

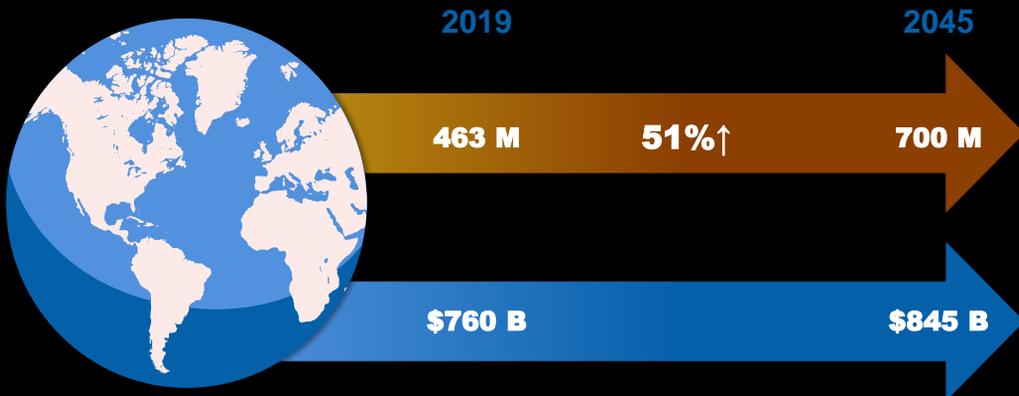
Role of Anti VEGF in management of Diabetic Retinopathy



Dr. Mohammed Al Amri

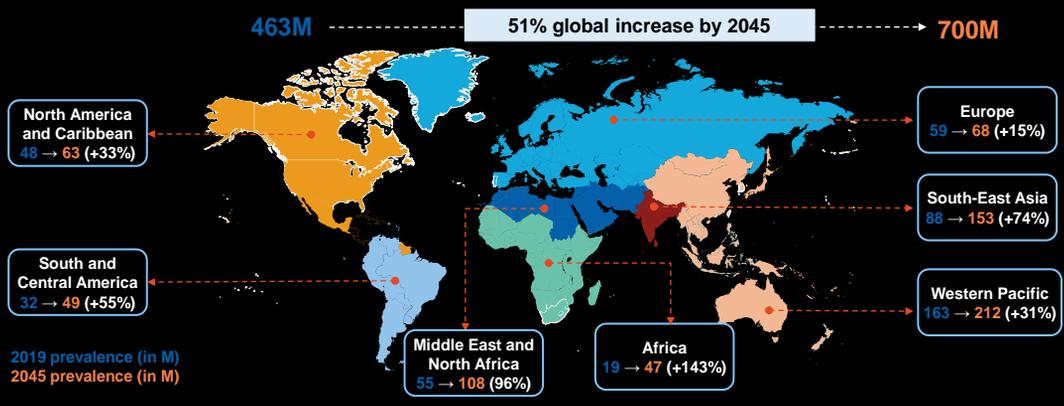
MBBS, HSDO, MD , MRS
 Consultant Ophthalmologist Al Qassimi Hospital, Sharjah UAE
 Anterior segment surgeon & medical retina specialist
 Adjunct professor in medical college, Sharjah University. 2011-2018
 Founder & President of Middle East Ophthalmology Meeting (MEOM)
 Founder, Vice-president & head of scientific & organizing committee of QOIC
 Founder & first president of gulf retina group (GRG)
 Member of UAE right for sight committee

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

Dubai Diabetes Endocrinol J 2020;26(1-38)
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Emirates Diabetes Society Consensus Guidelines for the Management of Type 2 Diabetes Mellitus – 2020

Fatheyh Alnowadi^{1,2}, Salah Abuosama³, Bashar Almasri^{4,5}, Khalid M. Aldahmani^{1,6},
Denniyat Alhajeri^{1,7}, Khalid Aljaberi⁸, Juma Alkaabi⁹, Abdurazzaq Almadani¹,
Alaeldin Bashir¹, Salem A. Beshyah^{10,11}, Buthaina bin Salala¹², Mohammad Faragly¹³,
Muhammad H. Farooq^{14,15}, Rhadja Halidh¹⁶, Mohamed Hassanein^{17,18}, Ahmed Hassoun^{19,20},
Abdul Jabbar²¹, Iyad Kivleir^{22,23}, Husla E. Mustafa²⁴, Hussein Saadi²⁵, Sara Sulman²⁶

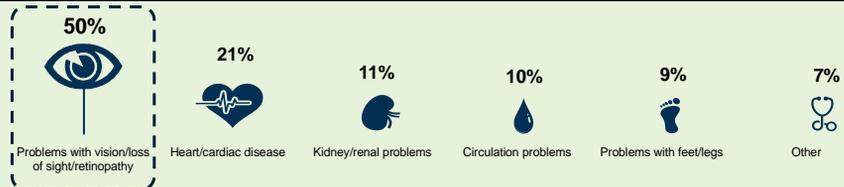
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Abstract

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

Complications that patients were most concerned about¹:



Feelings about complications at diagnosis¹:



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.

