Role of Anti VEGF in management of Diabetic Retinopathy

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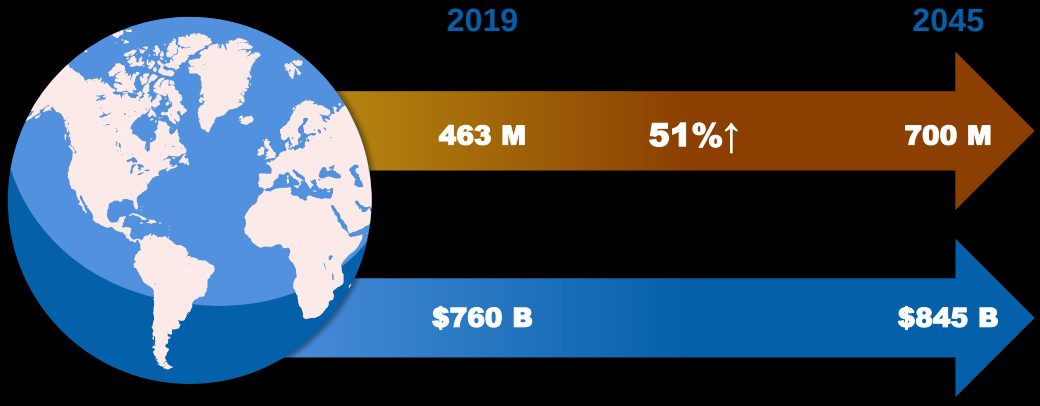
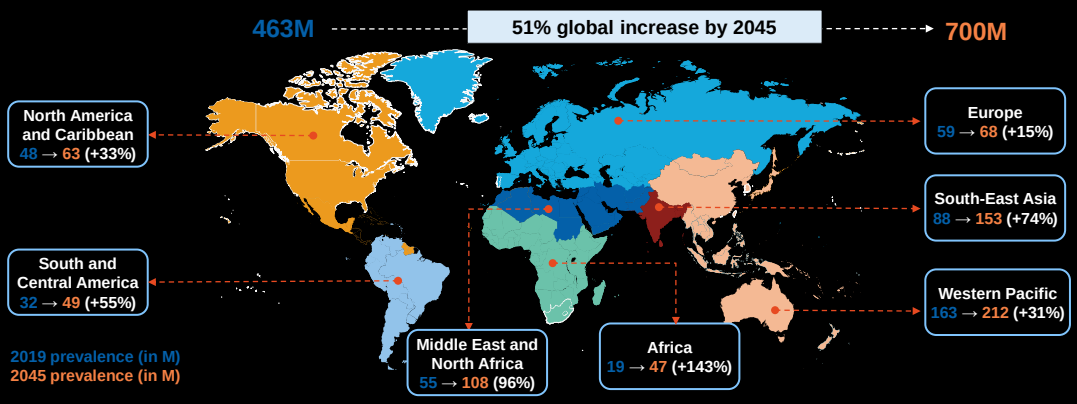
Diabetes: a growing worldwide epidemic affecting the working-age population



*Number of people with diabetes worldwide and per the International Diabetes Federation regions in 2019, 2030, and 2045 (age: 20–79 years); #Total diabetes-related health expenditure for adults (age: 20–79 years) with diabetes in 2019 and 2045. B, billion; M, million.International Diabetes Federation. Diabetes Atlas 9th Edition, 2019.

Prevalence of diabetes is projected to increase worldwide



Number of people with diabetes worldwide and per International Diabetes Federation region in 2019, 2030, and 2045 (age: 20–79 years); map not drawn according to scale or geopolitical borders.
M, million. International Diabetes Federation. *Diabetes Atlas* 9th Edition, 2019.

The percentage of DM in UAE

Dubai Diabetes and Endocrinology Journal

Guidelines

Emirates Diabetes Society Consensus Guidelines for the Management of Type 2 Diabetes Mellitus – 2020

Fatheya Alawadi[1,2] Salah Abusnana[3] Bachar Afandi[4,5] Khaled M. Aldahmani[1,6] Omniyat Alhajeri[1,2] Khaled Aljaberi[4] Juma Alkaabi[4] Abdulrazzaq Almadani[7] Alaaeldin Bashier[4] Salem A. Benhyah[8,1] Buthaina bin Belaila[4] Mohammad Fargaly[9,1] Muhammad H. Farooq[10,11] Khadija Hafidh[12,5] Mohamed Hassanein[13,14] Ahmed Hassoun[15,16] Abdul Jabbar[17,7] Iyad Kuseiry[18,1] Huda E. Mustafa[19,1] Hussein Saadi[20] Sara Suleman[21,16]

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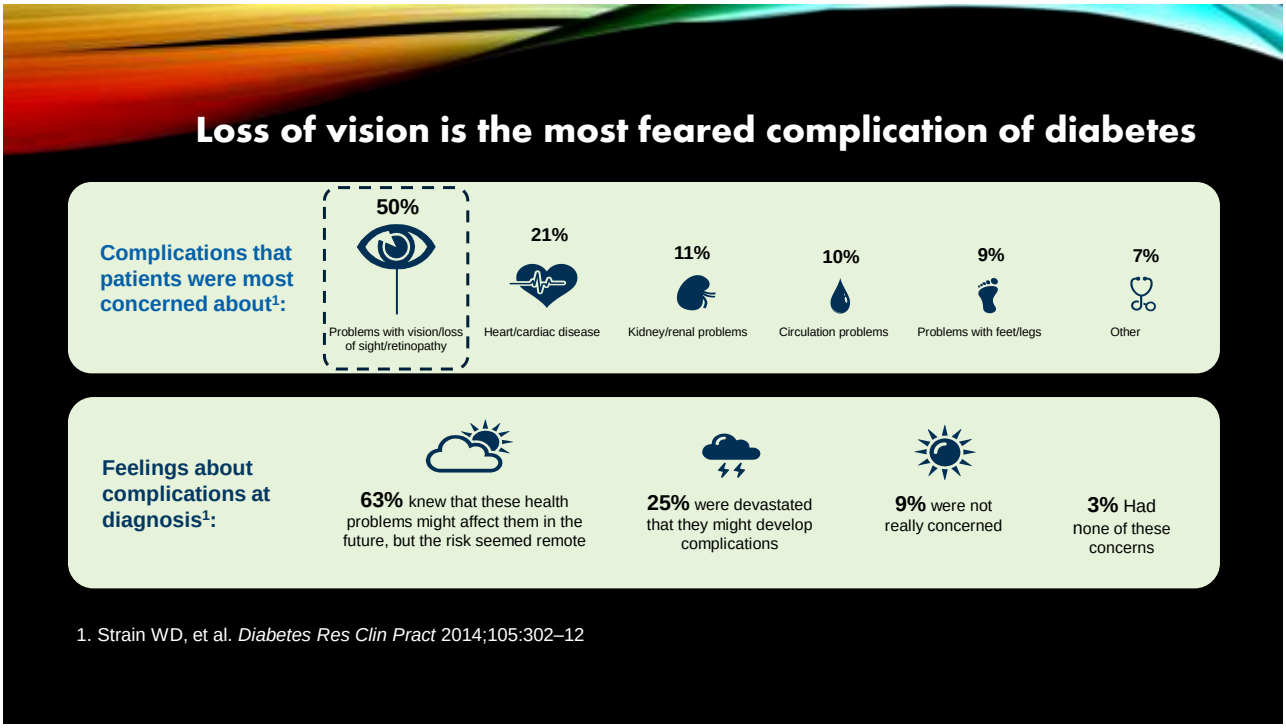
Abstract

