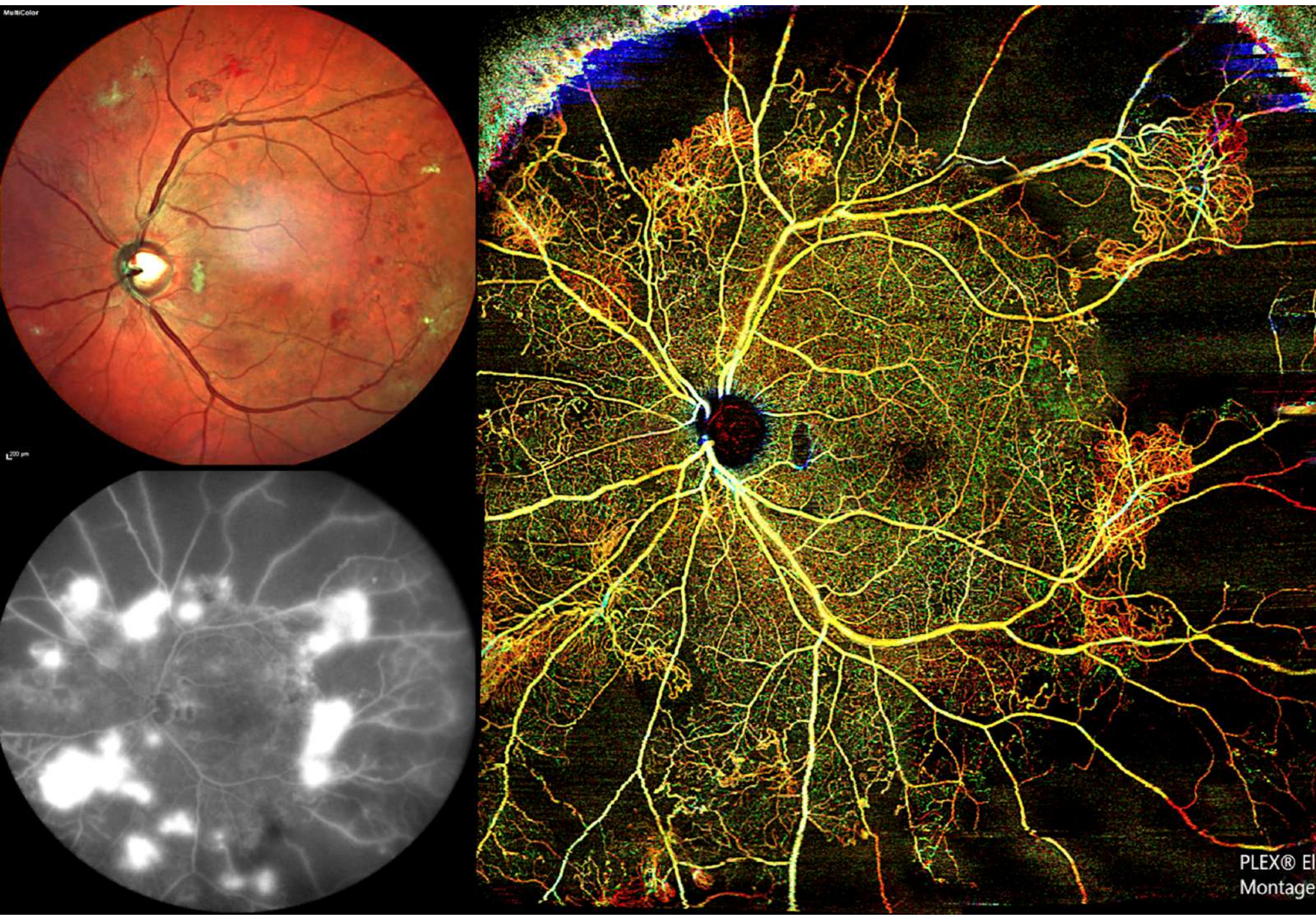
December 2022

The Official Newsletter of the

# VITREORETINAL SOCIETY-INDIA



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# COVER IMAGE

**Dr Priyanka Agarwal**
Vitreo-retina and uvea Consultant
Shroff Eye Centre, New Delhi

Multi-color image, fundus fluorescein angiography and OCT angiography of the left eye with proliferative diabetic retinopathy showing multiple neovascularization elsewhere (NVE) and capillary non perfusion areas

# FROM THE PRESIDENT'S DESK

Dear Friends

The last newsletter for this year is in your hands. Dr Mahesh Shanmugam and his team have been doing exemplary job in bringing out issues that are focused on particular problems. This issue is on Diabetic Retinopathy, which continues to be a major problem and is expected to increase as we face 'epidemic' of Diabetes in India. This issue is going to be worth preserving for reference!

By the time you have this issue in your hand, we will be in the midst of our annual meeting at Nagpur. It will be a rich scientific fare, as the Scientific committee has put together an ambitious program. Dr Sulabha Deshpande, Dr Prashant Bawankule and their team are putting in tremendous efforts to make this meeting a success. We look forward to seeing you at Nagpur.

VRSI is joining hands with AIOS to tackle the problem of blindness due to DR. We are also closely collaborating with RSSDI, which has a large number of physicians treating diabetes. We hope to be able to drive home the need for DR screening in a large way. VRSI is also actively seeking collaboration with other VR societies in the Asia-Pacific region. In the coming years, this should lead to larger participation of these societies in our meetings and vice versa.

Looking forward to meet you at Nagpur in large numbers…..

Dr Muralidhar

# FROM THE HONORARY SECRETARY'S DESK

Dear Seniors and friends,

We are all aware that India is the diabetic capital of the world and we all recently celebrated the "World Diabetes day" on the 14th of November and various activities were performed by our society to enhance the awareness of diabetic retinopathy. This included an active campaign on FM radio channels in 49 cities, an awareness walk along with members of AIOS and SAO, making an awareness film along with AIOS for TV channel, collaborating with 1mg for awareness articles and notifications to their diabetic customers. DR screening camps for Delhi police officials, army men in Jammu and border security force in Gujarat were conducted (an initiative taken by Novartis Company), and above all collaborating with RSSDI which is the largest organization of Diabetologists in India to spread awareness amongst their members for a timely referral of their patients for DR screening. We also got an enthusiastic response for the DR slogan and poster competition. A few glimpses of these activities has been shared in this newsletter for the benefit of all our members. DR screening and management training module for general ophthalmologists has been designed. Our society is working hard at every level under the able guidance of Dr. N S Muralidhar and Dr. R Kim to spread awareness and avoid blindness secondary to diabetic retinopathy. This issue of the newsletter thus focuses on diabetic retinopathy and is an interesting read for all.

## FROM THE HONORARY SECRETARY'S DESK

The annual conference is a few days away and we have had a record number of registrations. An excellent scientific program has been designed by our Scientific Chair Dr Mahesh P Shanmugam, which surely will be an academic feast for all the delegates. Dr Prashant Bawankule and his team have been working round the clock to ensure a comfortable stay for all of us with utmost detailing and I thank him for hosting it and all the effort made by his team.

On behalf of the society we look forward to welcoming you all to the 31st Annual conference at Nagpur from 2-4th Dec and hope you all have a comfortable stay along with an enriching experience of both academics and fun.

Regards

Dr. Manisha Agarwal

Hon General Secretary

# FROM THE CONVENER, SCIENTIFIC COMMITTEE'S DESK

Dear Friends,

Greetings!

We are reading the last newsletter of this year and it is indeed a big one - as is the problem it addresses - that of diabetic retinopathy, particularly relevant to us in India. Dr. Daraius and Dr. Pradeep have brought out a keeper of an issue, combining the contemporary and the future - a status statement on optimal management of diabetic retinopathy and also where we stand in reference to emerging treatments. Congratulations and thanks to them. Heartfelt thanks to all the authors who have managed to present to us the voluminous data in a brilliant précis, easy read format. This issue will be an ideal reference for the novice and the expert alike.

Most of us will be at the annual meeting when we receive this issue - we have made some changes to the format of this year's meeting - it has been shortened to two and a half days; more discussion time than the presentation time to enable hi-lighting the salient points for better learning. A great panel of 5 or more experts in each of the sessions will further enhance the learning and a dynamic moderator will carry each session on her / his shoulder to bring out the best in each of us. We have also distributed the non competitive free papers as part of each session so that they get the better audience they deserve. Audience

participation is very welcome and all of us can ask questions using our mobiles during the sessions. Hope the experiment works and finds favour with you!

GBM is one thing most of us miss during the annual meetings but it will be great if you can be there this time! We are introducing the VRSI study group, tentatively named the VRSI.net wherein the VRSI will curate and facilitate multicentric studies where all of us can participate and contribute to create our own data that can impact our practice positively. We have completed the first study which is due to publication in "EYE" in the near future.

Looking forward to seeing you all soon and thank you for reading.

Warm regards

Mahesh

# GUIDELINES:
# MANUSCRIPT SUBMISSION FOR VRSI NEWSLETTER

**Original Articles :**

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

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

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

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# INTRODUCTION TO THE ISSUE

Dear VRSI members

Welcome to the December edition of the VRSI newsletter.

14th November is known as **World Diabetes Day (WDD)**. WDD was created in 1991 by the World Health Organization and the International Diabetes Federation (IDF) in response to growing concerns about the escalating health threat posed by diabetes. World Diabetes Day is marked every year on **14 November**, the birthday of Sir Frederick Banting, who co-discovered insulin along with Charles Best in 1922.

To mark this important day, especially its significance to retinologists, we dedicate this issue as an update on diabetic retinopathy.

India is deemed to be the world's capital of diabetes. The diabetic population in the country is close to hitting the alarming mark of 70 million by 2025 and 80 million by 2030. This is set to increase to over 134 million in the next 25 years.

What is of greater concern is that diabetic retinopathy is the commonest cause of vision loss in the working age group population.

We are fortunate to have an interesting mix of articles from National and International experts. Two of these are based on the DRCR network. The mission of the DRCR Retina Network is to conduct high quality, collaborative clinical research that improves vision and quality of life for people with diabetic retinopathy. This is a US based consortium.

## INTRODUCTION TO THE ISSUE

In the future we look forward and plan to conduct such collaborative studies in India, under aegis of bodies like VRSI.

These articles also present advances in treatment options to reduce treatment burden, the role of advanced imaging and AI in diabetic retinopathy, and biosimilars, which is currently a hot topic across the globe.

We are extremely grateful to our members for excellent submissions of interesting diabetic cases and images. These are featured in our newsletter as well as on the cover.

Looking forward to an exciting VRSI annual meeting in Nagpur

Regards

Dr Daraius Shroff,

Deputy Editor VRSI Newsletter, and member Governing Council, VRSI

Dr Pradeep Sagar,

Deputy Editor, VRSI Newsletter

# TOP TAKE HOME PEARLS FROM THE DRCR STUDIES FOR MANAGING DIABETIC EYE DISEASE

**Dr. Sabyasachi Sengupta**

Consultant vitreoretina surgeon

Future Vision Eye Care and Research center, Mumbai

As clinicians following evidence based medicine, and especially as vitreoretinal specialists, we are well aware of the Diabetic Retinopathy Clinical Research Network (DRCR.Net) that has revolutionized the management of diabetic macular edema (DME) and proliferative diabetic retinopathy (PDR) over the past decade. In particular, the protocol I and later the protocol T have influenced how we manage DME with antiVEGF injections and the protocol S has shown glimpses of how PDR can be managed without laser photocoagulation in certain scenarios. In this write up, we will discuss some of the most important lessons learned from the DRCR.Net studies that are readily applicable to patient care. I have adopted a chronological order for these pearls based on the timing of publication so that this write up, in addition to being a ready reckoner on these studies, also serves as a précis on "*how treatment patterns have evolved over time*". Finally, we will round it off with my take on how we can modify these protocols and regimens slightly for the Indian scenario.