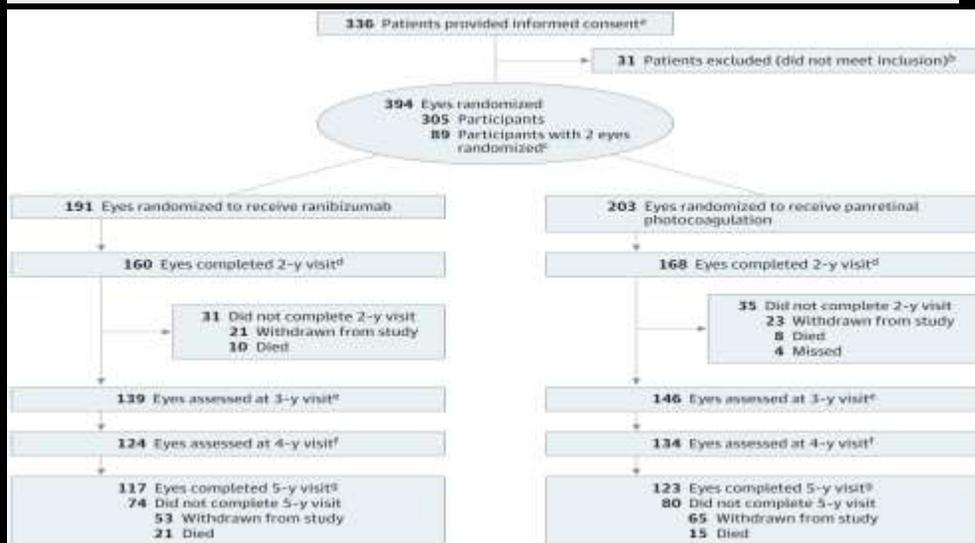
A Randomized clinical trial DRCR.net protocol S

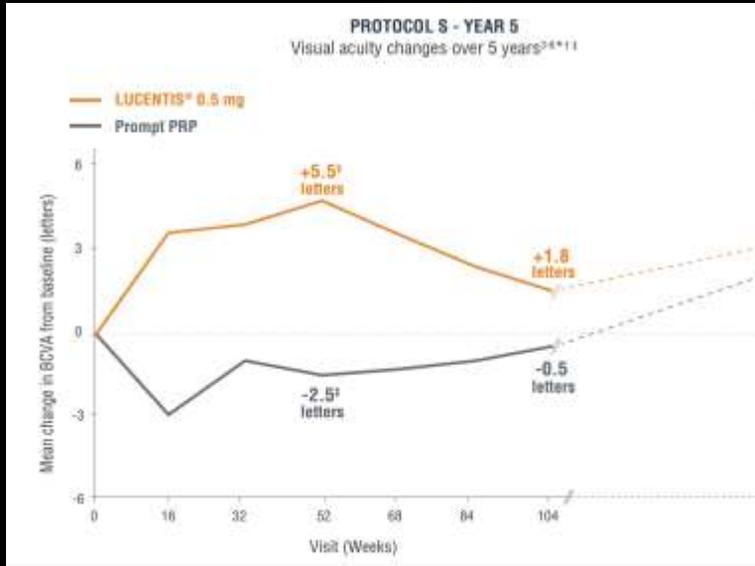
PROTOCOLS

- **Objective** To evaluate efficacy and safety of 0.5-mg intravitreal 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 intravitreal 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.

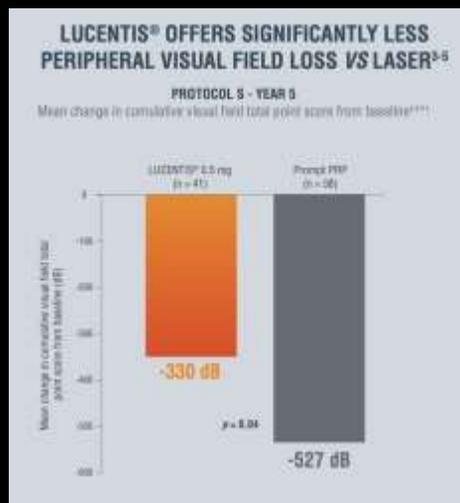
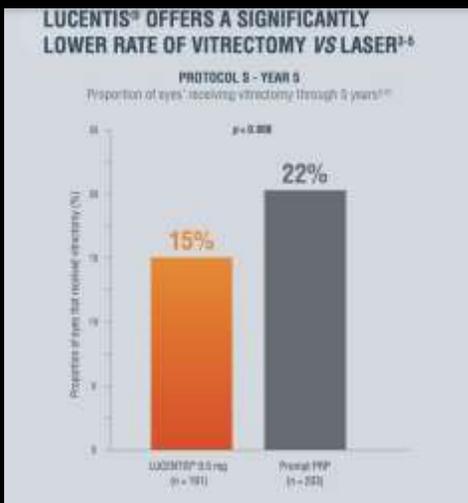
From: Five-Year Outcomes of Pan-retinal Photocoagulation vs Intra-vitreous Ranibizumab for Proliferative Diabetic Retinopathy: A Randomized Clinical Trial

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





PROTOCOL S



- Review Articles By San Raffaele University Milan, Italy.