Rapid urbanisation and socioeconomic development in the United Arab Emirates (UAE) have led to the widespread adoption of a sedentary lifestyle and Westernised diet in the local population and consequently a high prevalence of obesity and diabetes. In 2019, International Diabetes Federation statistics reported a diabetes prevalence rate of 16.3% for the adult population in the UAE. In view of the wealth of recent literature on diabetes care and new pharmacothera-

Loss of vision is the most feared complication of diabetes



1. Strain WD, et al. *Diabetes Res Clin Pract* 2014;105:302–12

Five- Year outcomes of Pan-Retinal Photocoagulation vs Intra-Vitreous Ranibizumab for Proliferative Diabetic Retinopathy.

A Randomized clinical trial DRCR.net protocol S

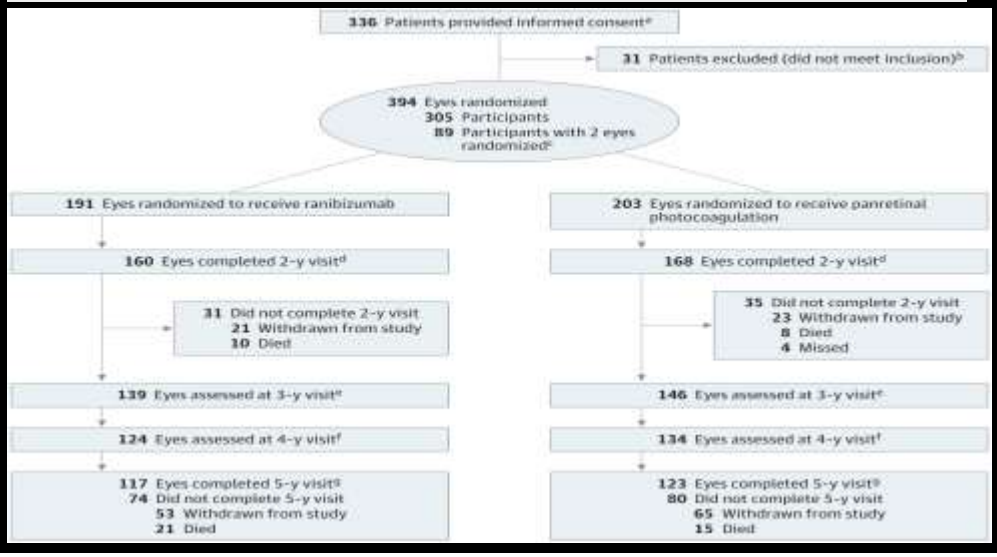
PROTOCOL S

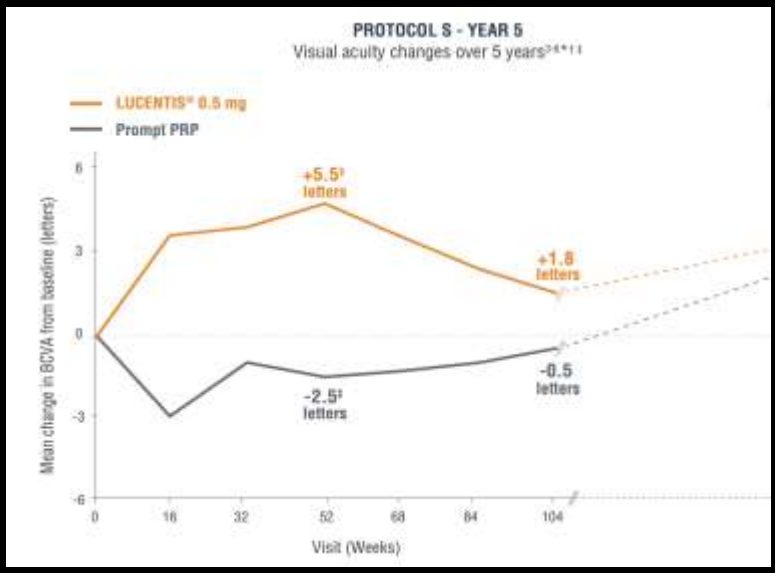
- **Objective** To evaluate efficacy and safety of 0.5-mg intravitreous ranibizumab vs panretinal photocoagulation (PRP) over 5 years for PDR.
- **Design, Setting, and Participants** Diabetic Retinopathy Clinical Research Network multicenter randomized clinical trial evaluated 394 study eyes with PDR enrolled February through December 2012. Analysis began in January 2018.
- **Interventions** Eyes were randomly assigned to receive intravitreous ranibizumab (n = 191) or PRP (n = 203). Frequency of ranibizumab was based on a protocol-specified retreatment algorithm. Diabetic macular edema could be managed with ranibizumab in either group.
- **Main Outcomes and Measures** Mean change in visual acuity (intention-to-treat analysis) was the main outcome. Secondary outcomes included peripheral visual field loss, development of vision-impairing diabetic macular edema, and ocular and systemic safety.