1. **Protocol B** was one of the earliest protocols that compared macular laser vs. triamcinolone for management of DME.(1) The study found that, over 2 years, focal/grid photocoagulation was more effective and has fewer side effects than 1 mg or 4 mg doses of preservative-free intravitreal triamcinolone. Similarly, **Protocol E** showed that, in cases of DME with good visual acuity, peribulbar triamcinolone, with or without focal photocoagulation, was unlikely to be of substantial benefit.(2) These ***twin studies negated the use of triamcinolone monotherapy for DME*** and hence, this was not considered in most of the comparative arms of future DRCR studies. Till then, macular laser was still the preferred treatment for DME
2. **Protocol F** compared application of PRP in 1 sitting compared with 4 sittings and concluded that the incidence of CME was no different.(3) Hence, *routine PRP in 1 sitting can also be undertaken if patient tolerates*, and especially if a multispot laser in available.
3. **Protocol I** was the first DRCR study to show that intravitreal ranibizumab with prompt or deferred (≥24 weeks) focal/grid laser was more effective through 2 years in increasing visual acuity compared with laser treatment alone for the treatment of DME involving the central macula.(4) In conclusion, the study investigators recommended ***initiating treatment with ranibizumab monotherapy*** [monthly for the first 6 months and then as needed based on predefined criteria (more on it later)], ***and focal/grid laser should be deferred for 6 months and used only as rescue therapy for persistent edema*** (adopted for the protocol T).

4. **Protocol T** compared aflibercept (2mg) vs. ranibizumab (0.3mg) vs. bevacizumab (1.25mg) in pairwise comparisons to treat DME.[5] Most of the current treatment guidelines for DME are based on the Protocol T and hence we will spend more time understanding its recommendations.
   A. Patients received 6 monthly loading doses of one of the three drugs based on the randomization, followed by ***reinjections based on the 5/10 rule*** (for ease of recollection) i.e. >5letter (1 Snellen's line) loss of vision or 10% worsening of central macular thickness (CMT) on OCT. If the vision and CMT did not change (i.e. within the 5/10 limits) even after 2 consecutive injections, then injections were stopped and restarted if these thresholds were crossed. These retreatment guidelines are very practical and useful in clinics every day.
   B. The most striking finding was that ***bevacizumab, despite its intensive use, did not lead to comparable vision gains and CMT reduction*** compared to the other two drugs. Additionally, 2/3rd (i.e. 66%) of eyes receiving bevacizumab continued to have persistent DME even at 2 years' time point, suggesting that ***bevacizumab is perhaps not the best drug we can offer our patients*****,** especially in the biosimilar era.
   C. Compared to ranibizumab, ***aflibercept*** offered better and more rapid visual gains and was ***superior at the one year time point*** when baseline visual acuity was worse than 69 letters (i.e. 20/50 or 6/12 Snellen's), something that we see very often in our clinics. This superiority comparison was built into the overall non-inferiority study design and hence is statistically robust. However, ***the visual advantage of aflibercept diminished at 2 years as the ranibizumab eyes caught up.*** Overall, both drugs showed about 16 – 18 letter gain (3 ½ lines) at 2 years in eyes with vision below the 6/12 mark.

D. ***Fewer aflibercept injections were needed*** over time compared to ranibizumab to maintain the same effect

E. The area under the curve (i.e. cumulative effect across the entire time period and not at each time point) showed a significant benefit for aflibercept vs. ranibizumab over the entire 2 years, with a +3.4 letter advantage, despite needing fewer injections. Also, >50% patients showed a 15 letter gain compared to 45% in the ranibizumab arm.

F. Rescue focal macular laser was done in 41% in the aflibercept group vs. 52% in the ranibizumab and 64% in the bevacizumab group. These are significant numbers and ***we should remember that rescue macular laser is still required in almost half the patients over the long run***.

G ***Aflibercept also led to more reversal in the diabetic retinopathy grades*** compared to the other drugs, especially in those with severe NPDR.

H. Overall, the clear message was that an intensive anti-VEGF treatment in Year 1 may facilitate a reduced injection burden thereafter with better visual gains.

I. Lastly, when interpreting results from the Protocol T, one must remember that 0.3mg ranibizumab was used while we have 0.5mg available commercially. Assuming that the therapeutic effect of these drugs is dose – dependent, this could offset the clear advantage aflibercept has demonstrated in Protocol T but we will never know this for sure.

5. **Protocol S** evaluated Prompt PRP vs. Ranibizumab ± Deferred PRP for PDR and concluded that ***PRP has been effective for PDR over last 4 decades; and it remains effective in 21st century.***(6) Some other important conclusions were:

A. Ranibizumab is an effective treatment alternative to PRP with no substantial safety concerns for at least 2 years, though the cost of repeated injections is perhaps not yet justified.
B. However, ***ranibizumab monotherapy*** may be the preferred initial treatment approach for a subgroup of patients, ***who have both PDR and DME.***
C. Ranibizumab should be avoided when there is substantial tractional component in the PDR.
D. Nearly 50% patients continued to have some active neovascular component at two years, a surprising result that we don't quite see in clinics after a well done PRP.
E. The study also reported a higher vitrectomy rate (15% vs 4%) in the PRP group compared to the ranibizumab group at two years, again drawing our attention to careful case selection for ranibizumab in eyes with coexistent PDR and DME without a significant tractional component.

6. **Protocol U** showed no added advantage of adding intravitreal dexamethasone to ranibizumab in eyes with persistent DME even after 3 loading doses.(7)
7. **Protocol V** showed that we can safely observe eyes with center involving DME and good baseline vision of 6/9 or better.(8)
8. **Protocol W** showed that injecting aflibercept vs. sham in eyes with moderate NPDR slowed progression to PDR but did not have visual benefits, and hence is not yet recommended.(9)

***The Indian scenario*** – the holy grail lies in how we adapt these ideal treatment recommendations for our patients. We want to ideally choose a drug that gives better vision, better drying, is longer acting (therefore needing fewer injections), has minimal side effects and is relatively cost effective in the long run. Also how often do we reinject, and do we start with 6 monthly loading doses as recommended by Protocol T? We would really need to get together and do some Indian studies to answer these pivotal questions.

Till then, it is reasonable to adopt the following strategy for treating DME in Indian patients: Three monthly loading doses of ranibizumab at least (or its biosimilar) followed by monthly visits and reinjection using the 5/10 rule i.e. reinject if there is 10% increment in CMT or 5 letter (1 Snellen's line) drop in vision. Aflibercept should be considered strongly for those with lower vision at baseline (more common in our setting) and able to afford. Interval between visits may be extended progressively but judiciously so that a fine balance of optimal dosing is achieved with minimal follow ups. Various payment schemes offered by manufacturers these days have meant that the annual spend per eye per year is more or less similar, irrespective of the drug you choose. Hence why not choose the most potent one?

Lastly, a PRN regimen from baseline, using the 5/10 rule, may also be feasible for DME (unlike AMD where a loading dose is an absolute must), more so with aflibercept use, provided the patient pledges monthly follow ups and is maintaining good glycemic control. This is far away from the DRCR recommendations, but a few studies have shown some merit in this approach.[10,11]

In conclusion, the DRCR.Net studies have revolutionized the way we treat DME, and PDR and many ongoing and future protocols may as yet mould how we treat these diseases in the coming decade. It will be worthwhile to keep an eye out for these papers and adopt them in your practices with due diligence.

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# CURRENT STATUS AND ROLE OF BIOSIMILARS FOR MANAGEMENT OF DIABETIC RETINOPATHY

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Coimbatore

**Dr. Nikulaa Parachuri**

Sankara Eye Hospital

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**Dr. Nilesh Kumar**

Madhavi Netralaya

Ara

A biosimilar is a biological product that is highly similar to and has no clinically meaningful differences from an existing United States food and drug administration (US-FDA) approved reference product. Ophthalmology, especially retina as a subspecialty, has transformed since the introduction of anti-vascular endothelial growth factors (Anti-VEGF) more than 15 years ago. Approved innovator anti-VEGF molecules such as ranibizumab (2006) and aflibercept (2011) have made a significant difference in the management of various retinal vascular diseases such as diabetic macular edema (DME), retinal vein occlusion (RVO) and neovascular- age-related macular degeneration (n-AMD) apart from the off-label bevacizumab.[1] Ranibizumab's patent expired in 2020 and aflibercept's patent will be expiring soon (2023/26). The expiry of patents has opened up an era of biosimilars. Biosimilars are officially approved versions of the original "innovator" products and can only be manufactured in a well-equipped research and development facility when the original product's patent expires.[2] A manufacturer

developing a proposed biosimilar demonstrates that its product is highly similar to the reference product by extensively analyzing (i.e., characterizing) the structure and function of both the reference product and the proposed biosimilar. State-of-the-art technology is used to compare characteristics of the products, such as purity, chemical identity, and bioactivity. The manufacturer uses results from these comparative tests, along with other information, to demonstrate that the biosimilar is highly similar to the reference product. Minor differences between the reference product and the proposed biosimilar product in clinically inactive components are acceptable. For example, these could include minor differences in the stabilizer or buffer compared to what is used in the reference product. Any differences between the proposed biosimilar product and the reference product are carefully evaluated by FDA to ensure the biosimilar meets FDA's high approval standards.[3] A Biosimilar should not be confused with the Generic as the latter is simple to replicate due to its chemical formula whereas biosimilars are not identical copies of innovators as they have differences that are not clinically meaningful.[1] As mentioned above, slight differences (i.e., acceptable within-product variations) are expected during the manufacturing process for biological products, regardless of whether the product is a biosimilar or a reference product. For both reference products and biosimilars, lot-to-lot differences (i.e., acceptable within-product differences) are carefully controlled and monitored. Biosimilar anti-VEGF agents are relatively new to retina specialists worldwide except in India where the first ranibizumab biosimilar was approved way back in 2015. Currently, 6 biosimilar ranibizumab molecules are approved in different parts of the world. India has 3 Drug Controller General of India approved biosimilar ranibizumab. {Razumab (Intas Pharmaceuticals Ltd, Ahmedabad), Ranieyes (Lupin Ltd, Mumbai), Ranizurel (Reliance life sciences, Mumbai)}. Japan has one

biosimilar ranibizumab molecule (Ranibizumab BS 1, Senju Pharma) approved by the Japan Ministry of Health, Labour, and Welfare. The above biosimilar ranibizumab molecules are approved for use within the specific country where it is approved. They are not approved by the FDA and European Medical Agency (EMA). Biosimilar anti-VEGF molecules have gained significant attention in the recent past after the approval of two biosimilar ranibizumab molecules by the FDA. The first drug was Byooviz/ ranibizumab-nuna (Byooviz, Samsung Bioepis, South Korea / Biogen, USA) which received FDA approval in September 2021 and EMA approval in August 2021. The second drug was CIMERLI/ ranibizumab-eqrn (Coherus BioSciences, CA, USA) that has received FDA approval in August 2022. It has already been approved by UK Medicines & Healthcare Regulatory Agency (MHRA) in 2022. The biosimilar has received EMA approval recently (29th August 2022) with the name Ranivisio. Submission for Canadian approval is expected to be completed in late 2022.