- Published in Annals of Medicine

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REVIEW ARTICLE

OPEN ACCESS

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

Alessandro Arrigo, Emanuela Aiagoni and Francesco Bandello

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

ABSTRACT
Diabetic retinopathy (DR) is the most common macrovascular complication of diabetes mellitus, representing a major cause of visual impairment in developed countries. Proliferative DR (PDR) represents the last stage of this seriously complex retinal disease, characterized by the development of neovascularization induced by the abnormal production and release of vascular endothelial growth factor (VEGF). The same 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-inflammatory 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 chronic 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 treatment, 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.

KEYWORDS
Diabetic retinopathy; VEGF; PDR; anti-VEGF; intravitreal injections; panretinal photocoagulation

ARTICLE HISTORY
Received 27 September 2022
Revised 1 April 2023
Accepted 4 April 2023

KEY MESSAGES
• VEGF increased production, stimulated by retinal hypoperfusion and ischemia, is a major pathogenic factor of neovascular complications 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 scheduled treatments schemes.

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INTRODUCTION
Vascular endothelial growth factor (VEGF) is one of the most important mediators involved in the pathogenesis of diabetic retinopathy (DR). The abnormal production and release of VEGF induce vascular endothelial cell proliferation and migration and increased vascular permeability [1]. VEGF is involved in the pathogenesis of DR-related complications, such as diabetic macular edema (DME), neovascularization, and represents a fundamental

anti-VEGF intravitreal therapies radically changed the course of DR and patients' outcome, having a remarkable impact on the incidence of legal blindness. Nowadays, several anti-VEGF molecules exist, acting on different metabolic pathways and VEGF isoforms. The usage of anti-VEGF as first line treatment provided undeniable benefits for the management of DR; on the other side, the equipment of the proliferative form is quite controversial. Indeed, a big debate is still present in the literature

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

...treatments for PDR patients, if potential photocoagulation was often criticized as inducing excessive loss of the visual field, the 5-year report of DRCR Protocol 2 highlighted a critical point. Indeed, Maguire and colleagues [118] showed that, if the deterioration of the visual field was higher in the PDR group treated by laser during the first year, it was equal with the eyes treated by anti-VEGF injections, the long-term visual field outcomes were statistically similar between both groups at the end of the 5-year follow-up. These findings, showing similar long-term effect of laser and peripheral intravitreal anti-VEGF, further reinforced the role either of anti-VEGF and potential photocoagulation as effective treatments for PDR. As concluded by DRCR network, the therapeutic strategy for PDR should consider treatment recommendations, the relative advantages of each treatment approach and patients' compliance with follow-up planning [118]. The other take of the model is to always bear in mind the possible, although rare, risk of anti-VEGF "wash syndrome". This infrequent complication occurring in PDR is characterized by the progressive worsening of the fibrovascular tractional retinal detachment following anti-VEGF injections. This condition is still poorly defined because of the very low incidence and the presence of many possible confounding factors, including potential photocoagulation. It might be determined by the fibrovascular regression induced by anti-VEGF injections, causing increased fibrosis leading to the worsening of the tractional component of the vitreal detachment. As expected, the logical approach and visual outcome are worse than PDR cases not complicated by this occurrence [118]. The main interventional clinical trials specifically focused on PDR are reported in Table 3.