JAMA Network

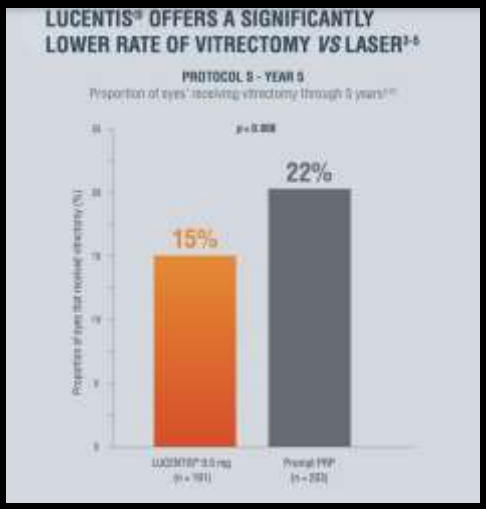
From: **Five-Year Outcomes of Pan-retinal Photocoagulation vs Intra-vitreous Ranibizumab for Proliferative Diabetic Retinopathy: A Randomized Clinical Trial**

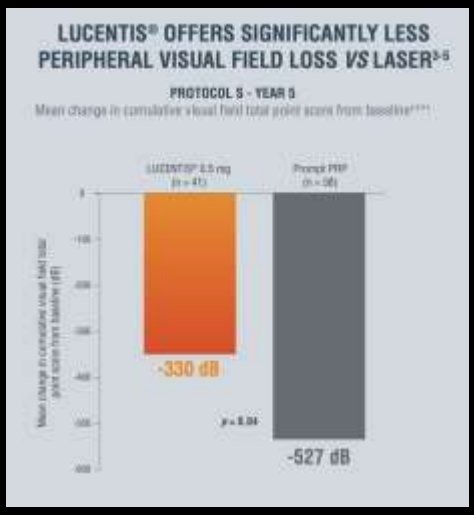
JAMA Ophthalmol. 2018;136(10):1138-1148. doi:10.1001/jamaophthalmol.2018.3255




PROTOCOL S - YEAR 5
Visual acuity changes over 5 years
LUCENTIS® 0.5 mg
Prompt PRP
Mean change in BCVA from baseline (letters)
+5.5
letters
+1.8
letters
-0.5
letters
-2.5
letters
6
3
0
-3
-6
0
16
32
52
68
84
104
Visit (Weeks)

PROTOCOL S


LUCENTIS® OFFERS A SIGNIFICANTLY LOWER RATE OF VITRECTOMY VS LASER
PROTOCOL S - YEAR 5
22%
15%


LUCENTIS® OFFERS SIGNIFICANTLY LESS PERIPHERAL VISUAL FIELD LOSS VS LASER
PROTOCOL S - YEAR 5
-330 dB
-527 dB

- **Review Articles By**
  San Raffaele University
  Milan, Italy.

- **Published in**
  Annals of Medicine

REVIEW ARTICLE

OPEN ACCESS

VEGF-targeting drugs for the treatment of retinal neovascularization in diabetic retinopathy

Alessandro Arrigo, Emanuela Aragona and Francesco Bandello

IRCCS San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan, Italy

ABSTRACT

Diabetic retinopathy (DR) is the most common microangiopathic complication of diabetes mellitus, representing a major cause of visual impairment in developed countries. Proliferative DR (PDR) represents the last stage of this extremely complex retinal disease, characterized by the development of neovascularization induced by the abnormal production and release of vascular endothelial growth factor (VEGF). The term VEGF includes different isoforms; VEGF-A represents one of the most important pathogenic factors of DR. Anti-VEGF intravitreal therapies radically changed the outcome of DR, due to combined anti-angiogenic and anti-edematous activities. Nowadays, several anti-VEGF molecules exist, characterized by different pharmacological features and duration. With respect to PDR, although anti-VEGF treatments represented a fundamental step forward in the management of this dramatic complication, a big debate is present in the literature regarding the role of anti-VEGF as substitute of panretinal photocoagulation or if these two approaches may be used in combination. In the present review, we provided an update on VEGF isoforms and their role in DR pathogenesis, on current anti-VEGF molecules and emerging new drugs, and on the current management strategies of PDR. There is an overall agreement regarding the relative advantage provided by anti-VEGF, especially looking at the management of PDR patients requiring vitrectomy, with respect to laser. Based on the current data, laser approaches might be avoided when a perfectly planned anti-VEGF therapeutic strategy can be adopted. Conversely, laser treatment may have a role for those patients unable to guarantee enough compliance to anti-VEGF injections.

ARTICLE HISTORY

Received 27 September 2021
Revised 1 April 2022
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KEYWORDS

Diabetic retinopathy; VEGF; PDR; vascular endothelial growth factor; VEGF-A; anti-VEGF; intravitreal injection; panretinal photocoagulation

KEY MESSAGES

- VEGF increased production, stimulated by retinal hypoperfusion and ischaemia, is a major pathogenic factor of neovascular complication onset in diabetic retinopathy and of DR stages progression.
- Nowadays, several anti-VEGF molecules are available in clinical practice and other molecules are currently under investigation. Each anti-VEGF molecule is characterized by different targets and may interact with multiple biochemical pathways within the eye.
- All the data agreed in considering anti-VEGF molecules as a first line choice for the management of diabetic retinopathy. Laser treatments may have a role in selected advanced cases and for those patients unable to guarantee enough compliance to intravitreal treatments schemes.

REVIEW ARTICLE

OPEN ACCESS

VEGF-targeting drugs for the treatment of retinal neovascularization in diabetic retinopathy

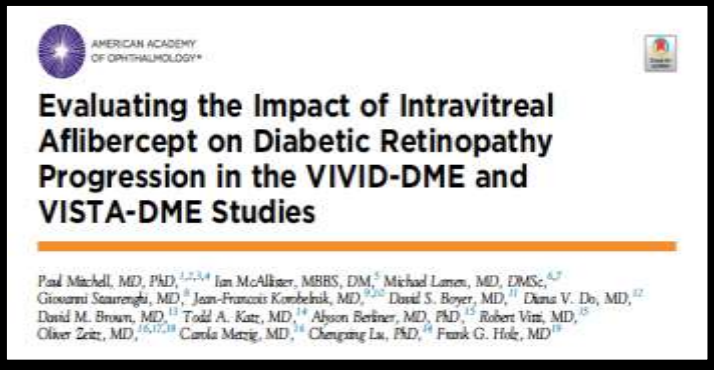
Alessandro Arrigo, Emanuela Aragona and Francesco Bandello

All the data agreed in considering anti-VEGF molecules as a first line choice for the management of diabetic retinopathy.

Laser treatments may have a role in selected advanced cases and for those patients unable to guarantee enough compliance to intravitreal treatments schemes.

