ECRONICON OPEN ACCESS

EC OPHTHALMOLOGY
Research Article

Switch to Aflibercept after Prior Anti-Vegf Therapy in Eyes with Persistent Diabetic Macular Edema: Real World Clinical Practice

Joana Maria Mendes Pereira*, António Campos, Mónica Santos, Henrique Aragão, Maria Vieira and JP Castro Sousa

Ophthalmology Department, Leiria Hospital Centre, Portugal

***Corresponding Author**: Joana Maria Mendes Pereira, Ophthalmology Department, Leiria Hospital Centre, Rua das Olhalvas, Leiria, Portugal.

Received: January 06, 2019; **Published:** January 31, 2019

Abstract

Purpose: To evaluate the functional and anatomic outcomes in eyes with persistent diabetic macular edema (DME) who were switched from ranibizumab to aflibercept.

Methods: Retrospective case series. Eyes of diabetic patients with DME that were treated with at least a 3-monthly injections' loading dose of ranibizumab and with at least a 3-monthly injections' loading dose of aflibercept thereafter, were included. After the loading dose of aflibercept, eyes were treated until six months on a pro re nata (PRN) regimen. Pertinent patient data were collected from clinical charts and tabulated for analysis.

Results: A total of 37 eyes of 27 patients were included. The mean best corrected visual acuity (BCVA) at the pre-switch visit was 65.1 ± 11.7 ETDRS letters. The mean BCVA improved to 68.6 ± 12.6 letters after the loading dose of aflibercept ($p < 0.05$). The mean central retinal thickness (CRT) at the pre-switch visit was 434.2 ± 128.2 µm and it improved significantly to 372.2 ± 99.4 µm after switching to aflibercept ($p < 0.05$). A total of 24 eyes were followed for 6 months after switching and the improvements in BCVA and CRT were not maintained following a pro re nata regimen.

Conclusion: Switching to aflibercept for persistent DME seemed to result in a significant CRT reduction and significant improvement in visual acuity after the loading dose of aflibercept, and though there was an increase in BCVA and CRT at 6 months, it was not significant.

Keywords: *Anti-VEGF; DME; Switch; Pro Re Nata*

Introduction

Diabetic macular edema (DME) accounts for most of the visual loss experienced by patients with diabetes [1]. The prevalence of DME, among recent population-based studies, ranged between 4.2 and 7.9% in patients with type 1 diabetes and between 1.4% and 12.8% in patients with type 2 diabetes [1].

Currently, anti-VEGF agents are a therapeutic option widely used. Two anti-VEGF agents have been approved by the U.S. Food and Drug Administration to treat DME: ranibizumab (Lucentis; Genentech, South San Francisco, CA) and aflibercept (Eylea; Regeneron, Tarrytown, NY). Off-label bevacizumab is used as well.

The DA VINCI, VISTA and VIVID studies, in the case of aflibercept and the RISE and RIDE, concerning Ranibizumab confirmed the efficacy of these drugs as DME treatment tools [3-6].

The mass use of anti-VEGF raises the need for scientific evidence to support the therapeutic management of these drugs. The DRCR.net group, studied their comparative effectiveness for DME. The 1-year results of Protocol T, showed overall similarity between the 3 drugs, but for some subgroups, aflibercept was superior. The advantage of aflibercept over ranibizumab observed in the 1-year results was no longer statistically significant at 2 years [7].

Currently, there remains a scarcity of evidence on sequential use or the switch of anti-VEGF drugs. The studies on this topic have divergent results. Perhaps due to different treatment regimen schemes or other confounding factors, such as multiple anti-VEGF being used previous to the switch.

Our goal was to evaluate the functional and anatomic outcomes in eyes with persistent DME who were switched from ranibizumab to aflibercept in a pro re nata (PRN) regimen.

Methods

A retrospective, consecutive case series of eyes of patients treated for persistent DME was performed. This study followed the tenets of the Declaration of Helsinki.

Eligible participants were 18 years of age or older, with a history of diabetes mellitus (type 1 or type 2) and baseline evidence of clinically significant macular edema as defined by the ETDRS group [8]. Exclusion criteria included patients having received fewer than 3-monthly ranibizumab injections prior to switch to aflibercept and complications such as tractional retinal detachment, vitreous hemorrhage, the need for vitreoretinal surgery and loss of follow-up.