Final remarks and conclusions

Neovascular complications may have a remarkable negative impact on patients' management and visual outcomes in DR and is characterized by increased production of VEGF as a major causative factor. In the present review, we provided an overall description of the use of anti-VEGF molecules for the management of PDR, focusing on the current high-level evidence under investigation and the possible targets using the neovascular process and the development of further complications. It is questionable that the introduction of anti-VEGF therapy radically changed the management and prognosis of all the stages of DR, including PDR, before the anti-VEGF era, the only therapeutic approach was represented by laser, performed on either periphery through photocoagulation, or at the posterior pole, through focal/grid treatments. Laser approaches turned out to be useful in managing DME and neovascular progression, although the investigation question is: what retinal structures had a negative impact on the morpho-functional status of diabetic eyes? As highlighted by the present review, a big debate is nowadays present in the literature regarding the comparison between anti-VEGF and laser approaches, and the consistent use of both treatments. Most of the current data do not provide enough level of evidence to draw definite conclusions. Through the many studies conducted, the DRCR network offered a strong contribution in the clinical and therapeutic management of DR, highlighting the importance of promptly and frequently repeated intravitreal injections. The overall feel is that laser approach might be avoided when a perfectly planned anti-VEGF therapeutic strategy can be adopted. However, we need more to reveal 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. The clinical status, including glycemic control and presence of comorbidities, patient's self-sufficiency, compliance with the frequency of follow-up visits and treatments represent key aspects ruling the overall clinical and ophthalmologic management of the DR patient. The future development of longer duration anti-VEGF treatments and of ever more optimized molecules will have a remarkable impact on the feasibility and sustainability of DR patients care for the hospital and the public health systems, and probably will modify the current indications to laser approaches. According to the WHO/UNA guidelines [42], anti-VEGF molecules represent the treatment of choice for most of DR patients because of the high efficacy and safety profiles, and the feasible management. Possible contraindications regard those patients characterized by high cardiovascular risks, where other approaches, such as cardiovascular CVD-CRE, should be preferred. Laser approaches still maintain a role for the safety eyes characterized by extremely severe form

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®



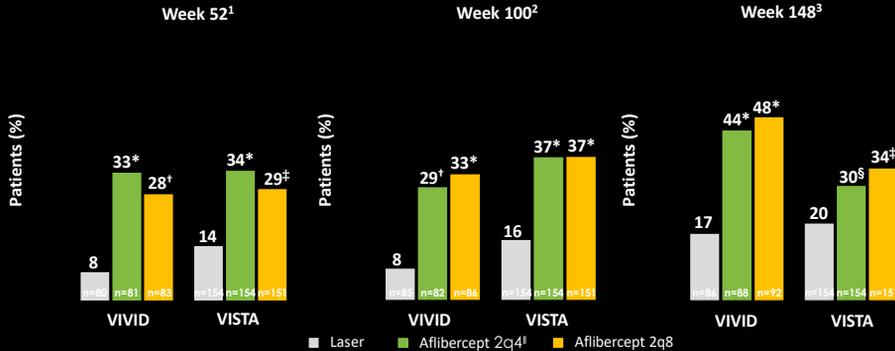
Evaluating the Impact of Intravitreal Aflibercept on Diabetic Retinopathy Progression in the VIVID-DME and VISTA-DME Studies

Paul Mitchell, MD, PhD,^{1,2,3,4} Ian McAllister, MBBS, DM,⁵ Michael Linnen, MD, DMSc,^{6,7} Giosanni Sauerregh, MD,⁸ Jean-Francois Kornblum, 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,¹⁶ Oliver Zeitz, MD,^{16,17,18} Carlos Merzj, MD,¹⁴ Chengping Lu, PhD,¹⁴ Frank G. Holz, MD¹⁹

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 patients¹

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

IMPORTANCE: Anti-vascular endothelial growth factor (anti-VEGF) therapy for diabetic macular edema (DME) reversibly 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: Postprandial secondary analysis of data from a comparative effectiveness trial for similar involved DME was conducted in 632 participants receiving aflibercept, bevacizumab, or ranibizumab. Retinopathy improvement and worsening were determined during 2 years of treatment. Participants were randomized in 2012 through 2015, and the trial concluded on September 23, 2016.

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;35(6):558-568. doi:10.1001/jamaophthol.2017.082
 Published online April 27, 2017.

CONCLUSIONS AND RELEVANCE

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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

Sudha Srinivasan, A Toby Pernet, James C Hascovitch, Amy Kilduff, Caroline Murphy, James Gally, James Barbridge, Khimraj Tudu-Ekwarh, David Hopkins, Philip Taylor, on behalf of the CLARITY Study Group*

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[‡]

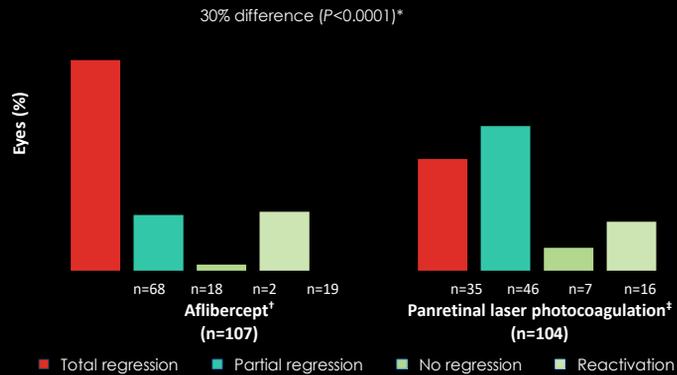
Primary endpoint:
Mean change in BCVA
from baseline at Week 52

Week 52 (Year 1):
Primary endpoint

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

Proportion of eyes showing total disease regression at week 52

Patterns of regression of retinal neovascularization at Week 52 (secondary endpoint)