The overall feel is that laser approach might be avoided when a perfectly planned anti-VEGF therapeutic strategy can be adopted.
However, we must bear in mind that the real-life situation is quite different from clinical trials settings.
Probably, there is no absolute winning therapeutic choice for managing DR, but the choice of the treatments and of the follow-up timeline must be planned based on personalized strategies designed on patients' characteristics

Evidence for improvement of retinopathy



AMERICAN ACADEMY OF OPHTHALMOLOGY®

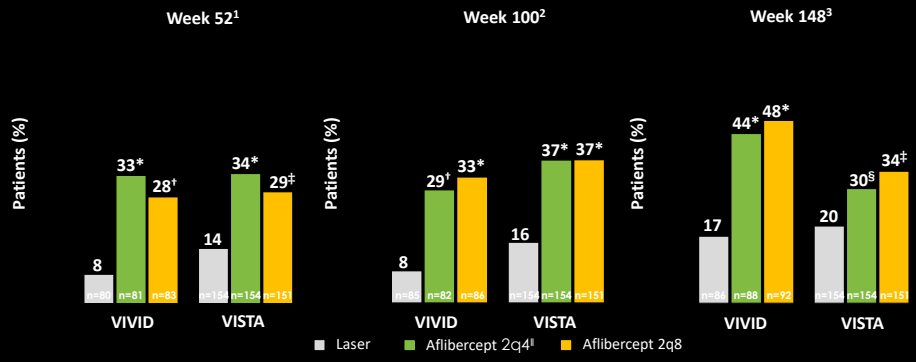
Evaluating the Impact of Intravitreal Aflibercept on Diabetic Retinopathy Progression in the VIVID-DME and VISTA-DME Studies

Paul Mitchell, MD, PhD,[1,2,3,4] Ian McAllister, MBBS, DM,[5] Michael Larsen, MD, DMSc,[6,7] Giovanni Staurenghi, MD,[8] Jean-Francois Korobelnik, MD,[9,10] David S. Boyer, MD,[11] Diana V. Do, MD,[12] David M. Brown, MD,[13] Todd A. Katz, MD,[14] Alyson Berliner, MD, PhD,[15] Robert Vitti, MD,[15] Oliver Zeitz, MD,[16,17,18] Carola Metzig, MD,[14] Chengxing Lu, PhD,[14] Frank G. Holz, MD[19]

VIVID and VISTA: a significant proportion of patients treated with aflibercept experienced regression in the signs of DR

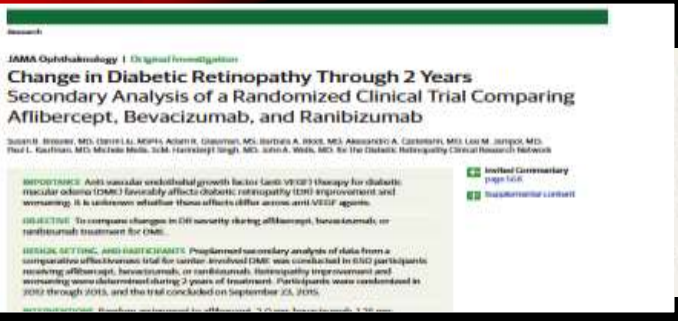
- Treatment with aflibercept 2q8 leads to significant improvements in DR severity after only 1 year of therapy in around 30% of patients[1]

Proportion of patients with ≥2-step improvements in DRSS



*P<0.0001, †P<0.001, ‡P<0.01, §P=0.035 vs. laser

Further evidence : Post Hoc analysis of protocol T



JAMA Ophthalmology | Original Investigation

Change in Diabetic Retinopathy Through 2 Years
Secondary Analysis of a Randomized Clinical Trial Comparing Aflibercept, Bevacizumab, and Ranibizumab

Susanna S. Brown, MD; David J. Ou, MSPH; Adam R. Glassman, MS; Barbara A. Blodi, MD; Alessandro A. Castellarin, MD; Lee M. Jampol, MD; Paul L. Kaufman, MD; Michele Melia, ScM; Harmeet Singh, MD; John A. Wells, MD; for the Diabetic Retinopathy Clinical Research Network

Invited Commentary page 565
Supplemental Content

IMPORTANCE Anti-vascular endothelial growth factor (anti-VEGF) therapy for diabetic macular edema (DME) favorably affects diabetic retinopathy (DR) improvement and worsening. It is unknown whether these effects differ across anti-VEGF agents.

OBJECTIVE To compare changes in DR severity during aflibercept, bevacizumab, or ranibizumab treatment for DME.

DESIGN, SETTING, AND PARTICIPANTS Preplanned secondary analysis of data from a comparative effectiveness trial for center-involved DME was conducted in 660 participants receiving aflibercept, bevacizumab, or ranibizumab. Retinopathy improvement and worsening were determined during 2 years of treatment. Participants were randomized in 2012 through 2013, and the trial concluded on September 23, 2015.

CONCLUSIONS AND RELEVANCE At 1 and 2 years, eyes with NPDR receiving anti-VEGF treatment for DME may experience improvement in DR severity. Less improvement was demonstrated with bevacizumab at 1 year than with aflibercept or ranibizumab. Aflibercept was associated with more improvement at 1 and 2 years in the smaller subgroup of participants with PDR at baseline. All 3 anti-VEGF treatments were associated with low rates of DR worsening. These data provide additional outcomes that might be considered when choosing an anti-VEGF agent to treat DME.

JAMA Ophthalmol. 2017;135(6):558-568. doi:10.1001/jamaophthalmol.2017.0823
Published online April 27, 2017.

CONCLUSIONS AND RELEVANCE

At 1 and 2 years, eyes with NPDR receiving anti-VEGF treatment for DME may experience improvement in DR severity.
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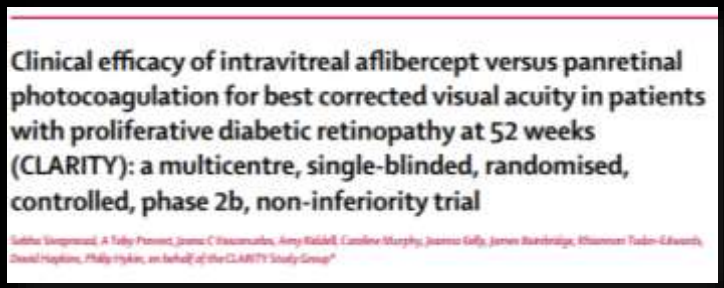
All 3 anti-VEGF treatments were associated with low rates of DR worsening.
These data provide additional outcomes that might be considered when choosing an anti-VEGF agent to treat DME.