CIMERLI/ ranibizumab-eqrn has also received approval for interchangeability with reference ranibizumab (Lucentis) for all the five indications n-AMD, RVO, DR, DME, myopic choroidal neovascular membrane with exclusivity for 12 months.[4]

All the described biosimilar molecules except ranibizumab-nuna are approved for the management of diabetic retinopathy. Except in USA, ranibizumab-nuna is also approved for the management of DR and DME. The reason for the non-approval of ranibizumab-nuna is the doses that were tested in the trial. US has 0.3 mg as the approved dose for DME which was not tested. The prevalence of diabetic retinopathy is much higher compared to other diseases in which anti-VEGF therapy is required for management. Developing countries such as India which has become the diabetic capital of the world after China needs more cost-effective therapies as the majority of the population is

not insured and patients need to pay from their pocket. Real-world outcomes have always been inferior compared to clinical trial results. One of the reasons is under treatment and cost does play a role in this. There could be an argument that off-label bevacizumab might be the best option for such situations. However, due to the unavailability of robust compounding pharmacy systems in these countries, there have been some incidences of endophthalmitis. This has led to apprehension in many retina practitioners and many of them have switched to biosimilar ranibizumab which provides the advantage of cost and a single vial. This might not be the same case in the developed world where off-label bevacizumab is the most cost-effective and safe option. However, on-label bevacizumab from Outlook is under investigation and if that is approved then there is a possibility that US physicians might not be allowed to use off-label bevacizumab legally. In that case, ranibizumab biosimilar might be of interest.[5] Real world data is the need as reflected by Bio-USER survey from our group {International Retina Biosimilar Study Group (Inter BIOS Group)}. Inter-BIOS group is intended to provide real world data on biosimilar anti-VEGF approved worldwide. [6,7]

To summarize, biosimilar anti-VEGFs have the potential to improve access to treatment by reducing the financial burden on patients and on the healthcare system.

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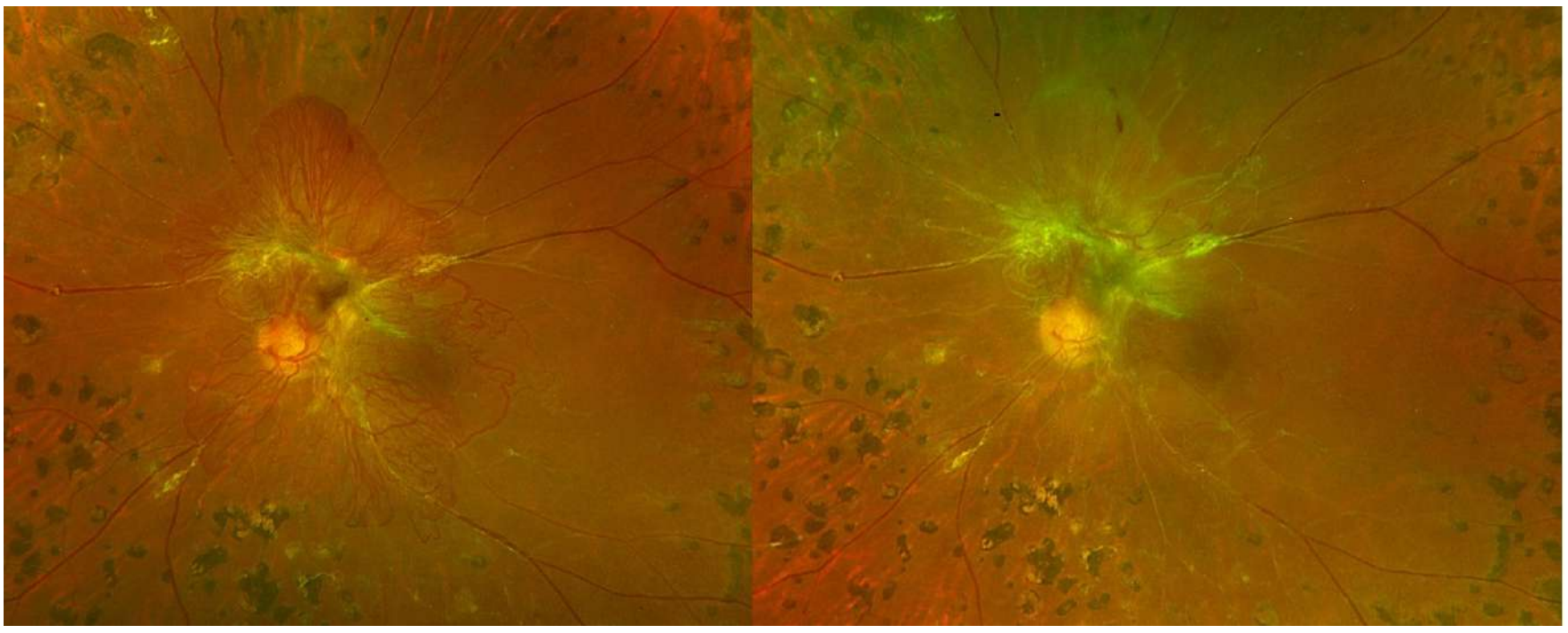
# INTERESTING IMAGE

## 1. DRYING THE BATTLE FIELD!!

**Dr. Shobhit Varma**

Vitreoretina Fellow

Shri Bhagwan Mahavir Vitreoretina Services, Sanakara Nethralaya, Chennai



The image on the left shows a case of tractional retinal detachment due to proliferative diabetic retinopathy. The image on the right shows regression of neovascularization at 3 days following intravitreal ranibizumab injection.

# DRCR.NET- WHAT'S HOT...AND WHAT'S IN THE PIPELINE?

**Dr. Kiran Chandra Kedarisetti**

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**Dr. Ritesh Narula**

L V Prasad Eye Institute

Hyderabad

Diabetic Retinopathy Clinical Research Network (DRCR.net), formed in 2002 as a collaborative retina research group with its first publication in 2008, has introduced landmark studies in the management of diabetic retinopathy that has improved the clinical care of diabetic patients.

As the diabetic retinopathy study (DRS) established treatment benefits of pan retinal photocoagulation (PRP) in proliferative diabetic retinopathy (PDR)[1] and the early treatment of diabetic retinopathy study (ETDRS) demonstrated usefulness of focal/grid macular laser photocoagulation in stabilizing the progression of diabetic macular edema (DME) and decreasing vision loss,[2] The DRCR. net established anti- vascular endothelial factor (anti-VEGF) agents as the primary modality of treatment for eyes with visual impairment due to complications of diabetic retinopathy particularly DME.

Protocol T did the head to head comparison of existing anti-VEGFs in DME and established the use of these agents as first line therapy in real world scenarios.[3] Protocol S took it further to show that anti VEGF are an effective alternative to PRP for eyes with PDR.[4] Protocol U evaluated short-term visual improvement at 6 months after the addition of corticosteroid therapy in patients with persistent DME despite anti-VEGF treatment[5] and then protocol V demonstrated that in eyes with centre-involved DME (CI-DME) and good visual acuity, observation may be as good as the available treatment options.[6]

This article provides a brief synopsis of recent results from the network and also looks ahead at some upcoming trials.

**Protocol AB[7]**

Protocol AB studied the outcomes of Anti VEGF versus prompt vitrectomy for vitreous hemorrhage (VH) in PDR patients. 205 patients from 39 DRCR centres who suffered vision loss (BCVA <78 letters) due to VH were randomised to receive either intravitreal anti-VEGF or undergo prompt vitrectomy with PRP. In eyes that underwent vitrectomy, recurrent VH was treated with 2 monthly aflibercept injections and additional injections every 4 weeks, if felt needed by the clinician. Repeat vitrectomy could be performed if VH failed to clear after 2 aflibercept injections. In the aflibercept group, injections were deferred if complete fundus could be viewed and neovascularization was absent. At 24 weeks, injections were given unless the eye stabilized. Starting at 16 weeks, vitrectomy could be performed if there was persistent VH causing vision impairment following 2 monthly injections.

At 24 week follow up, mean visual acuity letter score was 59.3 (95% CI, 54.9 to 63.7) in the aflibercept group vs 63.0 (95% CI, 58.6 to 67.3) in the vitrectomy group (adjusted difference, —5.0 [95% CI,-10.2 to 0.3]. Visual acuity improved faster with vitrectomy, but there was no difference at 24 weeks. Recurrent VH occurred at least once in 48 of 97 participants (49%) in the aflibercept group and 16 of 104 participants (15%) in the vitrectomy group [95% CI, 22% to 46%, P<.001]. The proportion of eyes with CI-DME at 24 weeks was 8% (7 of 87) in the aflibercept group vs 31% (28 of 90) in the vitrectomy group (difference, -23% [95% CI, -34% to-12%], P< .001) and at 2 years was 17% (15 of 88) vs 21% (17 of 80) respectively (difference, -4% [95% CI, -16% to 8%], P=0.48. Over 2 years, 33 eyes (33%) assigned to aflibercept received vitrectomy and 34 eyes (32%) assigned to vitrectomy received subsequent aflibercept.

*Take to the clinic point:* Both aflibercept and vitrectomy appear to have similar benefits in VH eyes except a faster visual recovery with vitrectomy. Also 1/3rd of injection patients did eventually need vitrectomy. The cost of treatment involved and the visual needs of a patient can be used as a guide to decide between the options in the clinic.

**Protocol AC[8]**

Protocol AC examined the real-world cost burden for patients and insurance systems and considering the potential results of a step-therapy approach to anti-VEGF therapy. The two arms included intravitreal aflibercept versus intravitreal bevacizumab + deferred aflibercept for treatment of CI- DME. Patients who had a visual-acuity letter score of 24 to 69 were randomised to receive either 2.0 mg of intravitreal aflibercept or 1.25 mg of intravitreal bevacizumab.

At 12 weeks, eyes in the bevacizumab-first group were switched to aflibercept therapy if protocol-specified criteria were met. Patients who had persistent DME, received an injection with bevacizumab in the last 2 visits with no recent improvement in the eye condition (visual-acuity letter score not improved by ≥5 letters and central subfield thickness on OCT not improved by ≥10% as compared with each of the two preceding visits) were switched from receiving bevacizumab to receiving aflibercept therapy.

Over the 2-year period, 70% of the eyes in the bevacizumab-first group were switched to aflibercept therapy. The mean improvement in visual acuity was 15.0 letters in the aflibercept-monotherapy group and 14.0 letters in the bevacizumab first group (adjusted difference, 0.8 letters; 95% confidence interval, −0.9 to 2.5; P=0.37). At 2 years, the mean changes in visual acuity and retinal central subfield thickness were similar in the two groups. No evidence of a significant difference in visual outcomes over a 2-year period between aflibercept monotherapy and treatment with bevacizumab first with a switch to aflibercept in the case of suboptimal response.

*Take to the clinic point:* The results carry a huge significance with regards the pharmaco-economics of anti-VEGF therapy for DME. It gives one confidence to start treatment with economically more viable bevacizumab and then later shift to aflibercept when required without compromising on the final visual outcomes for our patients.

**Protocol TX[9]**

Protocol TX was designed to study the 5 year outcomes of patients recruited in protocol T after protocol-specified treatment was stopped. Three years after the completion of

Protocol T, 317 participants with DME and visual acuity (VA) 20/32 to 20/320 were evaluated in a single visit. In Protocol T, 463 patients were randomised to receive either aflibercept, bevacizumab or ranibizumab with a protocol defined follow up and re-treatment. Following this for the next 3 years patients were managed at clinician discretion and were recalled at 5 years to observe the outcomes.