Case Presentation

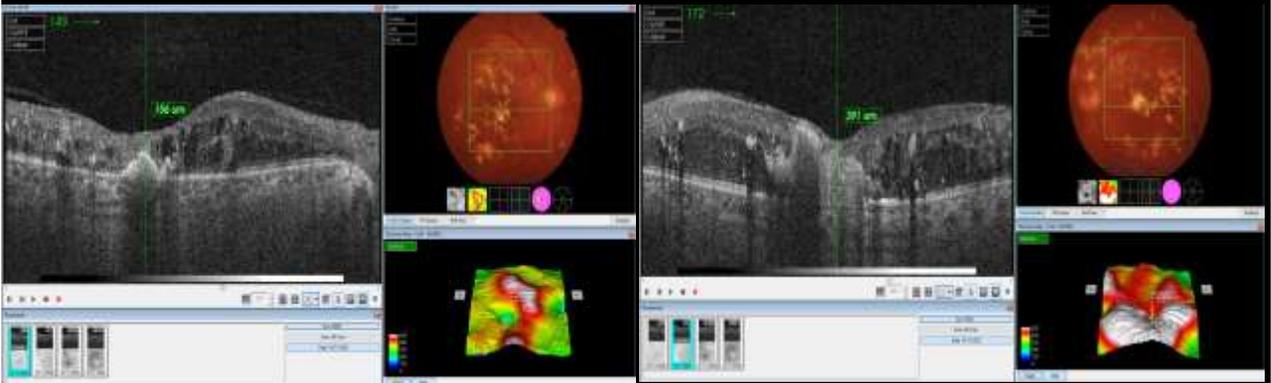
57 year old male patient
KCO : DM 15 years on Insulin & OHA
HTN
HLP