CLARITY



Clinical efficacy of intravitreal aflibercept versus panretinal photocoagulation for best corrected visual acuity in patients with proliferative diabetic retinopathy at 52 weeks (CLARITY): a multicentre, single-blinded, randomised, controlled, phase 2b, non-inferiority trial

Clarity evaluated the efficacy of aflibercept for the treatment of PDR compared with PRP

CLARITY (N=232)
Multicenter, prospective, single-blind, randomized, non-inferiority Phase IIb study in patients aged 18 years or older with type 1 or 2 diabetes and clinical evidence of PDR*

Patients randomized 1:1

Panretinal laser photocoagulation† (single spot or multispot)

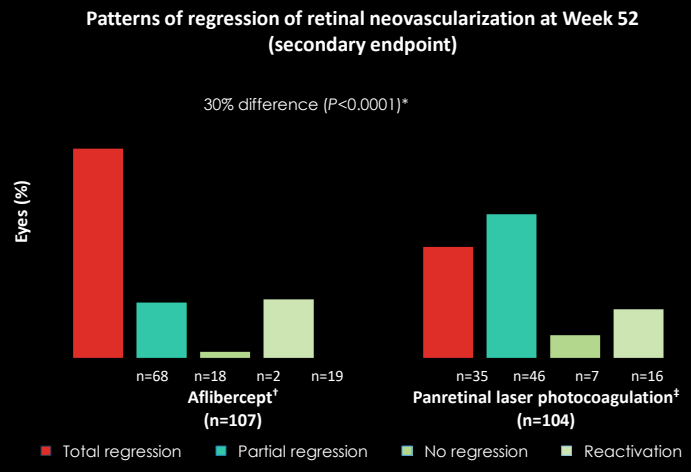
Aflibercept PRN‡

Week 52 (Year 1): Primary endpoint

Primary endpoint: Mean change in BCVA from baseline at Week 52

Secondary endpoints included: Change in DRSS levels at Week 12 and Week 52

Proportion of eyes showing total disease regression at week 52



Case Presentation

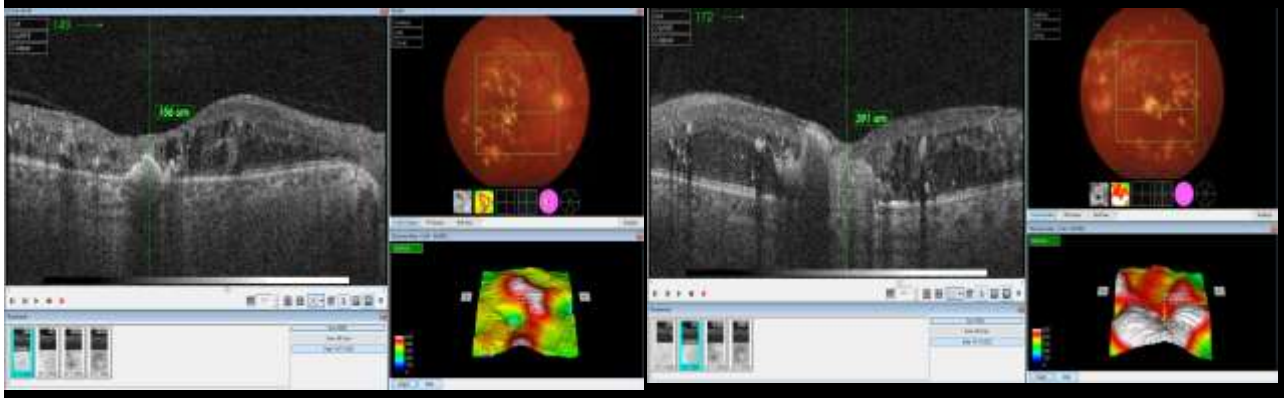
57 year old male patient
KCO : DM 15 years on Insulin & OHA
HTN
HLP