Eyes of patients with DME that were treated with at least three intravitreal injections of ranibizumab (0.5 mg) and with at least three intravitreal injections of aflibercept (2.0 mg) thereafter, between January 2015 and May 2018 were included.

Persistent DME was defined as no reduction, incomplete resolution, or an increase in central thickening by Spectral Domain Optical Coherence Tomography (SD OCT), in need of additional anti-VEGF therapy by the time of conversion. Indications for switching to aflibercept included persistent exudative fluid on SD OCT, determined as a reduction of less than 10% in the CRT or persistent cysts. Aflibercept was administered on a PRN regimen following the loading dose (three injections, 4 - 6 weeks apart).

Best corrected visual acuity (BCVA) in ETDRS letters and central retinal thickness as the central 1 millimeter macular subfoveal thickness (CRT) were recorded at baseline, after the loading dose and 6 months.

Pertinent patient demographic, examination and treatment data were recorded.

Statistical Analysis

Data were collected and transferred to SPSS® (SPSS® for Windows, IBM SPSS Statistics V22). Data were expressed as mean ± standard deviation. Statistical analysis was performed using a Wilcoxon signed-ranked test within the overall population. In the sub analyses, a nonparametric Mann-Whitney test was used. P values of less than 0.05 were regarded as statistically significant.

Results

Thirty-seven eyes of twenty-seven patients were included. Mean age was 61.4 ± 9.3 years. Eyes were given a mean of 7.1 ± 3.5 ranibizumab (RNB) injections prior to conversion. Clinical and ocular characteristics are further described in table 1.

Age Mean **±** SD (years)	 61.4 **±** 9.3
Sex Male Female	 17 10
Duration of known diabetes Mean **±** SD (years)	 11.6 ± 8.3
Type II diabetes/Type I diabetes	36/1
Hemoglobin A1c level Mean **±** SD (%)	 7.4 ± 1.2
Diabetes treatment Oral antidiabetics (n) Oral antidiabetics + Insuline (n)	 14 13
Number of anti-VEGF injections preswitch Mean **±** SD (n)	 7.1 ± 3.5
Baseline BCVA Mean **±** SD (ETDRS letters)	 65.1 ± 11.7
Baseline CRT Mean **±** SD (µm)	 434.2 ± 128.2

Table 1: *Demographics and Ocular characteristics of patients at baseline (n=37)*

Anti-VEGF: Anti-Vascular Endothelial Growth Factor; BCVA: Best-Corrected Visual Acuity; CRT: Central Retinal Thickness.

After the loading dose with aflibercept, from three months (M3) to six months (M6), eyes received a mean of 1.5 ± 1.1 injections. The mean BCVA at the pre-switch visit was 65.1 ± 11.7 letters. After the loading dose of aflibercept, BCVA improved to 68.6 ± 12.6 letters ($p < 0.05$). The mean CRT at the pre-switch visit was 434.2 ± 128.2 µm and it significantly improved to 372.2 ± 99.4 µm ($p < 0.05$) after the loading dose (Figure 1).