VA Right Eye 0.1 cc
Left Eye CF 1m

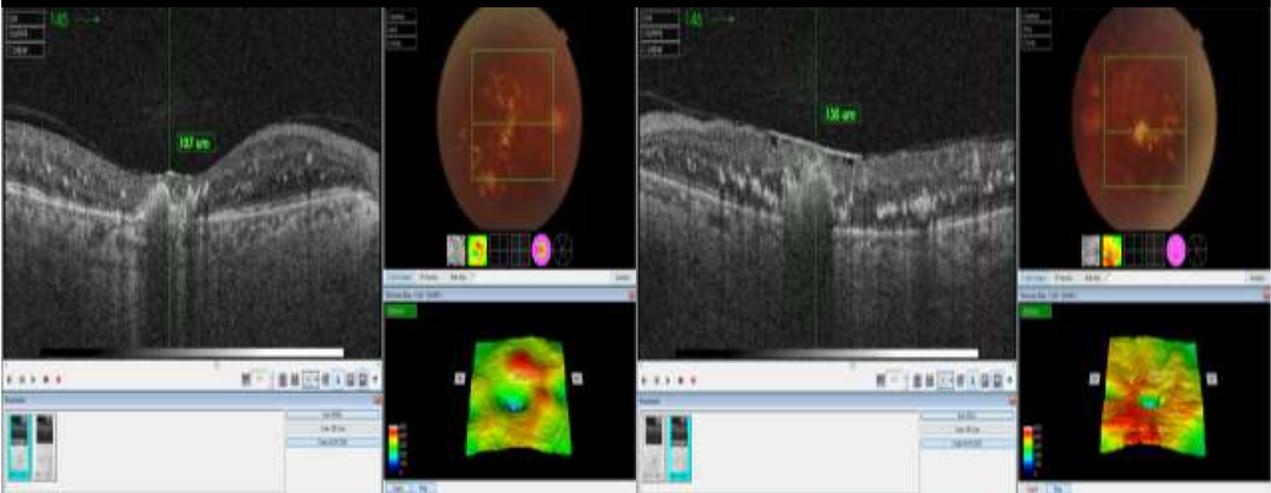
Anterior segment WNL
IOP : Both eye WNL

Fundus :
Both eyes PDR and DME

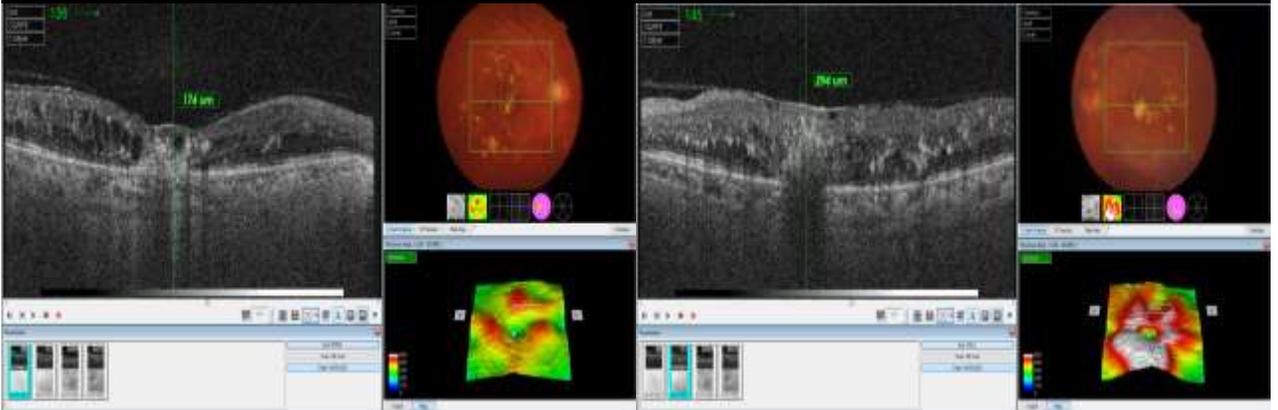
Pre Injection OCT and Fundus



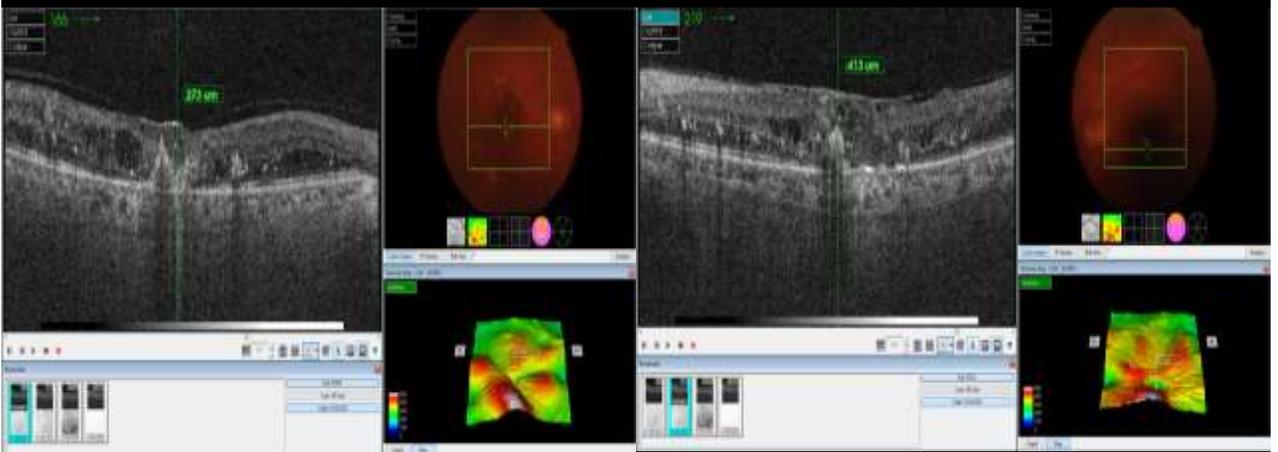