During the extension period, 98% had at least 1 visit with a retina specialist and 68% received at least 1 anti VEGF (median 4 injections). At 5 years, mean VA improved from baseline by 7.4 letters (95% confidence interval [CI]: 5.9 to 9.0), but decreased by 4.7 letters (95%CI: 3.3 to 6.0) between 2 and 5 years. Mean central subfield thickness decreased from baseline to 5 years by 154µm (95% CI: 142 to 166) and was stable between 2 and 5 years (-1µm [95% CI: -12 to 9]). Through the study they concluded that initial intensive care stabilizes the vision, being better than no treatment. However VA declines in the real world scenario after stopping intensive care.

*Take to the clinic point:* The study emphasises the importance of continuous monitoring of patients with DME in real world scenario. This study also makes one ponder over the need for a treatment option with more sustained visual acuity outcomes over long term. Being a multifactorial disease, the retinal status in DME may be influenced by lot of other systemic and local factors, which is shown in this study by a clear discordance between VA and CMT change.

**Protocol AE[10]**

Protocol AE is a pilot study that evaluated the role of photobiomodulation therapy for DME: a potential at-home therapy to treat DR and DME. Photobiomodulation is

irradiation of the macula using light in the far-red to near-infrared region of the spectrum (630 to 900 nm). It is believed to have a beneficial effect in eyes with DME through the amelioration of oxidative stress and reduced expression of pro-inflammatory proteins in the retina. The device is worn as a single eye patch which emits red light of 670 nm at a dose of 4.5 J/cm2 with an irradiance not >50 mW/cm2 . The placebo device seems identical to the active device, except that a broad-spectrum, low-power white light, believed not to have any biologic effect, is emitted.

On OCT, CST increased from baseline to 4 months by a mean (SD) of 13mm in PBM eyes and 15 mm in placebo eyes (adjusted mean difference [95% CI] -2 [20 to 16] mm; P 0.84) The treatment compliance at home was 100%, however there was no significant benefit found with PBM therapy. No significant difference was identified between the PBM and placebo groups in terms of change in OCT CST or VA letter score from baseline to 4 months. PBM was safe and well-tolerated over 4 months of use, with no serious adverse events reported by study participants. The duration of exposure and the different treatment algorithm using PBM at different frequencies, dosages, or wavelengths might lead to different results

*Take to the clinic point:* Photobiomodulation is still in its nascent stage of understanding and needs more evidence before it could be taken to clinics as a therapeutic option

**ONGOING AND ENROLLING TRIALS**

Ongoing and currently enrolling trials by the DRCR Retina Network for DR include protocols AF, AK and AM.

**Protocol AF[11]**

A randomized, double-masked, placebo-controlled clinical trial evaluating fenofibrate for prevention of diabetic retinopathy worsening. Participants with mild to moderately severe NPDR without centre involving DME will be evaluated over 4 years to observe for worsening of diabetic retinopathy. If an oral agent is effective in reducing the worsening of diabetic retinopathy, it would decrease treatment burden and help control DR at the level of primary care provider such as internists/endocrinologist. The study is currently recruiting the participants and the results are estimated to be reported by 2027.

**Protocol AK[11]**

It will study the home OCT monitoring system as a baseline feasibility study.

Notal Vision has developed an OCT system for at-home use, called Home OCT system. Through daily home OCT monitoring in 15 patients over 6 months, the study aims to observe intra retinal fluid and sub retinal fluid, that may allow customization of treatment that may reduce treatment burden and improve the chance for better long-term VA outcomes.

**Protocol AM[11]**

Randomized trial comparing immediate versus differed surgeries for epiretinal membrane. The study aims to assess the relative risks vs benefits of delaying surgery in these eyes. Apart from VA change seen over 36 months, the study will also look at other visual functions such as metamorphopsia, reading vision, speed and also the number of patients from the observation arm requiring surgery over the 36 month period as per predefined safety criteria. The study plans to include 200 subjects amongst the two groups.

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# ROLE OF WIDEFIELD OCT AND OCTA IN DIABETIC RETINOPATHY

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Although diabetes may also cause structural damage to the retina with loss of neurons and supporting cells,[1,2] the retinal vascular modifications represent the main clinical manifestation of this disease within the retina. The introduction of optical coherence tomography angiography (OCTA) has offered a quick and noninvasive imaging tool to obtain angiographic images of the retinal and choroidal vasculature.[3–6] OCTA has significantly improved the evaluation and quantification of the retinal and choroidal vasculature in patients with diabetic retinopathy (DR).

Structural OCT and OCTA imaging modalities have recently granted the acquisition of wider images (widefield OCT and OCTA).

Widefield OCT can help in various case scenarios of vitreoretinal interface disorders occurring in patients with DR and it may be helpful in the pre-operative assessment of patients undergoing vitrectomy.[7] Conversely, widefield OCTA has been largely employed in patients with DR. Given that widefield (and ultra-widefield) fluorescein angiography

(FA) imaging is considered as the gold-standard in the identification of DR-associated retinal neovascularization, previous reports have compared widefield OCTA and FA images in order to validate the former imaging modality in patients with diabetic retinopathy.[8] Overall, these reports showed that widefield OCTA may detect minute neovascularizations which are not individuated on clinical examination or color photographs and can therefore improve the clinical assessment of DR. Of note, the rate of identification of neovascularization with either widefield OCTA or FA was equivalent.[9] Main issues in widefield OCTA imaging are the occurrence of artifacts,[10] and the incapacity of OCTA in detecting neovascular leakage. Furthermore, widefield OCTA is still characterized by a limited extension in the visualization of the retina as compared with ultra-widefield FA systems[11] and this may result in an underestimation of the retinal ischemia.

Widefield OCTA (with combined structural OCT information) may be also employed to detect DR-associated vascular lesions [microaneurysms, intraretinal microvascular abnormalities (IRMA), and regions of non-perfusion].[9]

Venous loops are visualized as lesions containing flow and localized in proximity to hypoperfused areas, the latter feature in agreement with the ischemic pathogenesis of these alterations.[12] Furthermore, OCTA may be able to detect IRMAs as tiny retinal vascular networks within the superficial capillary plexus (SCP) and near ischemic regions.[13,14] In contrast to retinal neovascularization that protrude into the vitreous, IRMAs are completely located within the retina as assessable using OCTA B-scans.[15] Shimouchi and colleagues[16] were also able to identify five subtypes of IRMAs [unchanged, tuft regression, reperfusion, mixed (combined tuft regression/reperfusion), and worsening with new appearance of tuft] according to the IRMAs' changes following panretinal

photocoagulation (PRP). Of note, the latter study displayed that some IRMAs were not characterized by morphological changes before and after PRP, these results suggesting that IRMAs may represent vascular remodeling of existing capillaries without neovascularization.[16] Using OCTA, retinal and optic disc neovascularization are visualized as well-defined microvascular structures composed of fine vessels protruding into the vitreous, as asserted above.[17] Assuming that OCTA is limited in the detection of neovascular leakage, the presence of an exuberant vascular proliferation was suggested as an indirect OCTA biomarker of leakage.

Microaneurysms are retinal capillaries' dilations that usually emerge as gross outpouchings of the vessel wall (Figure 1). On 2D OCTA *en face* and B-scan images, microaneurysms usually appear as saccular or fusiform capillary dilations.[18–20] A rotational 3D OCTA assessment was employed by our group to assess diabetic microaneurysms in vivo.[21] In the latter study, we analyzed data from 20 patients (20 eyes) with DR who had OCTA imaging obtained with the PLEX Elite 9000 device (Carl Zeiss Meditec Inc., Dublin, CA, USA). OCTA volume data were first manipulated with a novel volume projection removal algorithm and subsequently imported in imageJ software[22] in order to gain a 3D representation of microaneurysms. In the latter study we analyzed fifty-two microaneurysms and we showed that a 3D visualization may be helpful for an accurate assessment of these vascular abnormalities. In the 3D analysis, microaneurysms were demonstrated to invade at least two retinal layers with the inner nuclear layer as the most frequently occupied by microaneurysms.[21] Importantly, these 3D OCTA findings were in agreement with previous histopathological microaneurysms' characterizations[23] and with reports employing structural OCT.[24,25] Moreover, given that a single microaneurysm may be contained in different retinal layers, microaneurysms

may be erroneously visualized on two distinct 2D *en face* OCTA images (e.g. SCP and deep vascular complex - DVC) and thus counted twice with a 2D OCTA visualization.[18] A volume rendered 3D visualization on microaneurysms also demonstrated that most of analyzed microaneurysms may be connected with two retinal vessels,[21] the latter feature suggesting microaneurysms have no tendency to grow at vascular junctions, as previously suggested with histology.[23] Of note, a small number of microaneurysms was graded to be connected with both SCP and DVC retinal vessels, this feature likely indicating the eventuality of microaneurysms to occur at the level of vessels connecting the SCP and DVC vascular beds.[21] Using 3D OCTA, our analysis was also able to assess the spatial orientation of microaneurysms with respect to the retinal layers.[21] Our results showed that microaneurysms are characterized by peculiar orientations on the three dimensions and most of them have an oblique orientation this probably reflecting the presence of Müller cells driving microaneurysms' arrangement, as these cells are known to be characterized by an oblique orientation.[21]

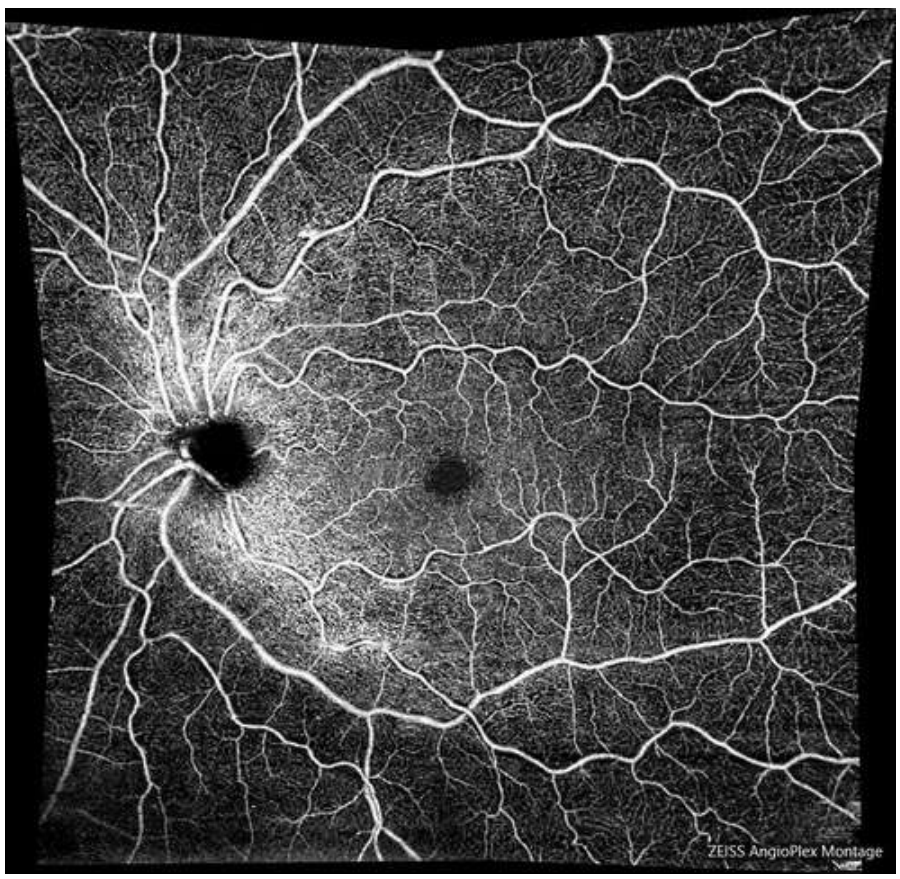


**Figure 1. OCTA in diabetic retinopathy.** Left eye of a diabetic patient with non-proliferative diabetic retinopathy. The widefield *en face* OCTA images segmented at the level of the superficial capillary plexus mainly shows microaneurysms in the macular region.