VA Right Eye 0.1 cc
Left Eye CF 1m

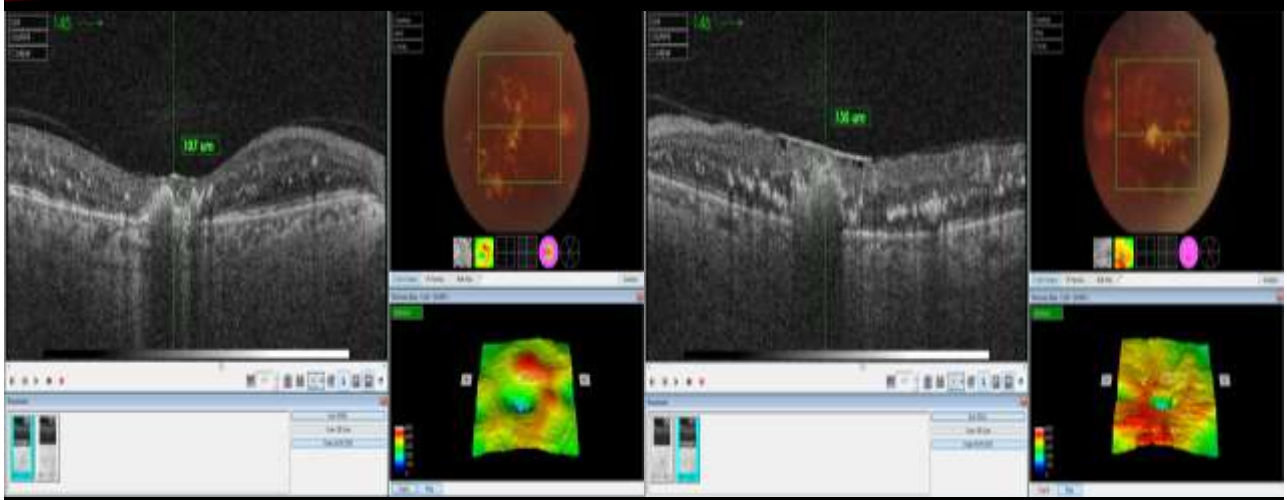
Anterior segment WNL
IOP : Both eye WNL

Fundus :
Both eyes PDR and DME

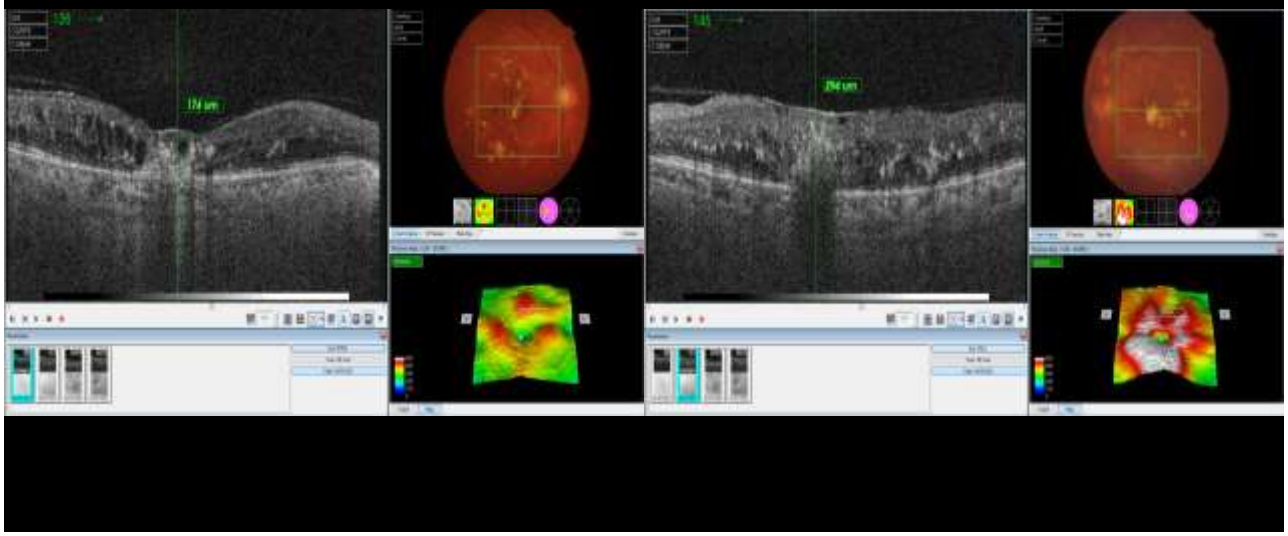
Pre Injection OCT and Fundus



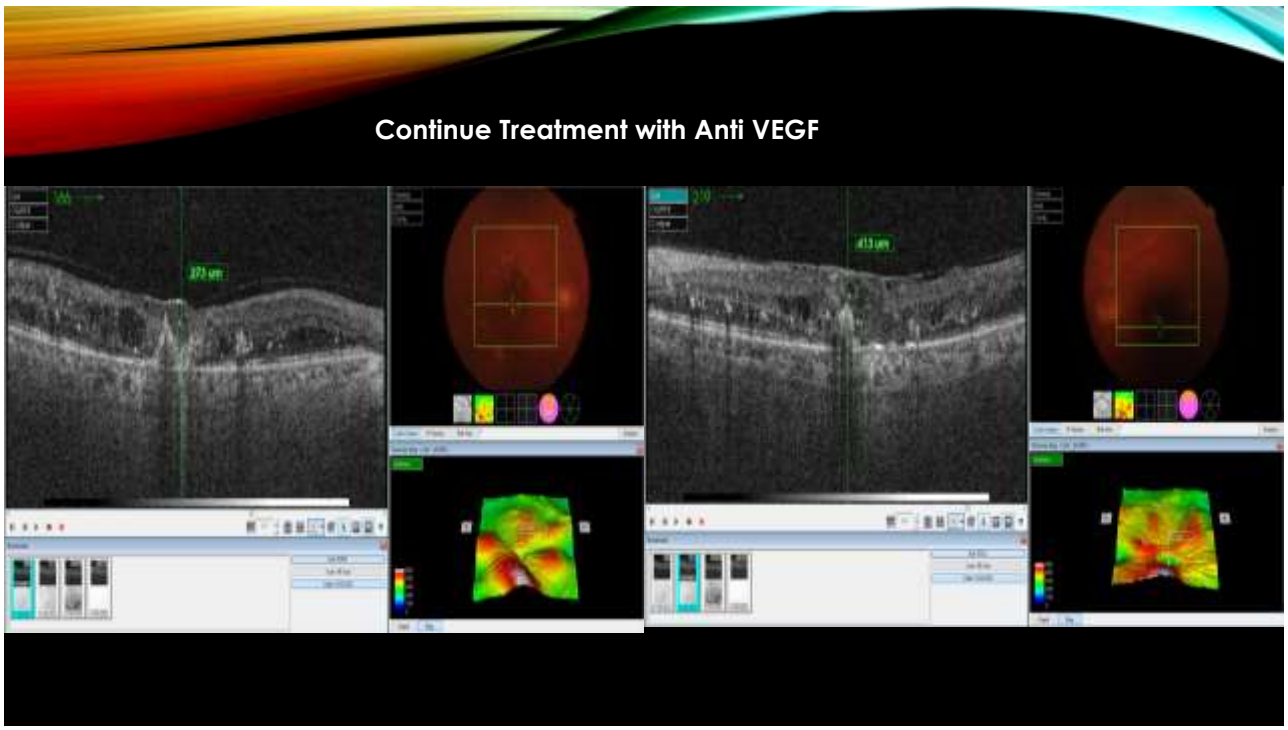
Post treatment with Anti VEGF

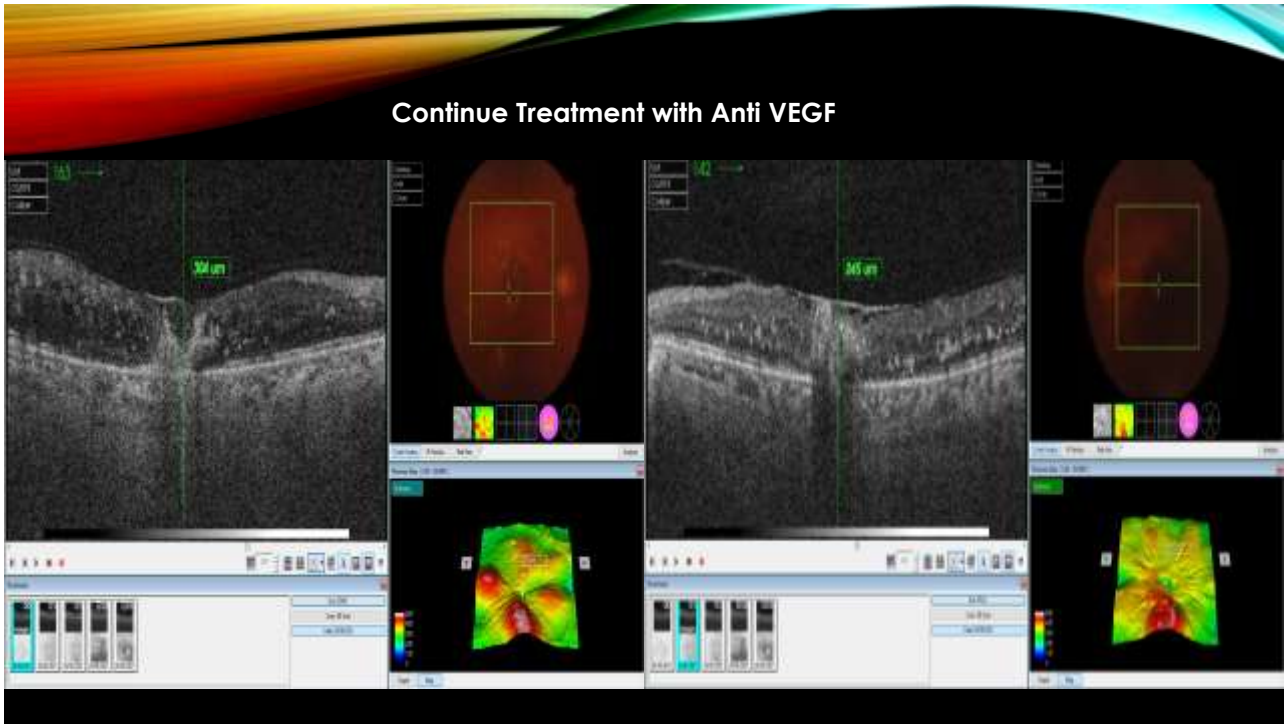


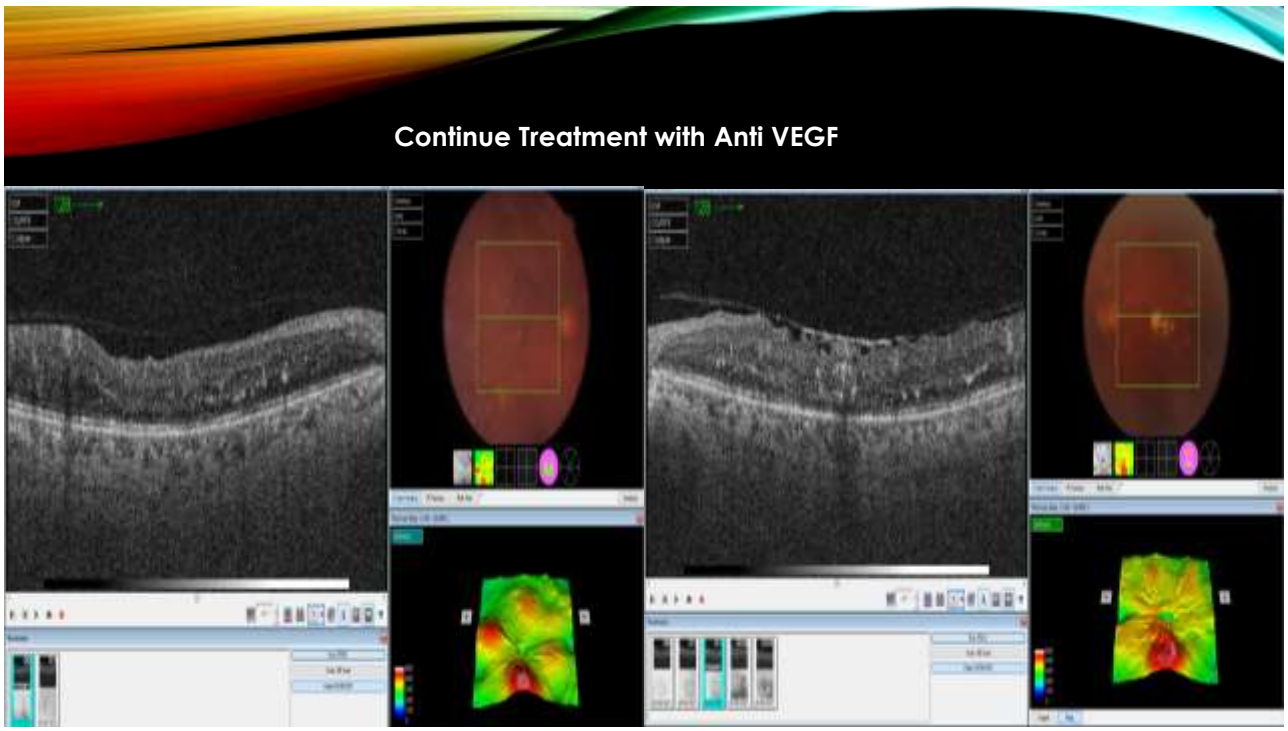
Continue Treatment with Anti VEGF



Continue Treatment with Anti VEGF




Continue Treatment with Anti VEGF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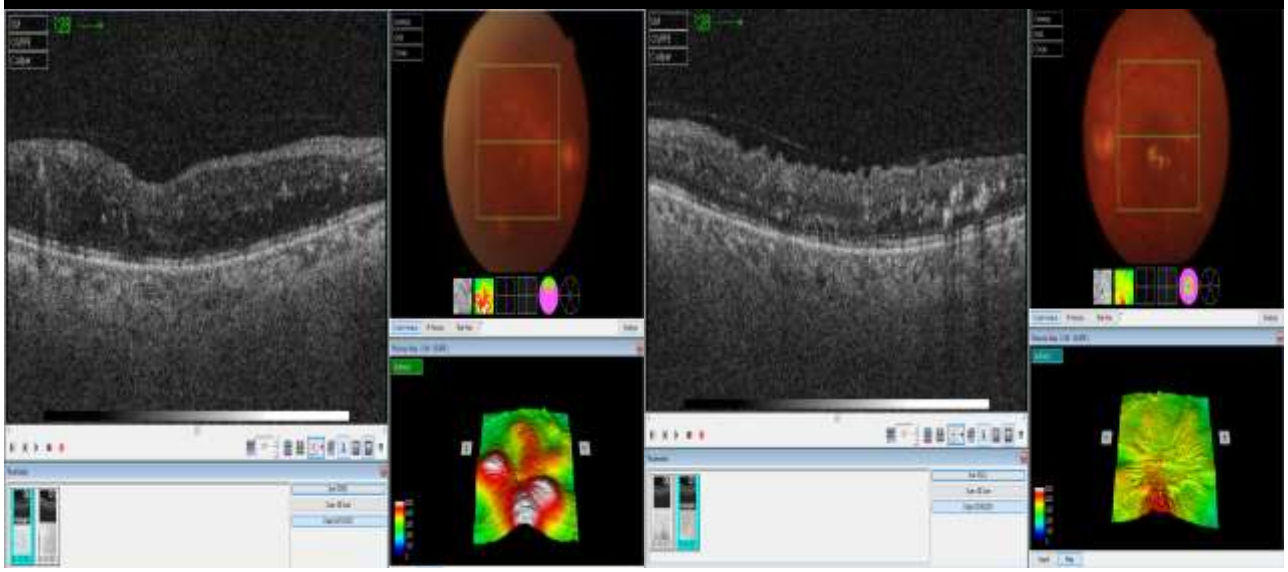
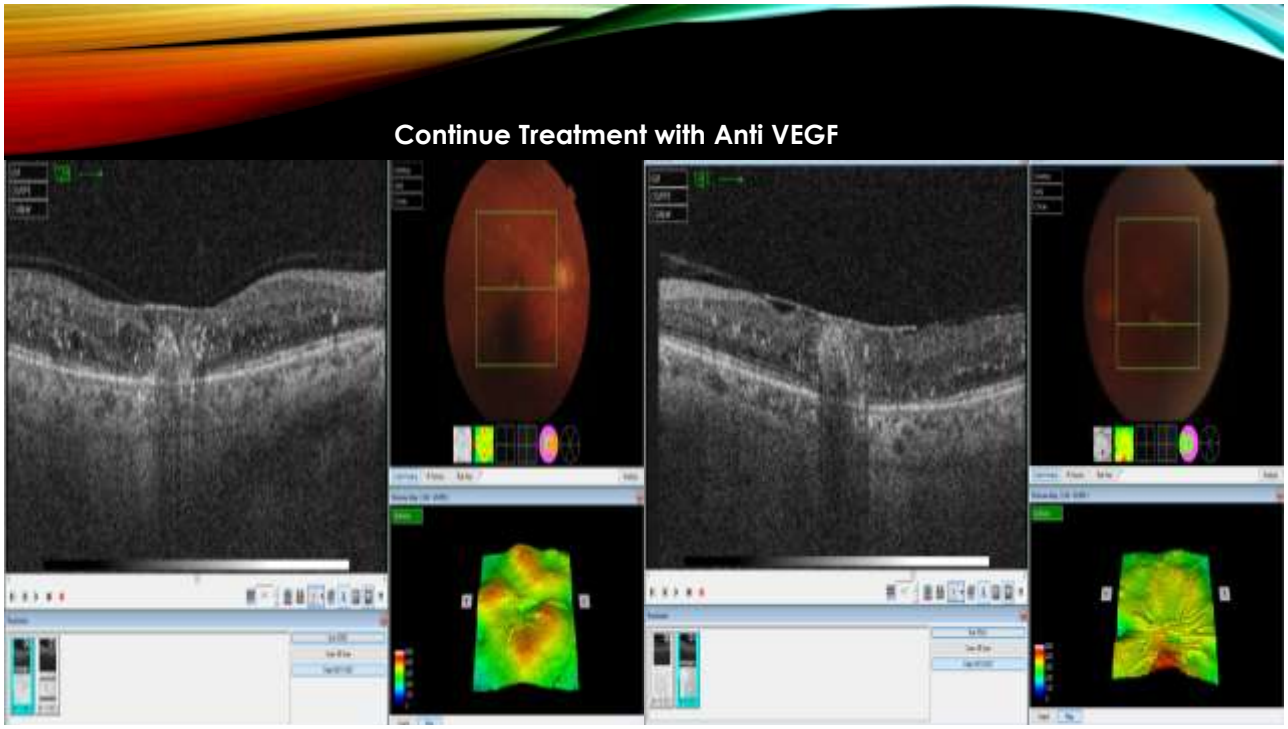