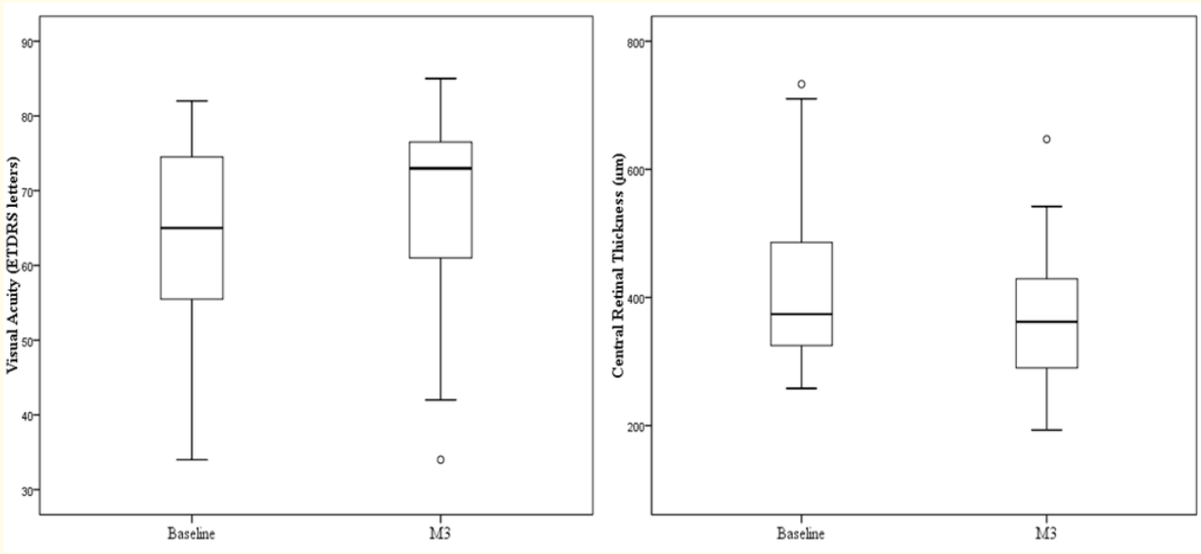

Figure 1: *Mean best-corrected visual acuity (BCVA) and mean central retinal thickness (CRT) at baseline visit and after three injections of aflibercept (n = 37). Box plots representing the distribution of data from bottom to top: minimum, first quartile, median, third quartile and maximum. The difference between BCVA and CRT at baseline and after the loading dose was statistically significant. p < 0.05 (Wilcoxon signed-rank test).*

A total of 24 eyes were followed for 6 months after switching. The mean BCVA increased from 62.9 ± 12.3 to 64.7 ± 11.1 letters at 6 months ($p > 0.05$) and CRT decreased from 472.2 ± 133.7 µm to 416.5 ± 124.3 µm ($p > 0.05$) (Figure 2).

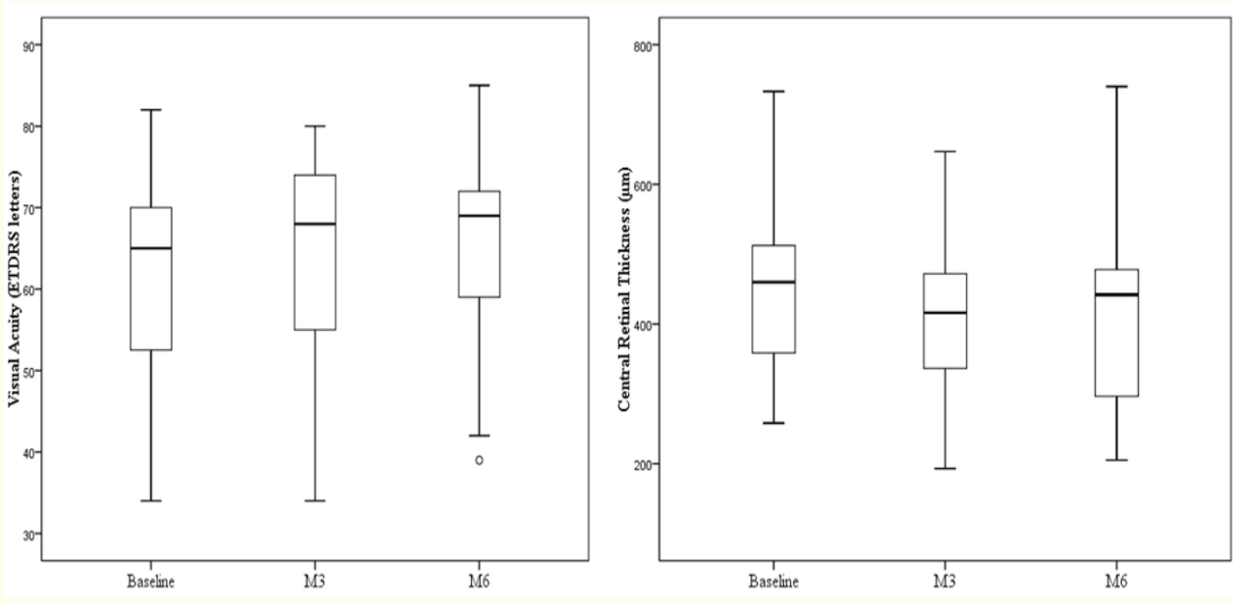

Figure 2: *Mean best-corrected visual acuity (BCVA) and mean central retinal thickness (CRT) at baseline visit, at 3 months and at 6 months follow-up (n = 24). Box plots representing the distribution of data from bottom to top: minimum, first quartile, median, third quartile and maximum. The difference in BCVA and CRT at baseline and at six months was not significant. p > 0.05 (Wilcoxon signed-rank test).*

Eleven eyes (30%) had an epiretinal membrane without significant vitreofoveal or vitreomacular traction. Nine eyes (24%) had performed panretinal photocoagulation (PRP) before or during the aflibercept intravitreal treatment.

