Comprasion of aflibersept and ranibizumab response in patients with DMO unresponsive to bevacizumab treatment: early versus late switch

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ABSTRACT

Purpose: We aimed to compare the anatomical and functional effects of aflibersept or ranibizumab in diabetic macular edema (DME) cases with non-responsiveness to bevasizumab.

Material and Methods: A retrospective study involving 95 eyes of 65 patients with DME previously treated with bevacizumab. Patients were switched either to ranibizumab or aflibercept. Detailed ophthalmological examination, best-corrected visual acuity (BCVA), and optical coherence tomography (OCT) (Spectralis; Heidelberg Engineering, Heidelberg, Germany) were performed on the first visit, pre-switch visit and final visit.

Results: Ninety five eyes of 65 patients were included in the study, of whom 40 patients (62 eyes) were switched to aflibercept and 25 patients (33 eyes) were switched to ranibizumab. Post-switch, there was a statistically significant improvement in the BCVA in both groups (aflibercept and ranibizumab). In addition, there was a statistically significant decrease in the central macular thickness (CMT) in both groups. There was no significant difference with regard to the change in macular thickness, OCT biomarkers or BCVA between the aflibercept and ranibizumab groups. In the subgroup analysis, the change in mean BCVA was significantly higher in the patients in the early switched group than the patients in the late switched group.

Conclusion: Significant anatomical and functional improvement was observed with ranibizumab and aflibercept treatments in DME patients who were non-responsive to bevasizumab. Early switching therapy may contribute to better visual outcomes than late switching therapy.

Key words: Aflibersept, Ranibizumab, Diabetic Macular Edema, Early Switch, Late Switch.

INTRODUCTION

Diabetic retinopathy (DR) is a neurodegenarative and microangiopathic disease that is the most common complication of diabetes mellitus in the adult working population. DR is divided into two groups; non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR) with or without diabetic macular edema (DME).[1] DME is among the most frequent causes of decreased visual acuity characterized by swelling or thickening of the macula.

Incresaed inflammatory cytokines, leakage of the blood-retinal barrier (BRB), dysfunction of müller cells and retina pigment epithelium involves in the complex pathophsiology of DME.[2] Oxidative stress and apoptosis in the DR cause microglial activation and aggravate vascular damage. Microglia proliferate and migrate from the inner to outer retina, and secrete multiple inflammatory cytokines. These may increase vascular permeability and induce intraretinal fluid accumulation by disrupting tight junction proteins and triggering breakdown of BRB.[3] Vascular endothelial growth factors (VEGFs) are the primary cytokines produced by activated microglias and macrophages that cause BRB leakage.[2] Therefore targeting VEGF (anti-VEGF) has emerged as a first-line therapy

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Received: 01.04.2024
Accepted: 25.07.2024
J Ret-Vit 2024; 33: 226-233
DOI:10.37845/ret.vit.2024.33.37

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at DME. Three anti-VEGF agents are available which are ranibizumab (Lucentis; Genentech, Inc, South San Francisco, CA, USA) (IVR), aflibersept (Eylea; Regeneron, Tarrytown, NY)(IVA) and off-label bevacizumab (Avastin; Genentech, Inc, South San Francisco, CA, USA) (IVB). The lower cost, perceived efficacy, and relative safety of bevacizumab make it a widely accepted treatment option compared to other agents, especially in underdeveloped countries.[3] Although The Protocol T study showed no superiority between those agents, they can be switched from each other in refractory cases.[4]

There are a few reports comparing the short-term effect of early switching to IVA or IVR in the patients who were unreponsive to prior IVB therapy.[3] However, comparison of early and late switching were not studied in those reports. Comparison of early or late switch was investigated only in patients switched to dexamethasone.[5] To the best of our knowledge, this data is lacking in anti-VEGF patients.

In the current study, we aimed to compare the anatomical and functional effects of both IVR and IVA switching in the patients who were refractory to an on-going IVB treatment. Secondly, we aimed to investigate the effect of early versus late switching and OCT biomarkers on the treatment outcomes.