A previous study performed a comparison between widefield OCTA and ultra-widefield color fundus photography in the identification of other DR-associated vascular lesions (i.e. microaneurysms, IRMA, and regions of non-perfusion).[9] This study showed that widefield OCTA is characterized by high detection rates for these alterations.

In conclusion, widefield structural OCT may be efficaciously employed to better characterize vitreoretinal disorders associated with DR. Although widefield OCTA systems are still limited in the assessment of the periphery in contrast to ultra-widefield FA technologies, an improvement in imaging extension with the upcoming devices may significantly spread the use of this technology in eyes with diabetic retinopathy.

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# INTERESTING IMAGE

## 2. PROLIFERATIVE DIABETIC RETINOPATHY STATUS POST PRP– HOW POSTERIOR TO GO ?

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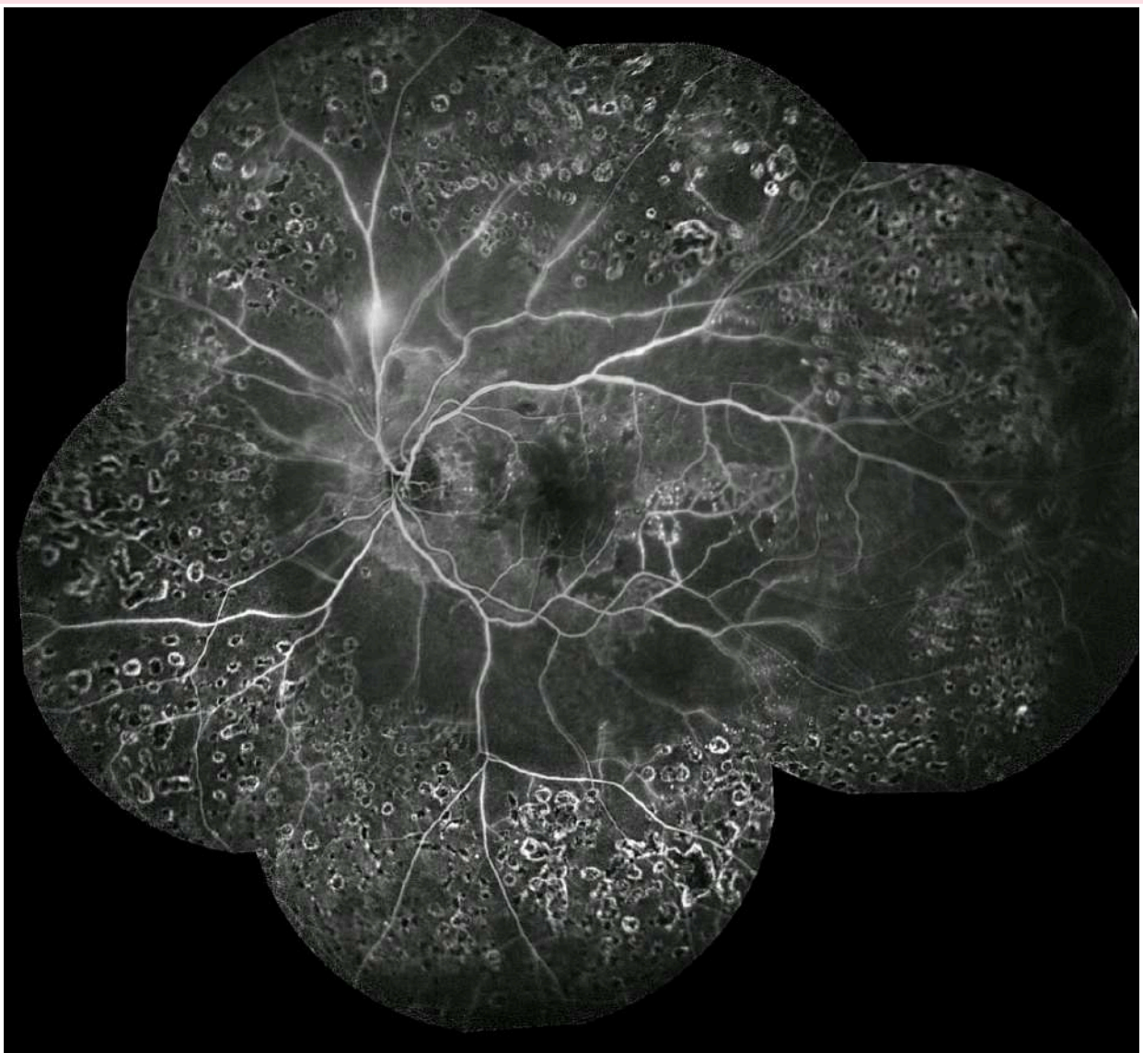

Fundus fluorescein angiogram of a 60 year old male patient, two years post laser photocoagulation. The left eye shows large areas of capillary non perfusion, temporally extending less than 2 DD from the fovea, in the absence of definite neovascularisation.

An area of vessel staining or leak from new vessel is seen superiorly. In such cases, the question arises- "How posterior must one laser”?

(So, it is preferable to take the laser burns closer to the arcade)

# CURRENT STATUS OF THE PDS FOR DIABETIC RETINOPATHY

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The Port Delivery System with ranibizumab (PDS) (Genentech, San Fransisco, CA) is a novel implant that is surgically inserted into the eye through pars plana. The device allows for continuous delivery of the customized formulation of ranibizumab into the vitreous cavity. The PDS design also allows for refill-exchange procedures that are performed in a clinic setting.

The PDS was approved in the USA by the FDA for neovascular age-related macular degeneration (nAMD) in October 2021 based on the results of the pivotal Archway study. [1] The study showed that PDS implant refilled every 24 weeks was equivalent and non-inferior to monthly ranibizumab intravitreal injections. The approval carries a black box warning that the implant has been associated with a three-fold higher rate of endophthalmitis than monthly intravitreal injections of ranibizumab. The increased rate of endophthalmitis has been linked to conjunctival retraction and erosion. These observations resulted in optimization of the surgical technique.

The PDS diabetic retinopathy (DR) and diabetic macular edema (DME) studies are currently ongoing with the study results anticipated to be released in the near future. Of note, as of October 2022, Roche/Genentech has initiated an immediate pause of all new PDS implantations and a recall for the PDS ocular implant and insertion tool assembly given an increasing trend in the incidence of septum dislodgement.[2] Currently the in-clinic refill-exchange procedures are being continued in both research and commercial settings.

There are two phase III trials focusing of diabetic eye disease. Pagoda is a phase III multi-center randomized clinical trial that is evaluating the efficacy, safety, and pharmacokinetics of the PDS in participants with DME when treated every 24 weeks (Q24W) compared with intravitreal ranibizumab 0.5 mg every 4 weeks (Q4W).[3] The primary outcome is change in BCVA score from baseline averaged over weeks 60 and 64.

Pavilion is a phase III multi-center randomized clinical trial that is evaluating the efficacy, safety, and pharmacokinetics of the PDS in participants with diabetic retinopathy without center-involved DME.[4] The inclusion criteria allows for subjects with moderately severe or severe NPDR (ETDRS-DRSS level 47 or 53). In this study, the PDS implant refill-exchange procedures are performed on a fixed interval every 36-weeks (Q36W). The primary outcome of this study is the percentage of participants with a ≥2-step improvement from baseline on the ETDRS-DRSS at week 52.

Continuous delivery of anti-VEGF offers advantages in patients with diabetic retinopathy and DME. This patient population has an inherent risk of noncompliance with the

treatment regimens due to high percentage of younger working age adults. These patients have multiple co-morbidities, frequent need for hospitalization and such time-consuming treatments as dialysis. Lack of compliance with treatments can lead to vision threatening complications, irreversible vision loss, and blindness. Thus, continuous delivery of ranibizumab and decreased number of office and treatment visits would benefit both patients with diabetic macular edema and diabetic retinopathy.

There are multiple studies that have demonstrated improvement of diabetic retinopathy based on DRSS scores in patients with non-proliferative and proliferative diabetic retinopathy treated with anti-VEGF agents.[5-7] However, the ongoing discussion persists on how frequent and for how long to treat these patients and if there is a disease modifying aspect to these treatments. Continuous delivery of ranibizumab would decrease the number of treatments such patients require and allow us to study the effects of continuous delivery of anti-VEGF on diabetic retinopathy over time.

In the past, there have been concerns raised in regards to having continuous suppression of anti-VEGF. The long-term effects remain to be elucidated, however the concerns of macular atrophy have not been supported in the nAMD cohort implanted with PDS and there has been a lack of evidence of retinal damage from frequent anti-VEGF injections in patients with DME or retinal vein occlusion (RVO). [8,9]

Additional arguments include the fact that patients with diabetic macular edema require less treatment as time goes on. For instance, in Diabetic Retinopathy Clinical Research Network Protocol I it was shown that sustained improvement in median and mean

vision up to five years was noted with a reduced treatment burden down to a median of 0–1 anti-VEGF injection in the 4th and 5th years of follow-up.[10] However, that does not necessarily negate the benefits of sustained delivery, as a clinician will have a choice of whether the implant needs to be re-filled and at what frequency. Furthermore, the treatment will continue to have beneficial effects on diabetic retinopathy.

It has been shown that DR and DME are multifactorial disease states with significant contribution of inflammatory cytokines.[11] It is possible that despite anti-VEGF suppression provided by the PDS, some patients will require additional treatments.

The results of the Pagoda and Pavilion studies will reveal if the rate of complications, such as conjunctival erosion and retraction as well as endophthalmitis and septum dislodgement, is different in diabetic population compared to nAMD population. This will help the physicians determine the frequency of visits required to watch for these potential complications. Additionally, given that patients with DR and DME tend to be younger, the risk of implant-related complication over the lifetime of a patient should be considered.

In summary, PDS is a novel surgically implanted device that allows for continuous delivery of customized formulation of ranibizumab and in-office refill-exchange procedures. It was shown to be non-inferior and equivalent to monthly ranibizumab in nAMD patients. The results of Pagoda and Pavilion trials will elucidate the efficacy and safety in DME and DR patients, respectively. Potential complications need to be considered when considering PDS implantation in a diabetic patient.

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# CURRENT STATUS OF FARICIMAB FOR DIABETIC RETINOPATHY

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**Dr. Jayanth Sridhar**

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Advances in diabetic eye disease research continue to provide us with unique, more durable treatment options. Faricimab (Hoffman/La Roche) is a bispecific, dual-mechanism treatment approved by the U.S. Food and Drug Administration (1/28/2022) for intravitreal treatment of diabetic macular edema (DME) and neovascular AMD. The molecule features a fragment antigen-binding region (Fab) that binds vascular endothelial growth factor-A (VEGF-A) and angiopoietin-2 (Ang2) with high affinity and a fragment crystallizable region (Fc) with reduced systemic half-life.