As shown in table 2, the eyes that had received seven or more intravitreal injections (18 eyes, 51%) before switching, showed no significant differences ($p > 0.05$) regarding BCVA and CRT after the switch in comparison with the eyes that received less than 7 injections prior switching. The group of eyes that had an epiretinal membrane (11 eyes, 30%) showed no statistical significant difference in BCVA and CRT after the loading dose respecting the rest of the group ($p > 0.05$) The group of eyes that had had panretinal photocoagulation (9 eyes, 24%) before or during treatment had worse BCVA after the loading dose ($p < 0.05$) but there was no significant difference in CRT in these two groups ($p > 0.05$). Figure 3 shows a macular OCT of an eye before switching to aflibercept, and after the first injection with aflibercept, in a good responder.

Treatment/Condition	N/mean ± SD	Comparison of groups: BCVA and CRT
Ranibizumab intravitreal injections (mean ± SD)	7.1 ± 3.5	
≥ 7 injections	18	$p > 0.05$*
< 7 injections	19	
PRP before and during follow-up (n)		
PRP	9	$p < 0.05$* BCVA
Non-PRP	28	$p > 0.05$* CRT
ERM (without significant traction) (n)		
ERM	11	$p > 0.05$*
Non-ERM	26	

Table 2: *Other concomitant conditions and Diabetes related treatments prior and during follow-up.*

*PRP: Panretinal Photocoagulation; ERM: Epiretinal Membrane; BCVA: Best-Corrected Visual Acuity. The group that had had panretinal photocoagulation had inferior BCVA after three months, but there was no significant difference in CRT between the two groups. There were no significant differences in any other group in BCVA and CRT.*Statistical significance in these sub analyses was assessed with a Mann-Whitney U test.*

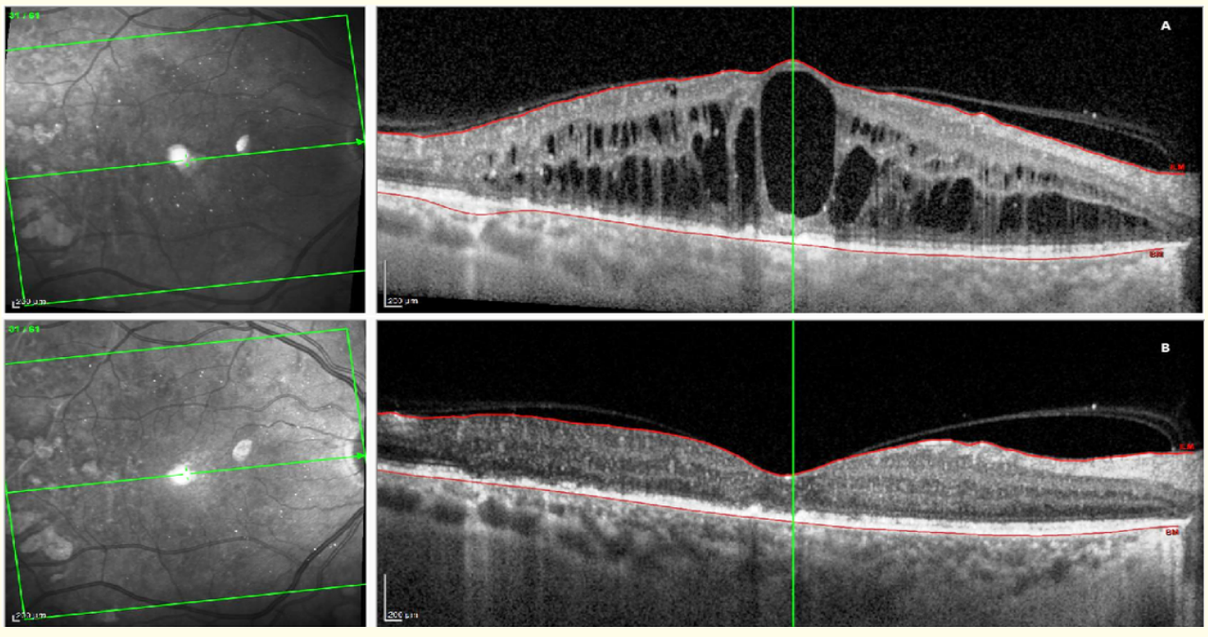

Figure 3: *Macular SD-OCT of a persistent DME patient treated with ranibizumab intravitreal injections showing diffuse cystoid macular edema with loss of ellipsoid zone (A) and marked decrease in central retinal thickness after one injection of aflibercept (B).*