MATERIAL AND METHODS

The protocol of the present study conformed to the Declaration of Helsinki. The ethical approval of the study was obtained from the Institutional Ethical Board of Prof. Dr. Cemil Taşcıoğlu City Hospital in Istanbul, Turkey (4.2022/114). We retrospectively studied diabetic patients with DME who underwent at least three consecutive monthly intravitreal injection of bevacizumab between January 2019 and January 2022 in the Department of Ophalmology, Prof. Dr. Cemil Taşcıoglu City Hospital. The selected patients were over 18 years of age and did not have any other vision-impairing retinal diseases such as retinal vascular occlusion or choroidal neovascularization, history of complicated cataract surgery, trauma, glaucoma, uveitis, having poor quality OCT scans and missed data/ informed consent form in the medical records. Besides, the patients who did not fulfill the inclusion criteria were excluded.

The best-corrected visual acuity, anterior segment biomicroscopy, fundoscopy, intraocular pressure (IOP), Spectral Domain-OCT (SD-OCT) imaging records at each visit, the total follow-up period in months and the total number of each anti-VEGF agent injections were noted from the medical records of the patients.

Among patients with diabetic macular edema, those with a central macular thickness (CMT) of 300 µm and above on SD-OCT (Spectralis, Heidelberg Engineering, Heidelberg, Germany) were included in the study. All the patients were followed with a pro re nata (PRN) regimen. Reinjection criteria were as follows; intraretinal or subretinal fluid with a central macular thickness > 300 µm, residual intra-subretinal fluid and a loss of ≥ 5 letters in the Early Treatment Diabetic Retinopathy Study (ETDRS) score without cataract progression. The patients were divided into two groups regarding to switching agent, either IVA or IVR groups. Further a subgroup analysis were performed according to the swicthing time, early versus late; the patients who were switched after 3 injection was included to early switch group and the patients who were switched after ≥4 injections were included to late switch group. Unresponsiveness to the ongoing IVB therapy was defined as follows; intraretinal or subretinal fluid with a central macular thickness > 300 µm, residual intra-subretinal fluid and a loss of ≥ 5 letters in the ETDRS.

For patients who received one eye treatment with intravitreal aflibersept and the other ranibizumab injection, both eyes were included.

The central macular thickness, types of DME and OCT biomarkers such as the presence of serous macular detachment (SMD), hyperreflective foci (HRF), hard exudate (HE), disoganisation of the retinal inner layers (DRIL), pearl necklace sign, epiretinal membran (ERM) were noted prior to IVB treatment, prior to switching and at final visit. The patients with vitreomacular traction were excluded.

Serous macular detachment is one of the OCT parameters defined as elevation of the retina cause of the edema between retina pigment epitelium and outer neurosensorial retina.[6,7] Also DRIL describe inability of the identify bounderies of the inner layers at OCT. Hyperreflective foci is hyperreflective dots at inner and outer retinal layers with aproximatly 30 μm diameter without back shadowing. Hard exudates those that larger than HF with back shadowing at outer retinal layers.[8] We classified HF under 3 groups as; 1-10; 11-20, ≥21. HEs were noted according to their presence or not. Pearl necklace sign is the name given to the ring-shaped arrangement of hyperreflective dots around the cystoid spaces at outer plexiform layer.[9] ERM is proliferation of the myofibroblastic cells which is overlying internal limitan membrane.[10]

All the intravitreal injections were performed under topical anesthesia. Firstly a lid speculum was used and povidone iodine was applied onto the ocular surface. When have a look at doses of the injections bevasizumab was performed as 1.25 mg, ranibizumab 0.5 mg and aflibersept 2 mg. Injections performed at 3.5 mm posterior to the corneoscleral limbus with a 30G needle. Eyes were closed with sterile eyepad. A topical moxifloxacin 0.5% was prescribed four times daily for 5 days.

All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS, Inc. Chicago, IL, USA), version 26.0. The mean, standard deviation, median, minimum and maximum value frequency, and percentage were obtained as descriptive statistics. Mean and standard deviation (SD) values were calculated for continuous variables, while frequency and percentage were calculated for categorical variables. The normal distribution of the continuous variables was tested using the Shapiro–Wilk test Parametric and nonparametric test were used to compare quantitative variables, and x^2 test was used to compare categorical variables. The results were considered statistically significant when p was less than 0.05.

RESULTS

Total 95 eyes included to this study, including 33 eyes switched to the ranibizumab and 62 eyes switched to the aflibersept. There were 31 (47.6%) female and 34 (52.3%) male patients. The mean initial HbA1c value of the patients was 8.2±1.4%, and 29(44,6%) patients had a diagnosis of systemic hypertension.