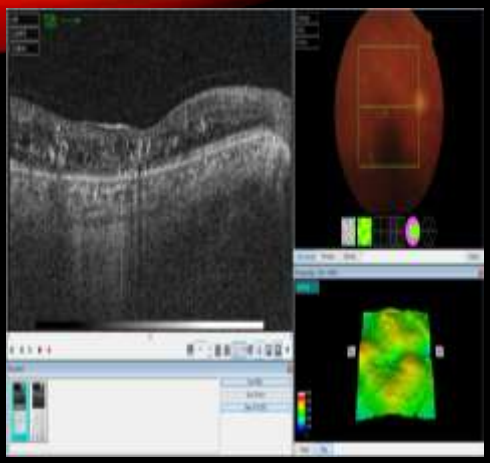
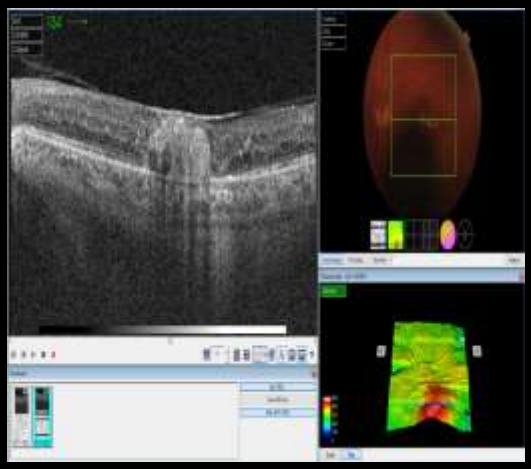


Continue Treatment with Anti VEGF



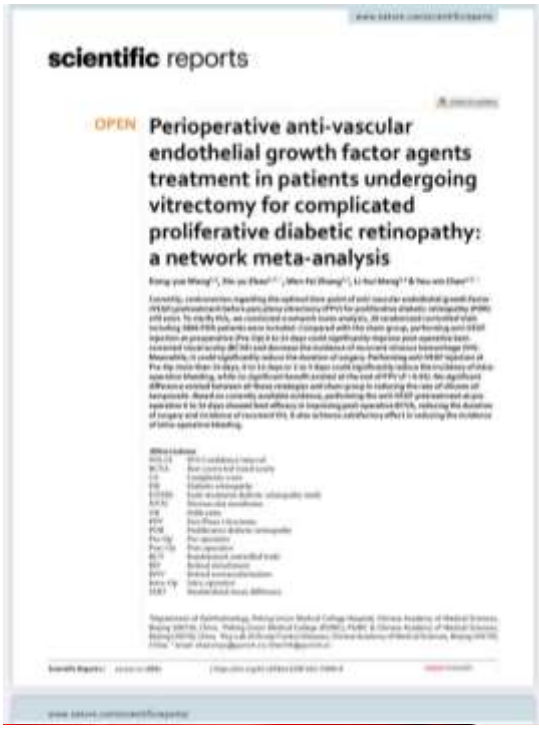
Continue Treatment with Anti VEGF





Patient received 8 Injections in first year and 6 injections in second year
VA Right eye 0.4 CC
Left eye 0.25 CC
FUNDUS both eye complete regression of PDR

OCT both eye very less Central DME



scientific reports

OPEN

Perioperative anti-vascular endothelial growth factor agents treatment in patients undergoing vitrectomy for complicated proliferative diabetic retinopathy: a network meta-analysis

Article Published: **03 November 2020**
Scientific Reports **volume 10**, Article number: **18880** (2020)

Perioperative anti-vascular endothelial growth factor agents treatment in patients undergoing vitrectomy for complicated proliferative diabetic retinopathy: a network meta-analysis

Conclusion

In summary, our study suggests that performing the anti-VEGF pretreatment at pre-operative **6 to 14 days** showed the **best efficacy** in improving post-operative **BCVA**,
reducing the **duration of surgery** and **incidence of recurrent VH**,
it also achieves satisfactory effect in reducing the incidence of **intra-operative bleeding**.