Discussion

The 1 year results of the DRCR.net Protocol T [7] demonstrated that in the subgroup of patients with baseline VA of 20/50 or worse and in patients with thicker maculae at baseline, aflibercept was superior to ranibizumab. This difference was not maintained at 2 years. After a poor or incomplete response to intravitreal treatment with ranibizumab, the clinician may decide to change to aflibercept, taking into account the greater affinity of aflibercept to VEGF-A (x 100), and the additional binding of VEGF-B and placental growth factor (PIGF) [9].

Recently, the DRCR net group (Protocol I) [10] suggested continuing treatment with injections every 4 weeks, up to 20 weeks, if DME persisted after 12 weeks of monthly treatment. In our study, anatomical and functional results after the initial dose of aflibercept were favorable, with an increase in BCVA and a decrease in CRT. However, in the twenty-four eyes that were followed for six months, there was not a significant alteration in the mean baseline BCVA or in the decrease of the mean CRT.

Our results at the end of three months are in line with other case series [11-14]. Lim and colleagues [11] conducted a study with 21 eyes, where they obtained an anatomical and functional improvement with a median follow up time of 5 months, after conversion to aflibercept, with an average interval between injections of 2.4 ± 2.2 months; Mira., *et al*. [12] showed an increase in BCVA and decrease of CRT, after three monthly aflibercept injections, and Nixon., *et al.* [13], in 2018, noted improvements in these two parameters after 5 aflibercept monthly injections, in 50 eyes.

Laiginhas., *et al*. [14] reported an improvement in mean VA from 0.55 ± 0.32 to 0.46 ± 0.33 logMAR and mean CMT decrease from 473 ± 146 to 349 ± 85 μm after switching to aflibercept. This retrospective study included eyes that had had a mean of 2.2 ± 0.9 aflibercept injections after a minimum of 3 bevacizumab injections and VA and CMT data were collected 3 - 4 weeks after the last aflibercept injection. Mean follow-up time was 2.4 ± 2.1 months after conversion.

The fact that Lim and Laiginhas., *et al.* [11,14], had patients with prior treatment with ranibizumab and bevacizumab, and Mira and Nixon., *et al.* [12,13] had fixed monthly schemes of aflibercept injections could explain the differences with our study.

Herbaut., *et al.* [15], with a treatment regimen similar to ours, has demonstrated a functional and anatomical improvement in eyes with persistent DME previously treated with ranibizumab or/and a dexamethasone implant, at six months.

The improvement in BCVA and decrease in CRT after conversion to aflibercept is not consensual, as demonstrated by Rahimy., et al. [16] in 2016, when treating 50 eyes, which had been previously injected with a mean of 13 injections of ranibizumab and bevacizumab. With a mean of 4.1 ± 1.7 injections during 4.6 ± 1.7 months, visual acuity increased, but it did not alter significantly, while CMT decreased.

In the subgroup of patients who underwent PRP before or during treatment, visual acuity results were inferior in our study. It is known that patients with proliferative diabetic retinopathy (PDR) treated with PRP develop macular edema and that patients with clinically significant macular edema worsen after the PRP. Visual field sensitivity changes are also associated with PRP. Foveal and parafoveal thickening might be the causes of this dysfunction [17,18].

We believe that the exclusive use of ranibizumab, as anti-VEGF, prior to conversion and the fact that all patients were treated with the PRN regimen after the initial dose may help shed some light on this topic. Our results report an improvement in the mean BCVA and decrease in the mean CRT after the initial dose, but these changes do not stand significant at 6 months. The PRN treatment scheme could be a reason for these results, especially if we take into account Protocol I from the DRCR net group, which suggests 5 to 6 intravitreal injections in a DME that persists at 12 weeks of treatment.

Limitations inherent to this study are its retrospective design with lack of control group, small sample and the enrollment of both eyes. There was no washout period between the two periods of treatment, therefore, carryover effects may still be present and represent a bias to data interpretation. A "ceiling effect" might also play a part in our results regarding visual acuity.

We would like to point out that although there was an anatomical improvement after the switch to aflibercept, unresolved macular edema was still present, indicating that further treatment was required. In this sense, it is important to remember that true superiority of one drug over another, should be based on results that imply disease decline or stagnation. Further follow up with enrollment of more eyes will probably yield more statistically significant data.