Post treatment with Anti VEGF



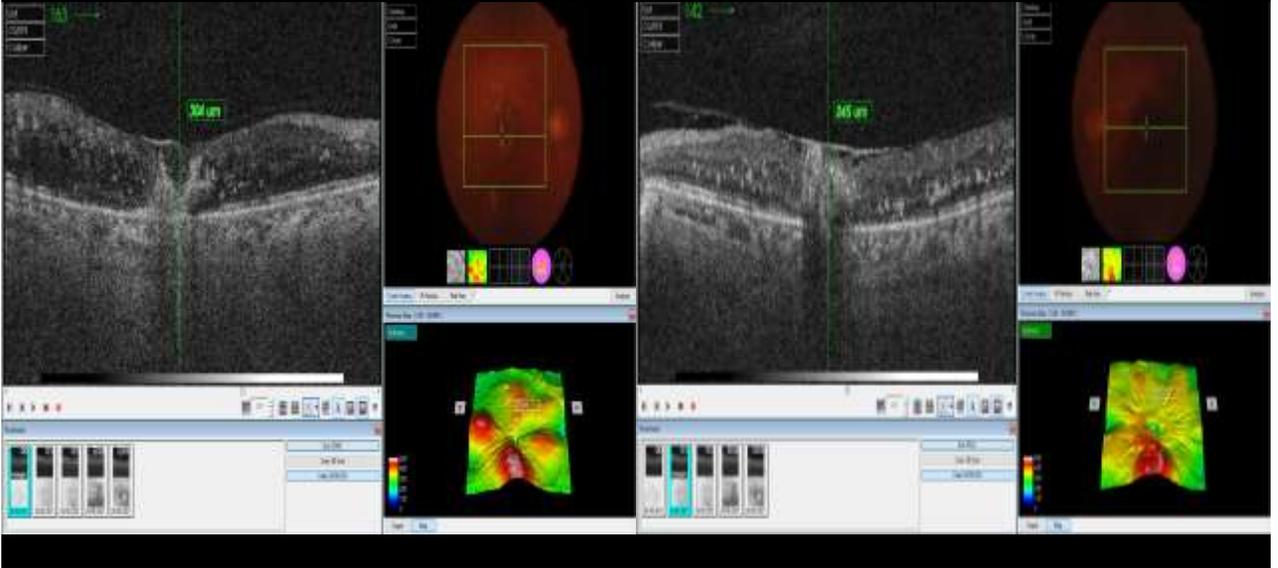
Continue Treatment with Anti VEGF



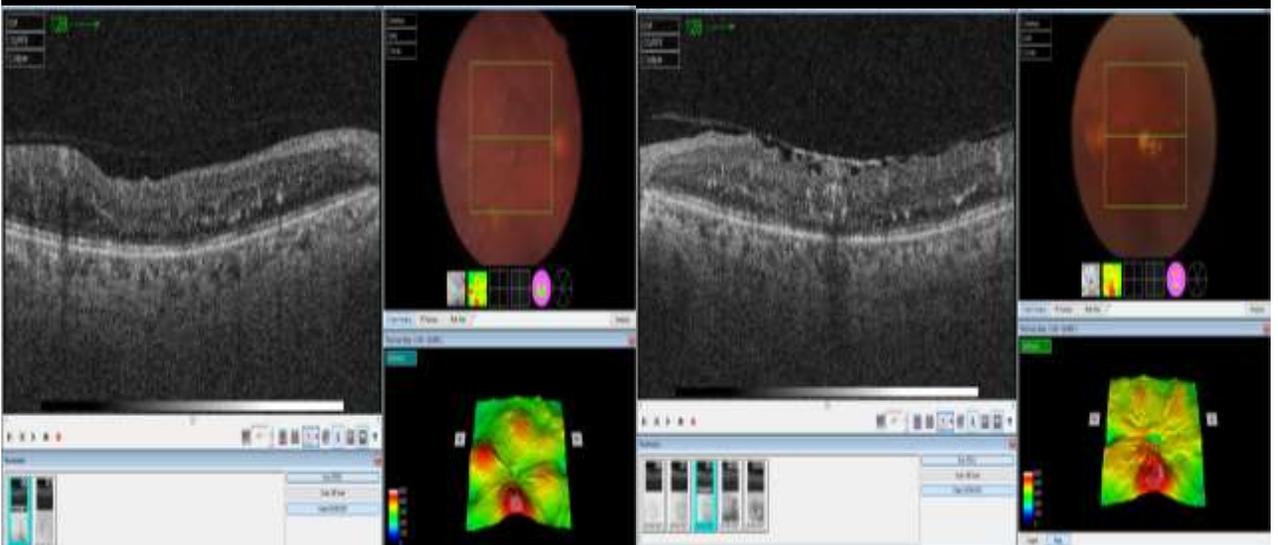
Continue Treatment with Anti VEGF



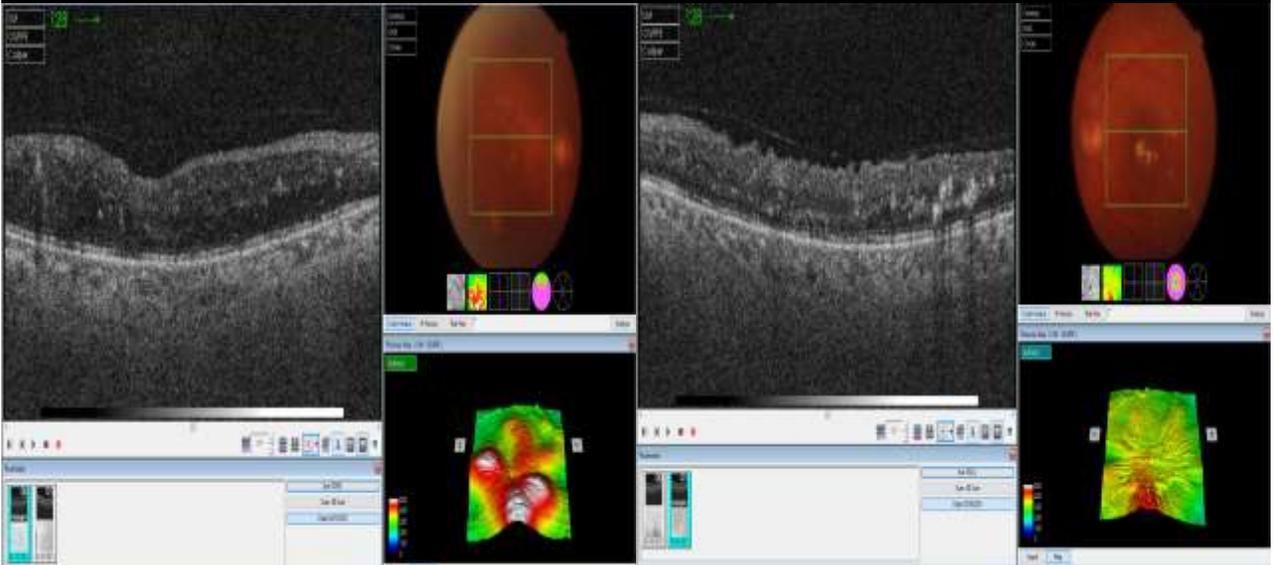
Continue Treatment with Anti VEGF