It is now well-established that angiopoietins play complex roles in vascular remodeling and neovascularization and interact with the VEGF axis. Angiopoietin 1 (Ang1) reorganizes the actin-myosin cytoskeleton of the endothelial cell in a way that results in increased cell tensile strength.[1] It also stabilizes vascular endothelial cadherin, an adherens junction protein, which is an important defense against inflammatory changes to the vascular wall. [1] Angiopoietin 2 (Ang2) is a competitive inhibitor of Ang1.[1,2]

Studies in diabetic retinopathy murine models previously demonstrated reduction in pericytes, increased intraretinal neovascularization, and increased VEGF expression when Ang2 was upregulated.[2,3] Modulation of the VEGF pathway and additional neovascularization pathways make faricimab an attractive treatment modality. Faricimab, through its Ang2 inhibition, is thought to promote vascular stability and desensitize vessels to the effect of VEGF.[3]

Two twin, phase 3, randomized, double-masked, active comparator-controlled non-inferiority trials YOSEMITE and RHINE investigated faricimab.[4,5] A total of 1,891 participants from 353 sites worldwide with DME were randomized to one of the three treatment arms: intravitreal faricimab 6.0 mg every eight weeks, intravitreal faricimab 6.0 mg per personalized treatment interval (PTI) with adjustable dosing up to every 16 weeks, or intravitreal aflibercept 2.0 mg every eight weeks.[4,5,6] The primary endpoints for YOSEMITE and RHINE, non-inferior vision gains at 1-year with faricimab every eight weeks or PTI versus aflibercept every eight weeks, were achieved. This was maintained at two years.[4,5] In RHINE, for example, average mean best corrected visual acuity (BCVA) change from baseline was +10.9 ETDRS letters and +10.1 ETDRS letters in faricimab every eight weeks and faricimab PTI, respectively.[7] In those receiving aflibercept every eight weeks, change from baseline BCVA was +9.4 ETDRS letters.[7]

Data through the end of year two showed extended dosing, meaning 12-week intervals or longer, reached nearly 80%, as opposed to 50% at year one.[8] At year two, approximately 60% of eyes reached 16-week dosing intervals compared to 50% at year one.[8] Only 7% of patients in YOSEMITE and 10% in RHINE were at monthly dosing at the end of year two.[9] Secondary anatomical outcomes showed slightly greater reductions in central subfield thickness (CST) and more patients with absence of intraretinal fluid with

faricimab every eight weeks and PTI up to every 16 weeks versus aflibercept every eight weeks through year two.[7] This reduction was achieved with a median of three Faricimab injections in the PTI arm compared to five injections in the aflibercept arm in year two. [8]

Safety monitoring through two years revealed no retinal vasculitis or occlusive retinal vasculitis events.[4,5] RHONE-X, a long-term extension study, will generate 4-year safety data based on 1,479 participants. Primary outcome measures are incidence and severity of ocular adverse events, incidence and severity of systemic adverse events, and number of participants with presence of anti-drug antibodies at baseline and during the study.[10]

Faricimab, with its simultaneous modulation of two different proteins involved in angiogenesis, offers an exciting new treatment option. Data through year two demonstrates an increased durability of effect and the possibility of reducing treatment burden. Continued study of faricimab will further demonstrate its use in treat-and-extend algorithms and will reveal safety concerns.

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# INTERESTING IMAGE

## 3. FATE OF PROLIFERATIVE DIABETIC RETINOPATHY IN INDIAN POPULATION

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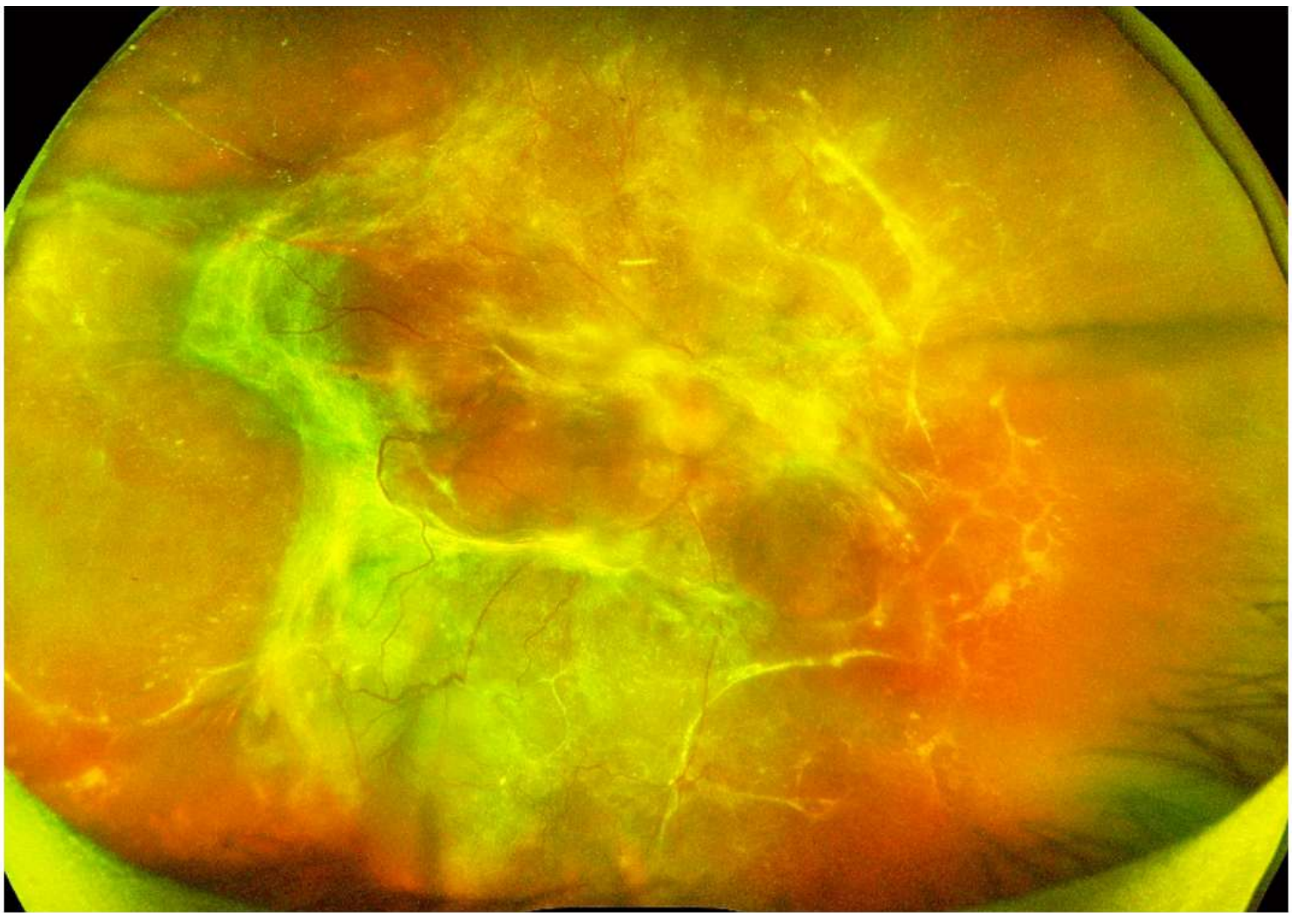

A 62 year old male, a known case of diabetes since 10 years on treatment and chronic kidney disease on dialysis since 2 years with no history of eye check up in the past presented with diminution of vision in right eye since 2 years and left eye since 15 days. Examination showed proliferative diabetic retinopathy with tractional retinal detachment in both the eyes. This image of the right eye shows the lack of knowledge and negligence among the patients regarding diabetic retinopathy and the need for screening.

# CURRENT STATUS OF AI AND TELEOPHTHALMOLOGY IN DIABETIC RETINOPATHY SCREENING

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There have been rapid strides in teleophthalmology and artificial intelligence (AI) in the last few years. Various factors have played a role in laying the soil, which is now fertile and ready to sow. The development in telecommunication, which has reached even the most remote locations across the country, has led to better connectivity through;[1] this, alongside technological developments like 5G, has addressed the speed and other latency issues associated with earlier generations. Recently, significant technological advances have radicalised retinal photography, from having a few large bulky equipments that required mydriasis to an array of many portable, handheld, non-mydriatic cameras with similar performance and come at a reduced cost.[2] Studies have identified risk factors for screening and timely referral for diabetic retinopathy (DR).[3] Regions that need prioritisation of screening and treatment pathways to reduce the burden of vision threatening DR have also been identified.[4] The involvement of the first point of contact and care for a person with diabetes, i.e., the physician/diabetologist, the pharmacy, or

the laboratory, may help detect the disease earlier without the added expense of reaching out in the community.[5]

***Developing an AI for DR***

The current role of AI in diabetes is mainly for screening and grading DR; however, more recently, its use in predicting response to treatment has been looked into.[3] Various software has been developed for the screening of DR (Table 1). These use different types of cameras, including smartphone-based fundus photography and even Ultra wide field imaging.[6,7] They have demonstrated high accuracy in predicting and classifying DR even in real-world settings.[8] Mydriasis improves the accuracy of the system. Deep learning (DL) methods have been found to have better performance.[9]

DL systems that predict treatment response have also been developed.[3,9] Though there are many advantages to using such a model, it comes with certain limitations; the performance of an AI depends on the camera on which it is trained. However, a recent study looked at the effect of different types of cameras on AI performance; they found the DL algorithm showed high sensitivity and specificity than human graders relative to the standard irrespective of the kind of camera used.[10,11] The purpose of developing such a system is meaningful if it reduces the burden on the existing healthcare system; thus, increasing the sensitivity and specificity of the model is important. Current AI models used for screening use hard exudates near the fovea as a marker to identify DME. However, this has limited specificity and sensitivity. In a recent study, Liu et al. used a deep learning system (DLS DME, which predicts OCT-equivalent quantitative macular thickness measures from colour fundus photographs) that detects diabetic

macular edema (DME) from 2-dimensional colour fundus photographs over different populations. They found that its classification of DME status was significantly more specific than experts while retaining non-inferior sensitivity.[12] Such models not only reduce the rate of false positives and also the need for an optical coherence tomography (OCT) (expensive machinery).

Lastly, any tool is only as valuable as it is adopted. Currently, the acceptance of a DL system is limited. This is because of its inability to explain how it reached a particular result. Some have used heat maps to highlight areas of the image that influence the decision; however, they are often difficult to interpret. The development of more interpretable results may increase the adoption rate among clinicians.[13] Policy for the proper use and resource development in the form of capacity building must be in place before implementing such a system. The current overburdened healthcare system may be unable to cope with the increased load of cases requiring treatment.[14] The role of AI in DR is rapidly growing. Although associated with certain limitations, its role in reducing the burden of eye disability, particularly in a low-resource setting, appears promising.

***Teleophthalmology in DR***

Telehealth in DR has four components: image acquisition, image review and evaluation, patient care supervision and data storage.[15] Image capture of both eyes is done via mydriatic or non-mydriatic cameras by general ophthalmologists, ophthalmic photographers, primary care physicians or technicians. “Targeted mydriasis” is dilating those eyes in which image quality is most likely to be poor due to various reasons like cataracts and vitreous haemorrhages. Ultra-wide field (UWF) imaging has reduced the number of ungradable images by a massive 81% with the added benefit of non-mydriasis.[16] Smartphone fundus photography and OCT imaging are also being used.

Raman et al. reported a 62.5 % and 70 % sensitivity in non-mydriatic and mydriatic cameras, respectively, compared to indirect ophthalmoscopy.[17] Sensitivities were 80% in detecting absent DR and low- or high-risk PDR, 70% in mild or moderate NPDR, DME and 53% in severe NPDR.[18] Images are graded by trained retina specialists or artificial intelligence. Few centres advocate specialised training for ophthalmologists before the commencement of grading. The images of patients are then stratified into those requiring urgent physical consultation and subsequent intervention and others who can be followed up.