Conclusion

Switching to aflibercept for persistent DME seemed to result in a significant CRT reduction and significant improvement in visual acuity after the loading dose of aflibercept, and though there was an increase in BCVA and CRT at 6 months, it was not significant.

Acknowledgements

We would like to thank the team of orthoptists from the Ophthalmology Department in Leiria Hospital Center, for performing the OCT exams in all patients. All the authors have read and approved the final manuscript. The authors have declared that no competing interests exist.

Compliance with Ethical Standards

All authors declare no conflict of interest. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institution and with the 1964 Helsinki declaration and its later amendments.

Bibliography

1. Lee R., *et al*. "Epidemiology of diabetic retinopathy, diabetic macular edema and related vision loss". *Eye and Vision* 2 (2015): 17.
2. Osaadon P., *et al*. "A review of anti-VEGF agents for proliferative diabetic retinopathy". *Eye (London)* 28.5 (2014): 510-520.
3. Do DV., *et al*. "One-year outcomes of the DA VINCI study of VEGF trap-eye in eyes with diabetic macular edema". *Ophthalmology* 119.8 (2012): 1658-1665.
4. Do DV., *et al*. "The DA VINCI Study: phase 2 primary results of VEGF Trap-Eye in patients with diabetic macular edema". *Ophthalmology* 118.9 (2011): 1819-1826.
5. Do DV., *et al*. "An exploratory study of the safety, tolerability and bioactivity of a single intravitreal injection of vascular endothelial growth factor Trap-Eye in patients with diabetic macular oedema". *British Journal of Ophthalmology* 93.2 (2009): 144-149.
6. Nguyen QD., *et al*. "Ranibizumab for diabetic macular edema: results from 2 phase III randomized trials: RISE and RIDE". *Ophthalmology* 119.4 (2012): 789-801.
7. Diabetic Retinopathy Clinical Research Network., *et al*. "Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema". *New England Journal of Medicine* 372.13 (2015): 1193-1203.
8. "Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study report number 1. Early Treatment Diabetic Retinopathy Study research group". *Archives of Ophthalmology* 103.12 (1985): 1796-1806.
9. Papadopoulos N., *et al*. "Binding and neutralization of vascular endothelial growth factor (VEGF) and related ligands by VEGF trap, ranibizumab and bevacizumab". *Angiogenesis* 15.2 (2012): 171-185.
10. Bressler SB., *et al*. "Persistent Macular Thickening After Ranibizumab Treatment for Diabetic Macular Edema With Vision Impairment". *JAMA Ophthalmology* 134.3 (2016): 278-285.
11. Lim LS., *et al*. "Conversion to aflibercept for diabetic macular edema unresponsive to ranibizumab or bevacizumab". *Clinical Ophthalmology (Auckland, NZ)* 9 (2015): 1715-1718.
12. Mira F., *et al*. "Switch to Aflibercept in Diabetic Macular Edema Patients Unresponsive to Previous Anti-VEGF Therapy". *Journal of Ophthalmology* (2017): 5632634.
13. Nixon DR and Flinn NA. "Evaluation of contrast sensitivity and other visual function outcomes in neovascular age-related macular degeneration patients after treatment switch to aflibercept from ranibizumab". *Clinical Ophthalmology (Auckland, NZ)* 11 (2017): 715-721.
14. Laiginhas R., *et al*. "Aflibercept in diabetic macular edema refractory to previous bevacizumab: outcomes and predictors of success". *Graefe's Archive for Clinical and Experimental Ophthalmology* 256.1 (2018): 83-89.

15. Herbaut A., *et al*. "Switching to Aflibercept in Diabetic Macular Edema Not Responding to Ranibizumab and/or Intravitreal Dexamethasone Implant". *Journal of Ophthalmology* (2017): 8035013.

16. Rahimy., *et al*. "Conversion to Aflibercept After Prior Anti-VEGF Therapy for Persistent Diabetic Macular Edema". *American Journal of Ophthalmology* 164 (2016): 118-127.

17. McDonald HR and Schatz H. "Visual loss following panretinal photocoagulation for proliferative diabetic retinopathy". *Ophthalmology* 92.3 (1985): 388-393.

18. Shimura M., *et al*. "Visual dysfunction after panretinal photocoagulation in patients with severe diabetic retinopathy and good vision". *American Journal of Ophthalmology* 140.1 (2005): 8-15.

Volume 10 Issue 2 February 2019