A total of 79 pseudophakic eyes of 65 patients were included in this study. When the demographic and clinical features of the patients were examined in all groups and subgroups, there was no statistically significant difference between the groups (p>0.05). Table 1 shows the demographic and clinical characteristics of the patients.

In this study, the patients were divided into two groups. Group 1 consists of patients who were switched to aflibersept after bevacizumab, and the second group consists of patients who switched to ranibizumab. Then, the patients were further divided into subgroups; early and late switch groups. The patients who were switched after a 3 consecutive bevacizumab loading phase were constituted early switch group. While the patients who were switched after a 6 consecutive bevacizumab injections were constituted the late switch group.

Follow-up times were 23.7±11.7 months at ranibizumab group and 25.7±11.4 month at aflibercept. Mean number of bevacizumab injection is 3.11±0.32 at ranibizumab group and 4.44±1.63 at aflibersept group. After switching the mean number of ranibizumab injection is 3.83±3.18 and mean number of aflibersept injection 3.55±2.29.

The mean baseline CMT was 447,5±121.2 µm, the mean preswitch CMT was 406,6±117,3 µm and final CMT was 344.4±100,3 µm at group 1; for group 2 mean baseline CMT was 396,3±142,1 µm, the mean preswitch CMT was 404,8±129,1 µm, final CMT was 330,1±71.5 µm. which was statistically significant for both groups (p=0.009). There is no statistically significant differences between two groups (p=0.381). The distribution of mean CMTs over time among groups is shown in Figure 1.

The mean baseline BCVA was 0.61±0.45 logMAR, the mean baseline preswitch BCVA was 0.58±0.44 logMAR and the mean final BCVA was 0.50±0.46 logMAR (20/80), which was statistically significant for aflibersept group (p=0.009). The mean baseline BCVA was 0.62±0.51 logMAR, the mean baseline preswitch BCVA was 0.61±0.43 logMAR and the mean final BCVA was 0.35±0.48 logMAR (20/80), which was statistically significant for group 2 (p=0.009). There is no statistically significant differences between two groups (p=0.228). The distribution of mean BCVA over time among groups is shown in Figure 2.

Table 1: *Demographic and clinical characteristics of the aflibersept and ranibizumab patients*

	IVA Group	IVR Group	P
Age (years ± SD)	63.4 ± 8.71	63.2 ± 8.72	0.946
Gender (female/male)	22 (55%)/18 (45%)	14 (56%)/11 (44%)	0.432
Side (right/left)	25/15	14/11	0.742
Duration of DM (years ± SD)	14.6± 5.27	12.9 ± 5.13	0.200
Hypertension (N[%])	15 (37,5%)	14 (56%)	0.314
CMT Prior to Treatment (µm)	447.5 ± 121.2 µm	396.38 ± 142.12 µm	0.381
BCVA Prior to Treatment (µm)	0.61 ± 0.45 loMAR	0.62 ± 0.51 logMAR	0.228