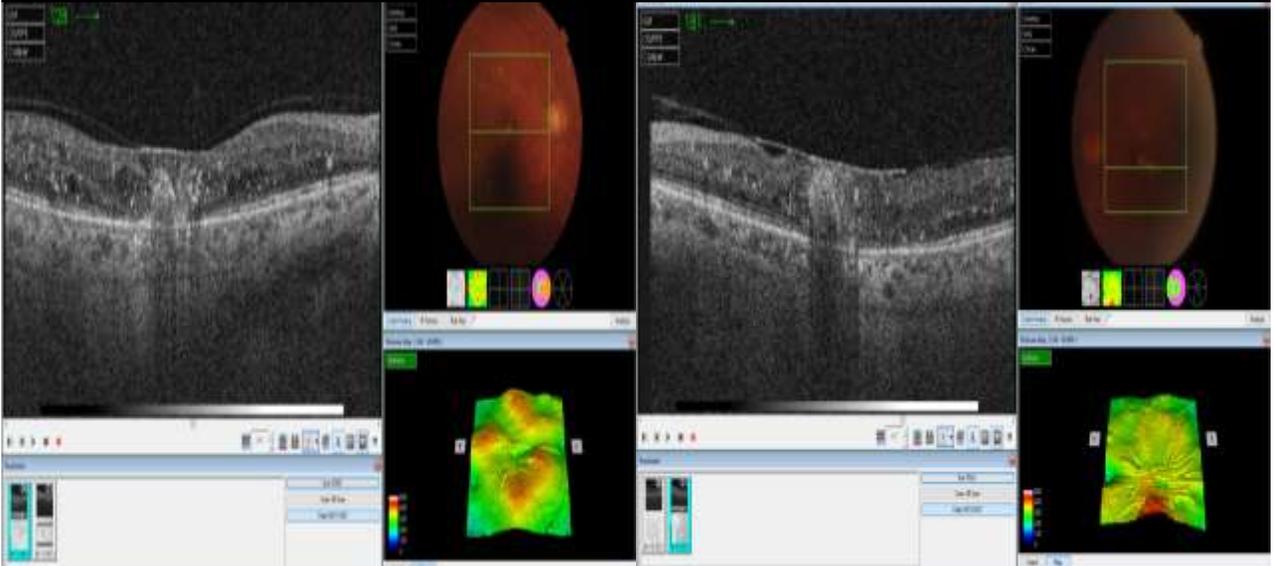
Continue Treatment with Anti VEGF

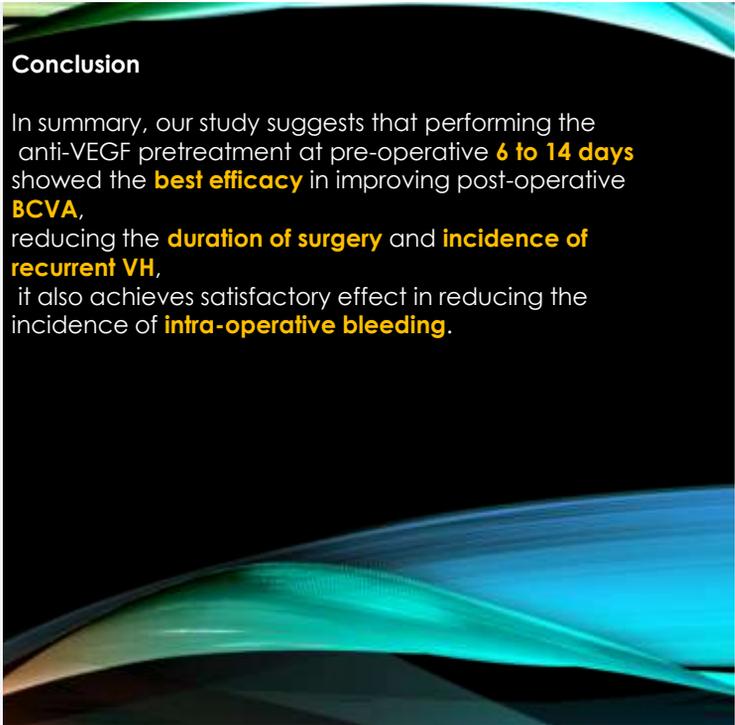


Continue Treatment with Anti VEGF



Continue Treatment with Anti VEGF





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