The data is stored, and patients are communicated about their disease state. Ninety-four per cent of patients are satisfied by teleophthalmology.[19] A study from rural India concluded the cost-effectiveness of teleophthalmology screening compared to no screening.[20] Teleophthalmology has some inherent limitations of lack of clinical examination, absence of standard guidelines on image acquisition/grading and costly equipment. Poor image quality and medical litigations act as deterrents for the consultants. Teleophthalmology services are provided at a specific cost to the people in most places which is not acceptable to rural people—lastly, the ordeal of grading and consulting causes an additional burden to the already overworked ophthalmologists. The main utility is providing healthcare access to all, especially those in remote areas of the world; however, safe data acquisition, technological advancements and patient feasibility have resulted in the switch to teleophthalmology in the post-COVID era. Ophthalmologists should emphasise the importance of regular fundus evaluation in people with diabetes and recommend the usage of teleophthalmology for inaccessible locations.

# CURRENT STATUS OF AI AND TELEOPHTHALMOLOGY IN DIABETIC RETINOPATHY SCREENING

| AI system | Authors | Algorithm | Type of camera | Mydriatic ornon-mydriatic | AUC | Sensitivity | Specificity |
|---|---|---|---|---|---|---|---|
| IDx-DR | Abràmoff et al.^{[4]} | CNN | TRC-NW400, Topcon | Non-mydriatic | N/A | 87.2 | 90.7 |
| | Van der Heijden | AlexNet, VGG | TRC-NW400, Topcon | Non-mydriatic | 0.94/0.87 | 91/68 | 84/86 |
| | et al.^{[22]} | net | | | | | |
| Retmarker DR | Oliviera et al.^{[23]} | Recognition of | Cannon CR6-45NM | Non-mydriatic | 0.849 | 95.8 | 63.2 |
| | | characteristic | fundus camera | | | | |
| | | lesions | attached to a Sony | | | | |
| | | | power HD 3CDD | | | | |
| | | | digital color camera | | | | |
| EyeArt | Solanki et al.^{[24]} | Image analysis | Canon CR-2 AF | N/A | 0.941 | 93.8 | 72.2 |
| | | technology | | | | | |
| | Rajalakshmi | Image analysis | Remidio fundus | Mydriatic | N/A | 99.3 | 68.8 |
| | et al.^{[5]} | technology | on phone (FOP), | | | | |
| | | | Remidio | | | | |
| | Bhaskaranand.^{[25]} | Image analysis | Multiple fundus | Both | 0.879 | 90 | 63.2 |
| | | technology | cameras | | | | |
| | Bhaskaranand.^{[26]} | Image analysis | Multiple fundus | Both | 0.965 | 91.3 | 91.1 |
| | | technology | cameras | | | | |
| Google | Gulshan et al.^{[6]} | Inception V3 | 1st data set: Multiple | Both | 0.990–0.991 | 87.00–97.50 | 93.9–98.5 |
| | | | cameras | | | | |
| | | | 2nd data set:Topcon | | | | |
| | | | TRC NW6 | | | | |
| | Gulshan et al.^{[27]} | Inception V4 | NM TRC, Topcon | Non-mydriatic | 0.963–0.980 | 88.90–92.10 | 92.20–95.20 |
| IDP | Abràmoff et al.^{[28]} | Non-DL | Topcon TRC NW6 | Non-mydriatic | 0.980 | 96.8 | 87 |
| | | | fundus camera+color | | | | |
| | | | video 3CCD camera | | | | |
| | Hansen et al.^{[29]} | Non-DL | Topcon NW6S | Mydriatic | 0.878 | 86.7 | 70 |
| | | | Fundus Camera | | | | |
| Airdoc | He et al.^{[30]} | Inception V4 | Topcon TRC-NW400 | Non-mydriatic | 0.95 | 91.8 | 98.79 |
| | | | Fundus camera | | | | |
| | Huang et al.^{[31]} | Inception V3 , | | | 0.94 | 95.3 | 79.5 |
| | | SVM | | | | | |
| VoxelCloud | Zhang et al.^{[32]} | Inception-Res | Multiple cameras | Non-mydriatic | N/A | 83.3 | 92.5 |
| Retina | | Net V2 | | | | | |
| VeriSee | Hseih et al.^{[33]} | Inception V4, | Canon CR-2 | Non-mydriatic | 0.95 | 89.2 | 90.1 |
| | | resnet | | | | | |
| Eyegrader | Keel et al.^{[34]} | Inception V3 | Digital Retinography | Non-mydriatic | 0.937–0.989 | 92.3 | 93.7 |
| | | | System (DRS, | | | | |
| | | | CenterVue) | | | | |
| PhelcomNet | Malerbi et al.^{[35]} | CNN | Smartphone-based | Mydriatic | 0.89 | 97.8 | 61.4 |
| | | | hand held devices | | | | |
| Retianalyze | | | | | | | |
| Bosch DL | Bawankar et al.^{[36]} | CNN | Bosch non-mydriatic | Non-mydriatic | N/A | 91.18 | 96.91 |
| | | | fundus camera | | | | |
| Singapore | Ting et al.^{[37]} | VGGNet | Multiple cameras | N/A | 0.889–0.983 | 91.4–100.00 | 73.3–92.20 |
| SERI NUS | | | | | | | |
| EyeWisdom | Zhang et al.^{[38]} | Resnet-34, | Topcon TRC NW6S, | Non-mydriatic | 0.958 | 92.96 | 93.32 |
| V1 | | Inception V3 | Cannon CR2, KOWA | | | | |
| | | | Non-myd a-DIII 8300 | | | | |
| Others | Gargeya and | Data driven | Multiple cameras | N/A | 0.97 | 94 | 98 |
| | Leng.^{[39]} | DL algorithm | | | | | |
| | Li et al.^{[40]} | Inception-v3 | Multiple cameras | N/A | 0.955 | 92.5 | 98.5 |
| | Cao et al.^{[41]} | Bayesian | Topcon TRC- | Mydriatic | 0.938 | 94.9 | 92.8 |
| | | model | NW6S/7S Fundus | | | | |
| | | | camera | | | | |

Table 1: AI software for the screening of DR

In conclusion, rapid strides in technology have made possible the use of teleophthalmology and AI for all ophthalmologists. This combination seems to be one of the best ways to screen people with diabetes for retinopathy. Early adoption of these techniques can reduce avoidable blindness in countries like India, where there is a big mismatch between the number of ophthalmologists and number of people with diabetes.

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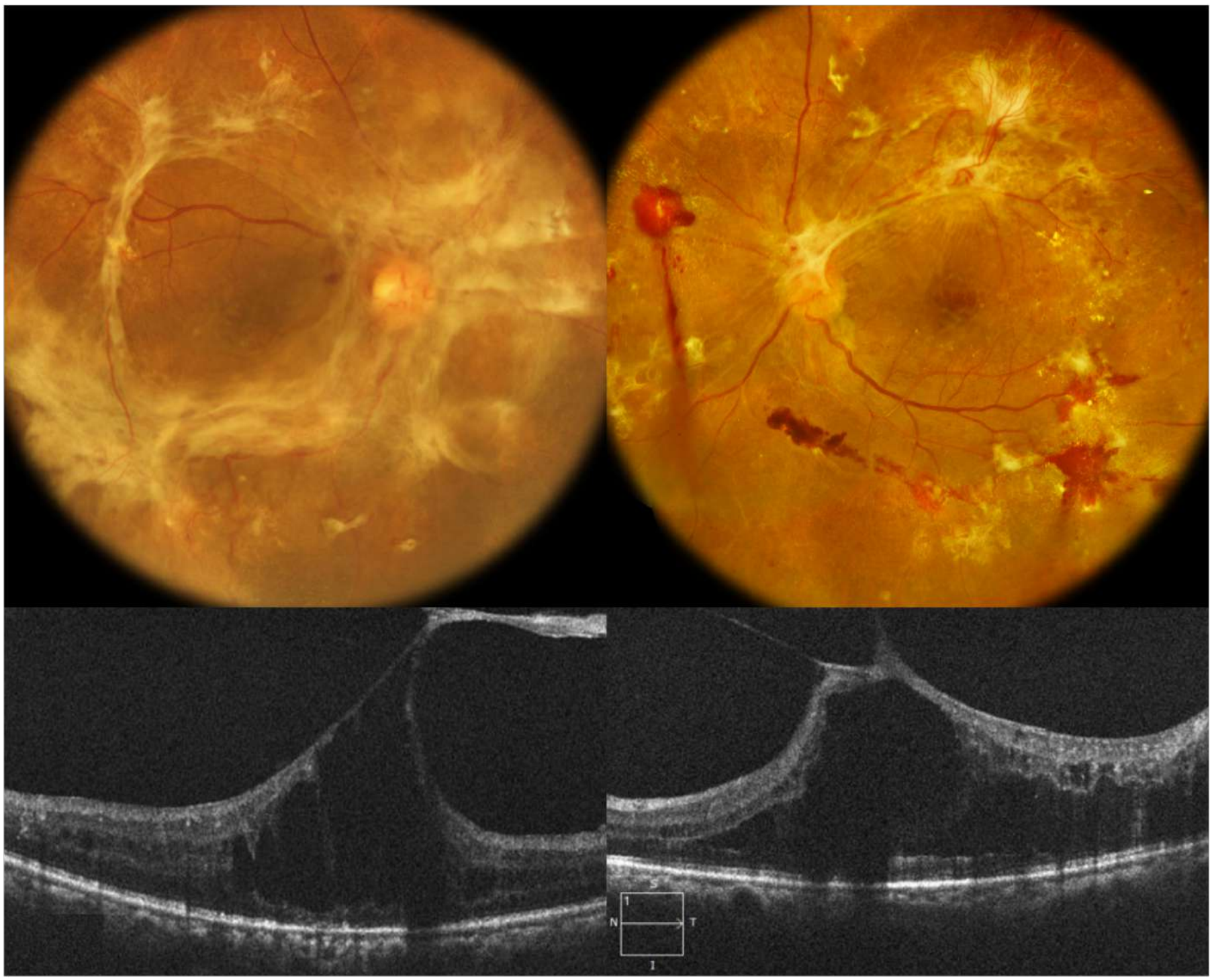
# INTERESTING IMAGE

## 4. FIREFLIES IN THE FUNDUS : HIGH RISK PROLIFERATIVE DIABETIC RETINOPATHY

**Dr. Sashwanthi Mohan**

Rajan Eye Care Hospital, Chennai



# INTERESTING IMAGE

## 4. FIREFLIES IN THE FUNDUS : HIGH RISK PROLIFERATIVE DIABETIC RETINOPATHY

A 54 year old female patient presented with complaints of decreased vision in both eyes since 2 years. She was a known diabetic with uncontrolled blood sugar level. Best corrected visual acuity was counting fingers at 2 metres in both the eyes. Anterior segment examination of both the eyes showed immature senile cataract. Fundus examination of both the eyes showed features of high risk proliferative diabetic retinopathy with extensive fibrovascular proliferation over the disc and along the arcades, more extensive in the right eye. There was also presence of taut posterior hyaloid and vitreomacular traction causing foveoschisis in both the eyes as confirmed on the optical coherence tomography scans. She was advised diabetic vitrectomy in both the eyes.