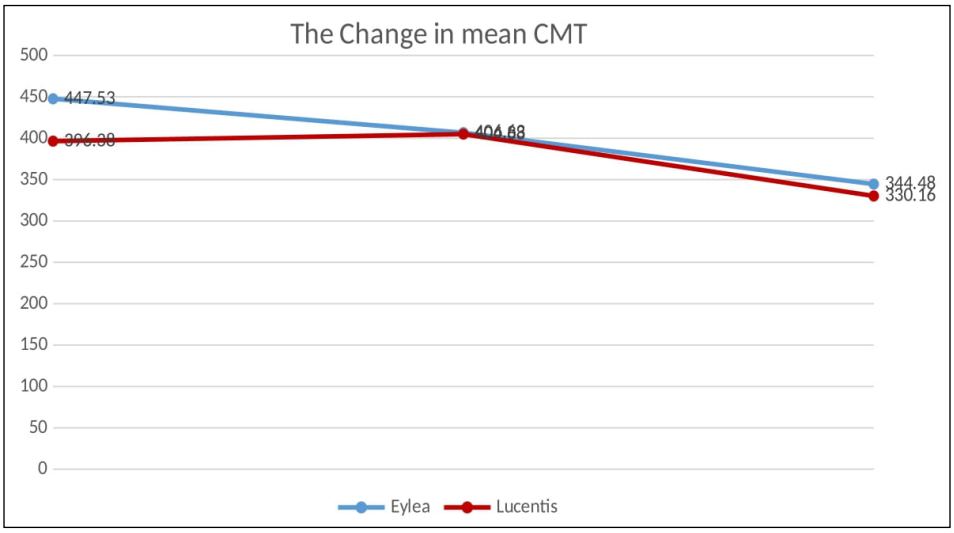

Figure 1: *The distribution of mean CMTs over time among groups.*

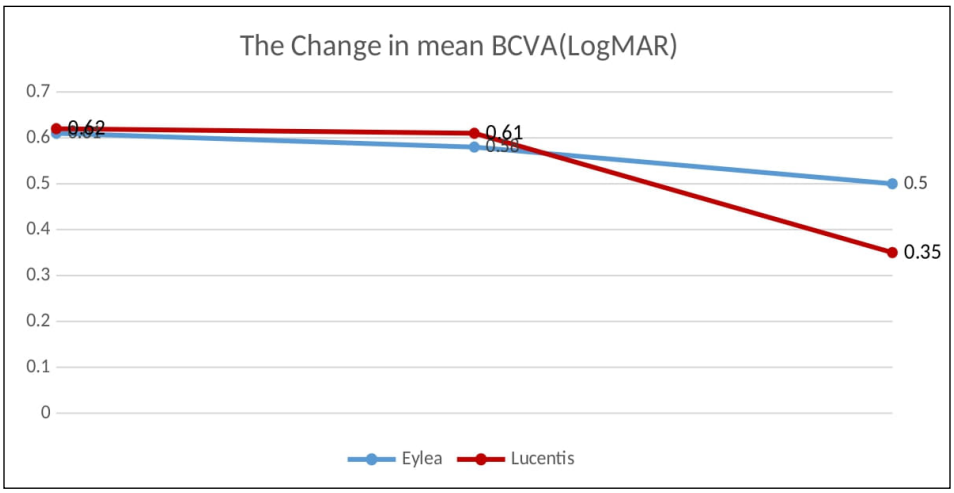

Figure 2: *The distribution of mean BCVA over time among groups.*

There are no statistically significant differences was detected between the two groups regarding to the OCT biomarkers throughout the study period. The changes in OCT biomarkers over time are summarized in Figure 3-4-5-6-7.

The initial BCVA, the presence of HE and the mean injection numbers were good predictors of final visual acuity.

No cerebrovascular disease or myocardial infarction occured during follow-up time. There were no statistically significant difference between the groups in terms of intraocular pressure(IOP) and lens status (p=0,281, p=0,354).

In the subgroup analysis, the change in mean BCVA was significantly higher in the patients in early switched group than the patients in late switch group (p<0.019) while the patients did not achieve any BCVA gain in late switch group, the patients in the early switch group achieved BCVA gain significntly (p=0.031). The changes in BCVA overtime in subgroups are summarized in Figure 8.

In our study, post hoc power analysis was performed using the G*power 3.1 program (Universität Düsseldorf). When the effect size is accepted as: 0.25 and alpha error: 0.05, the power value is calculated as 83.9%.

DISCUSSION

In the present retrospective comparative study, we evaluated the effectiveness of switching from bevacizumab to ranibizumab or aflibercept in eyes with DME refractory to bevacizumab. No significant differences were observed between groups; both anatomical and functional improvements were similar with ranibizumab and afibercept in persistent DME non responsive to bevacizumab. The switch agents are not superior to each

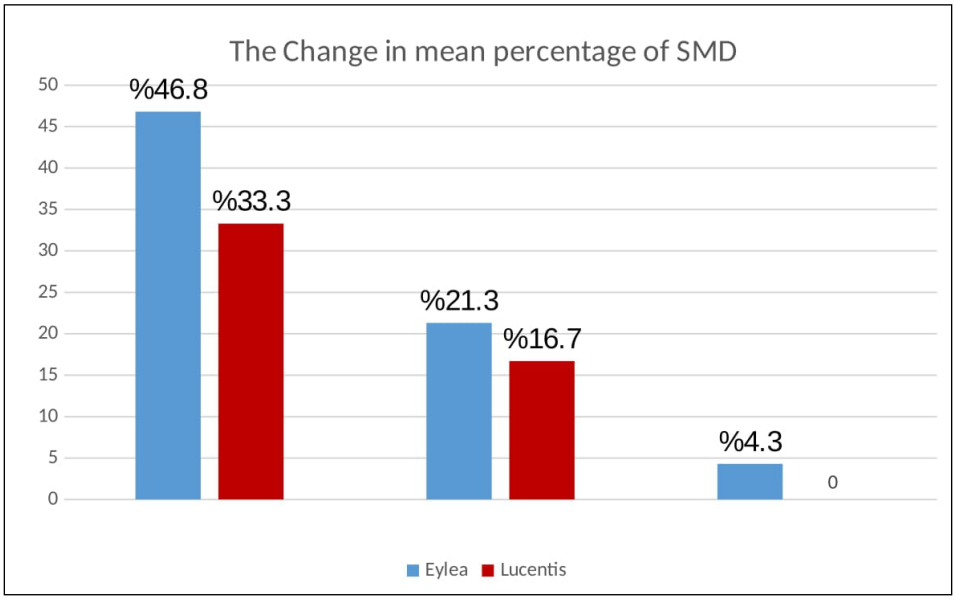

Figure 3: *The distribution of mean percentage of SMD over time among groups.*

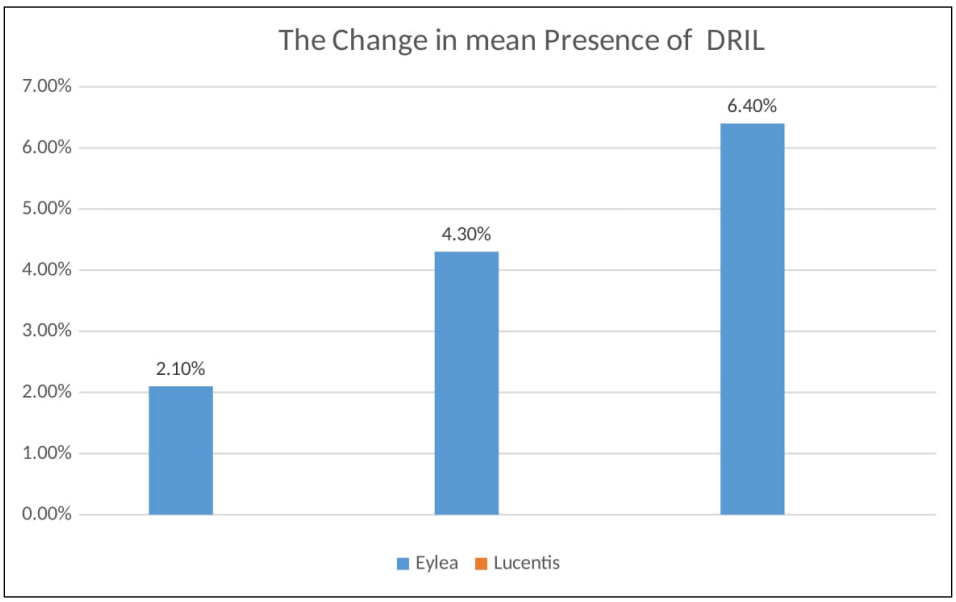

Figure 4: *The distribution of mean presence of DRIL over time among groups*

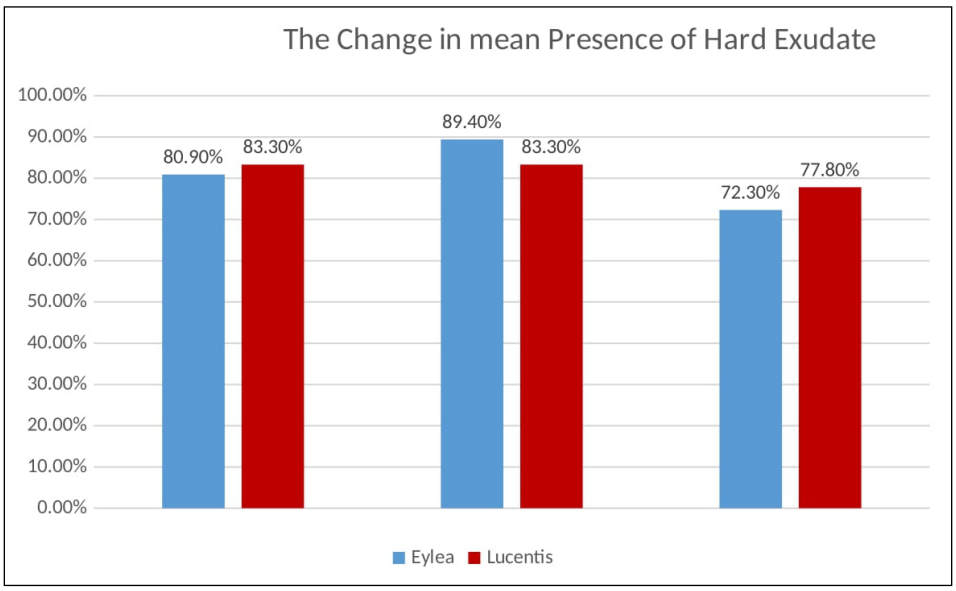

Figure 5: *The distribution of mean presence of hard exudate over time among groups.*