# DIABETIC RETINOPATHY AWARENESS INITIATIVES BY VRSI

## RUN FOR SIGHT

# DIABETIC RETINOPATHY AWARENESS INITIATIVES BY VRSI

## RUN FOR SIGHT



# COLLABORATION OF RSSDI AND VRSI

•In collaboration with RSSDI the formulation of the DR screening guidelines is in process

•Participation in their annual conference attended by over 10,000 Physicians and Diabetologists in Chennai – October 2022 with a talk on DR screening made easy for Diabetologists

•Video by Dr V Mohan on DR screening by the Diabetologists

•Talks on DR in their state chapter meetings

# SCREENING OF BSF JAWANS IN RANN OF KUTCH, GUJARAT– MARCH 2022

Netrasuraksha: an Initiative by Novartis

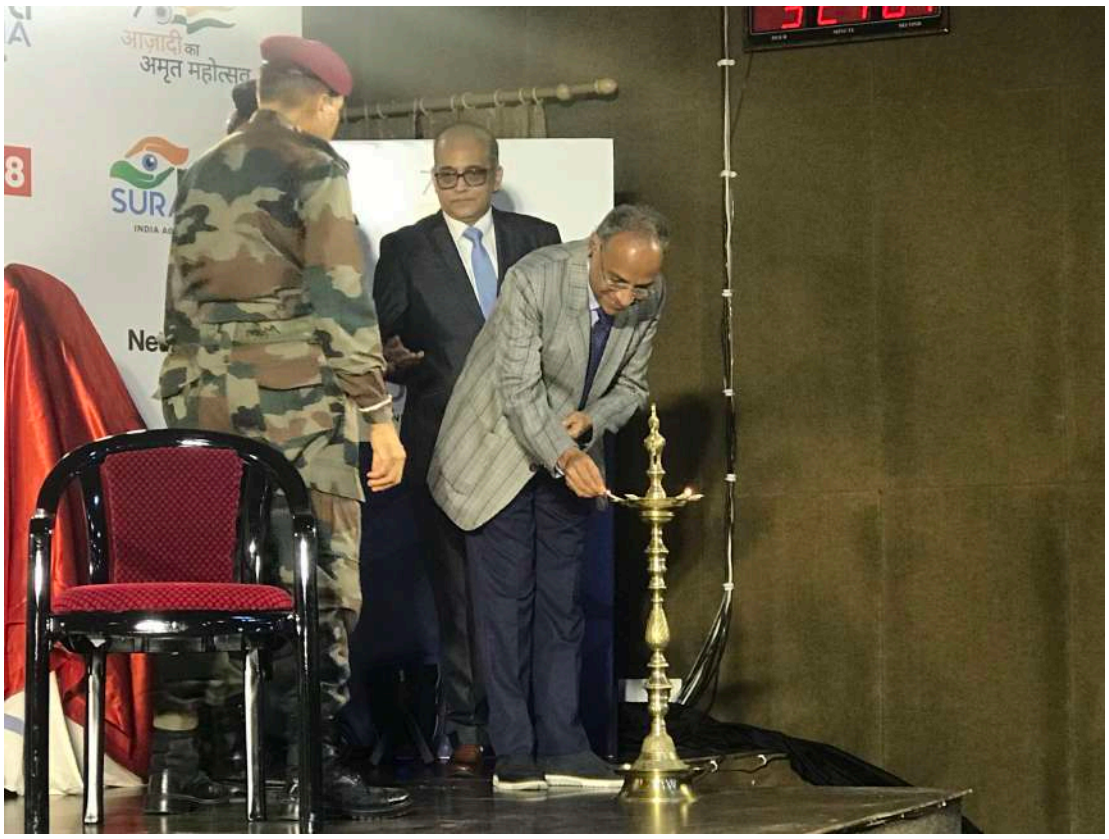


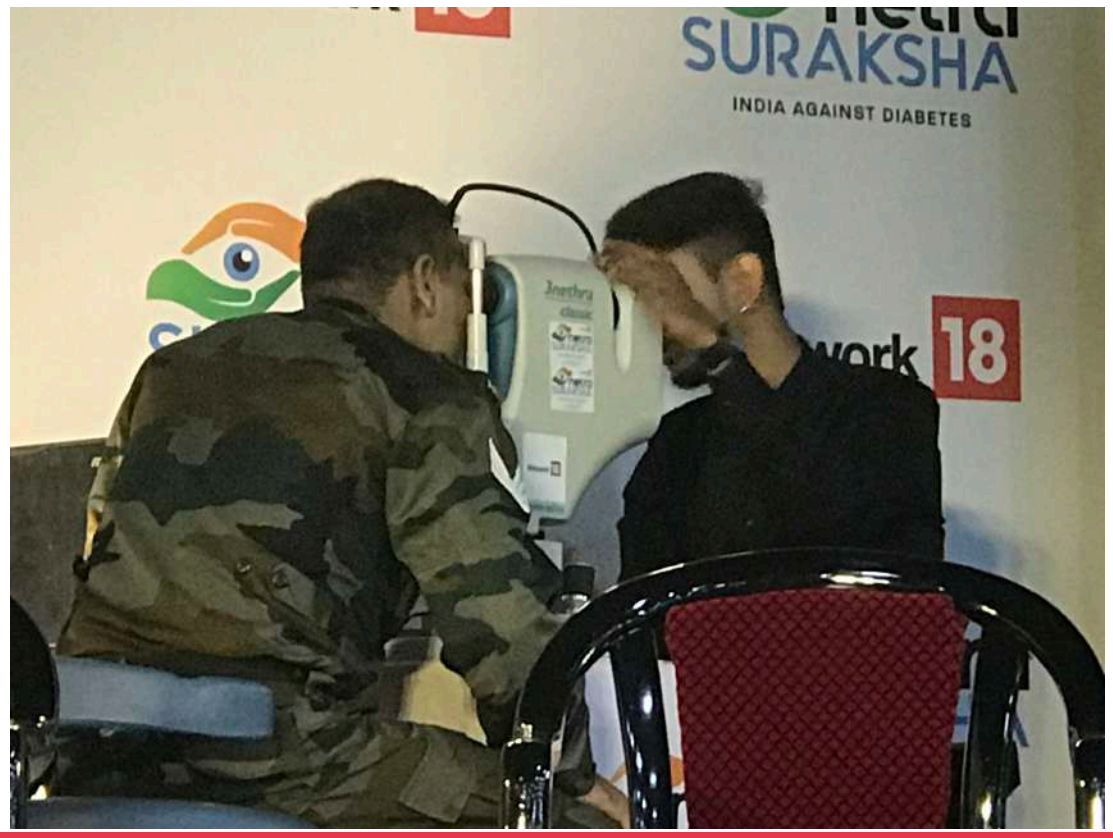

# DELHI POLICE PERSONNEL SCREENED FOR DR- JULY 2022

Netrasuraksha: an Initiative by Novartis


# SCREENING AT THE MILITARY HOSPITAL JAMMU- SEPT 2022

Netrasuraksha: an Initiative by Novartis



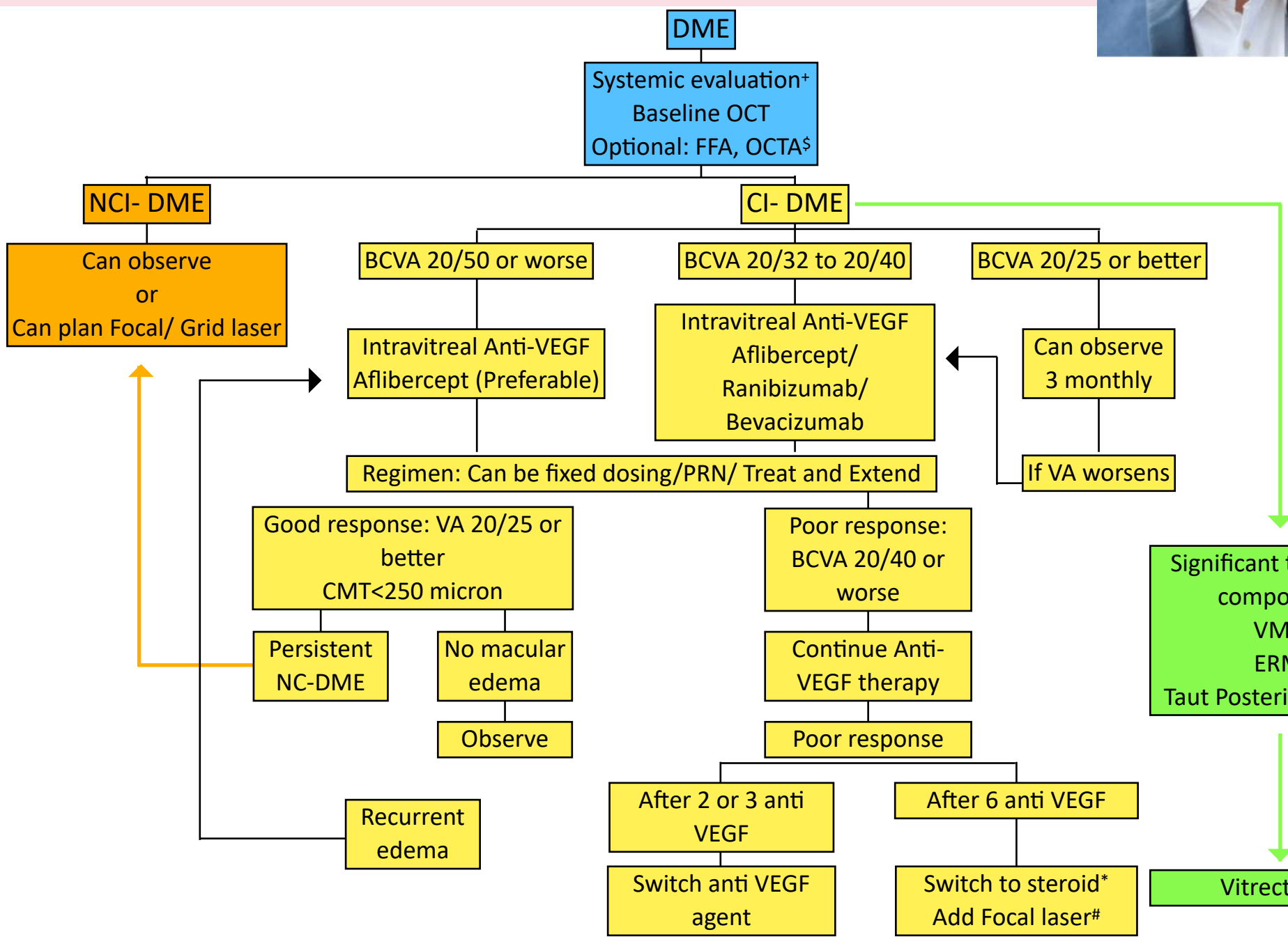



# MANAGEMENT OF DME IN A SCHEMATIC

**Dr. Sriram Simakurthy**

Sankara Eye Hospital

Guntur




+Systemic evaluation
Glycemic control
Hypertension
Anemia
Renal status
Blood dyscrasia
Drugs- Niacin, Glitazones, Prostaglandin analogue

$ FFA/ OCTA
Diagnosis of macular ischemia- Prognostic value

FFA- Identifies Leaky MA and area of leak which helps in planning laser

*Early switch to steroid
- Pseudophakic eyes
- Worsening DME in Pregnancy
- Post vitrectomy

#Early laser
- Can consider to reduce the number of injections
- Worsening DME in Pregnancy
- Presence of Retinal capillary macroaneurysms