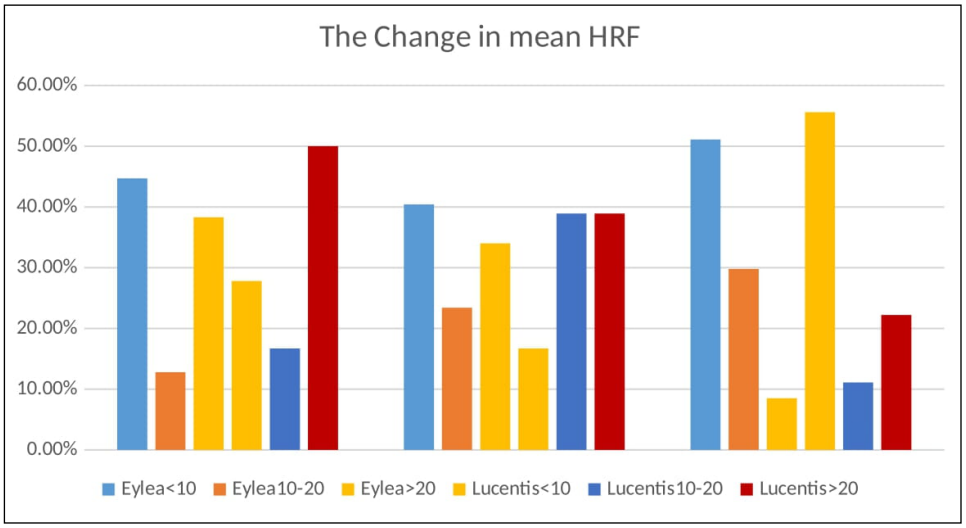

Figure 6: *The distribution of mean HRF over time among groups*

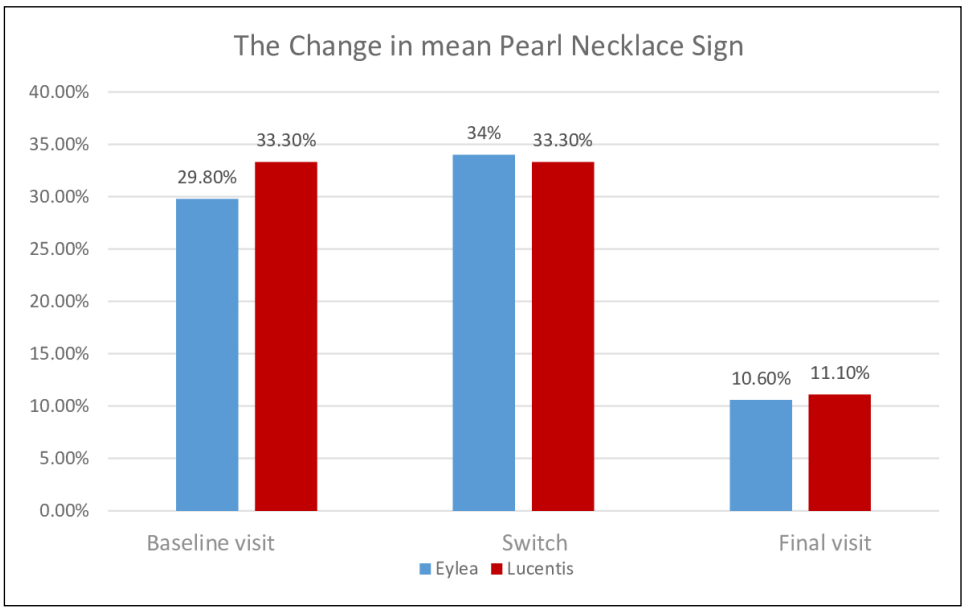

Figure 7: *The distribution of mean pearl necklace sign over time among groups.*

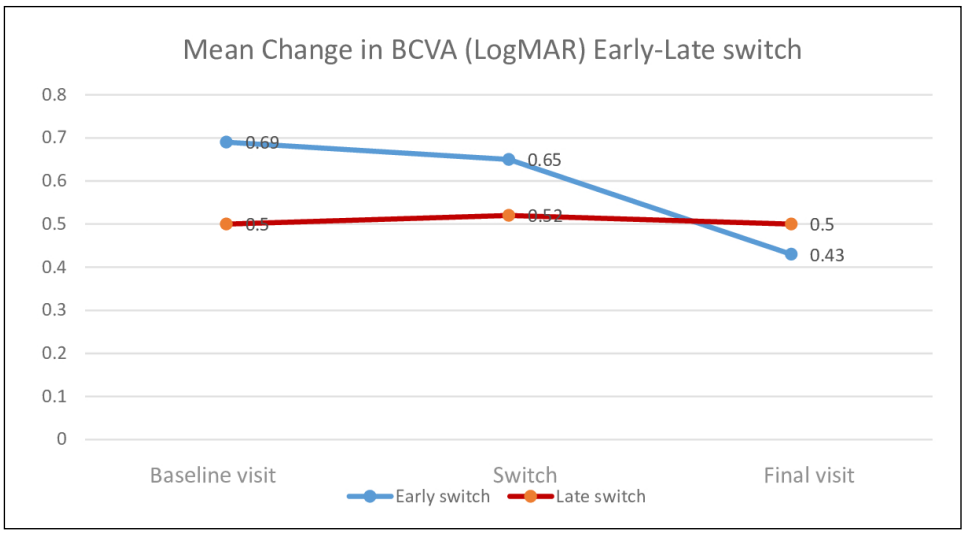

Figure 8: *Mean change in BCVA over time at early versus late switch groups.*

other. This is similar outcomes to Protocol T which is the only head to head study comparing effects of three anti-VEGF agents in DME.[4] Additionally, in this study, unlike Protocol T, we compared the two groups also with the findings of OCT biomarkers. While in Protocol T, it was shown that there was no significant difference between the groups only in terms of BCVA and CFT, we also found that there was no significant difference between the OCT biomarkers. Also similar to our study Pessoa et al. evaluated switch groups including examination of OCT biomarkers.[3] Unlike our study, Pessoa et al.[3] found that ranibizumab was superior to aflibercept in terms of BCVA gain. In their study, the only difference between the groups in the baseline characteristics was that the number of eyes without DRIL was higher in the ranibizumab group, and they associated the BCVA gain superiority of ranibizumab to aflibercept with the absence of DRIL. In our study thereis no such differences.

On the other hand, when we looked at the early and late switch groups as subgroup analysis, there is BCVA gain differences between groups, with only a statistically significant improvement in the early switch group. Similar outcomes have been described by Ataş et al. who reported that early switching therapy may contribute to better visual and anatomical outcomes.[11] In another retropective study Ashraf et al. also examined early switching from bevasizumab to aflibersept or ranibizumab and they found statistically significant improvement at BCVA in two groups.[12] In our study, addition to these studies, early versus late switch were also compared and the superiority of early switch to late switch was demonstrated in terms of BCVA gain. However, the aferomentioned studies did not have a late swtich group as a control group. So that, to the best of our knowledge this is the one of the only study with comparing ealy versus late switch at anti-VEGF agents. Ramsey at all compare early versus late switch IVB or IVR to IVA.[13] In their study patients who switch to aflibersept is only patients who maintained VA gains until the end of the follow ups. They associated early switch to less structural defect to the foveal center and lower cost of treatments.

Limitations of this study was mainly being retrospective, non-randomized study. But as it is known, real-life studies can be valuable in terms of reflecting real-life data. However, including as many patients as possible, using the same oct device in follow-ups, and ensuring that follow-ups are performed by the same physicians can compensate for these limitations.

This study also has strengths; Our results revealed that early switch was more effective on BCVA gain and more successful in functional results than late switch. Additionally, our study showed that there was no difference between aflibercept and ranibizumab when compared in terms of anatomical and functional gains. We believe that the results of our study will contribute to both our daily practice and the literature by effectively increasing treatment success with early switch decisions with both agent.

REFERENCES

1. Teo ZL, Tham YC, Yu M, et al. Global Prevalence of Diabetic Retinopathy and Projection of Burden through 2045: Systematic Review and Meta-analysis. Ophthalmology 2021;128:1580-1591. https://doi.org/10.1016/j.ophtha.2021.04.027
2. Qaum T, Xu Q, Joussen AM, et al. VEGF-initiated blood-retinal barrier breakdown in early diabetes. Invest Ophthalmol Vis Sci 2001;42:2408-2413.
3. Pessoa B, Malheiro L, Carneiro I, et al. Intravitreal Ranibizumab or Aflibercept After Bevacizumab in Diabetic Macular Edema: Exploratory Retrospective Analysis. Clin Ophthalmol 2021;15:253-260. https://doi.org/10.2147/OPTH.S280644
4. Cai S, Bressler NM. Aflibercept, bevacizumab or ranibizumab for diabetic macular oedema: recent clinically relevant findings from DRCR.net Protocol T. Curr Opin Ophthalmol 2017;28:636-643. https://doi.org/10.1097/ICU.0000000000000424
5. Ruiz-Moreno JM, Ruiz-Medrano J. Early-switch versus late-switch in patients with diabetic macular edema: a cost-effectiveness study. Graefes Arch Clin Exp Ophthalmol 2023;261:941-949. https://doi.org/10.1007/s00417-022-05892-3
6. Gaucher D, Sebah C, Erginay A, et al. Optical coherence tomography features during the evolution of serous retinal detachment in patients with diabetic macular edema. Am J Ophthalmol 2008;145:289-296. https://doi.org/10.1016/j.ajo.2007.09.029
7. Markan A, Agarwal A, Arora A, Bazgain K, Rana V, Gupta V. Novel imaging biomarkers in diabetic retinopathy and diabetic macular edema. Ther Adv Ophthalmol 2020;12:2515841420950513. https://doi.org/10.1177/2515841420950513
8. Suciu CI, Suciu VI, Nicoara SD. Optical Coherence Tomography (Angiography) Biomarkers in the Assessment and Monitoring of Diabetic Macular Edema. J Diabetes Res 2020;2020:6655021. https://doi.org/10.1155/2020/6655021

9. Gelman SK, Freund KB, Shah VP, Sarraf D. The pearl necklace sign: a novel spectral domain optical coherence tomography finding in exudative macular disease. Retina 2014;34:2088-2095. https://doi.org/10.1097/IAE.0000000000000207

10. Fung AT, Galvin J, Tran T. Epiretinal membrane: A review. Clin Exp Ophthalmol 2021;49:289-308. https://doi.org/10.1111/ceo.13914

11. Ataş M, Ozsaygılı C, Bayram N, Unal S. Retrospective analysis of the efficacy of early switching from bevacizumab to aflibercept or ranibizumab in diabetic macular edema. Eur J Ophthalmol 2023;33(2):1132-1139. https://doi.org/10.1177/11206721221137164

12. Ashraf M, Souka AA, ElKayal H. Short-Term Effects of Early Switching to Ranibizumab or Aflibercept in Diabetic Macular Edema Cases With Non-Response to Bevacizumab. Ophthalmic Surg Lasers Imaging Retina 2017;48:230-236. https://doi.org/10.3928/23258160-20170301-06

13. Ramsey DJ, Poulin SJ, LaMonica LC, et al. Early Conversion to Aflibercept for Persistent Diabetic Macular Edema Results in Better Visual Outcomes and Lower Treatment Costs. Clin Ophthalmol 2021;15:31-39. https://doi.org/10.2147/OPTH.S286665