Effect of switching treatment to ranibizumab or aflibercept for diabetic macular edema in patients refractory to bevacizumab

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Objectives: To study best corrected visual acuity (BCVA) and central subfield thickness (CST) changes after switching to ranibizumab or aflibercept in patients with diabetic macular edema who are unresponsive to treatment with bevacizumab.

Design: Retrospective study

Methods: Patients at a retina clinic, ophthalmology department, Thammasat University Hospital in 2020 were included. The selected samples in this study were 40 diabetic macular edema patients who were unresponsive to bevacizumab treatment and switched to ranibizumab or aflibercept.

Main outcome measures: The primary endpoint outcomes were mean changes from baseline in BCVA and CST at 1 year after switching to ranibizumab or aflibercept.

Results: The forty eyes of 40 patients were included in the study, of whom 19 patients were switched to ranibizumab and 21 patients were switched to aflibercept. Post-switch, there was a statistically significant improvement in the CST in both ranibizumab and aflibercept groups. In addition, the patients who switched from bevacizumab to ranibizumab or aflibercept had improvement in BCVA but there were no statistically significant changes.

Conclusions: One-year results suggest switching to intravitreal ranibizumab and aflibercept in patients who are nonresponsive to bevacizumab are effective in improving central subfield thickness in DME patients.

Keywords: Diabetic macular edema, Refractory to Bevacizumab

EyeSEA 2021;16(1):104-114

DOI: https://doi.org/10.36281/2021010211

Introduction

Diabetic macular edema (DME) is the primary cause of diabetic retinopathy (DR) that results in decreased visual acuity.[1] This is because people with diabetes have abnormally high blood sugar levels and the capillaries will be degenerated throughout the body including retinal blood vessels. Blood and other substances will leak out of the blood vessels, resulting in diabetic retinopathy. In the early stages, the patient may not feel any abnormalities. If the disease progresses, it may be a microaneurysm and/or intraretinal hemorrhage on the retina. If vascular leakage occurs, it induces vascular endothelial growth factor (VEGF) secretion. VEGF levels are associated with macular edema. Therefore, diabetic macular edema (DME) is the leading cause of reduced visual acuity in diabetic retinopathy (DR) patients.[2]

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Received : March 1, 2021
Accepted : March 10, 2021
Published : June 30, 2021

According to the DME test and diagnosis, fundus examination is an essential diagnosis method. The optical coherence tomography (OCT) is non-invasive to diagnose DME. It was found that OCT could be used for treatment planning or post-treatment evaluation. The characteristics in DME from OCT can be found as follows: diffuse retinal thickening, cystoids macular edema, serous retinal detachment and vitreomacular interface abnormalities.[2]

For DME treatments, the standard treatment before the anti-VEGF era were LASER treatment and/ or Grid macular photocoagulation studied by Early Treatment Diabetic Retinopathy Study (ETDRS).[3] But currently, the DME treatment has changed to be intravitreal vascular endothelial growth factor inhibitors (VEGF-inhibitors) which categorizes as first line treatment in patients for central involved DME. VEGF-inhibitors are effective in inhibiting neovascularization. The current-used VEGF-inhibitors are 3 characteristics as follows: bevacizumab (Avastin®), ranibizumab (Lucentis®) and aflibercept (Eylea®). It can treat neovascular aged-macular degeneration (AMD), DME and retinal vein occlusion with macular edema. Intravitreal ranibizumab (Lucentis®) is an anti-VEGF (VEGF inhibitor) that has been approved for the treatment of DME,[4] neovascular AMD[5-7] and retinal vein occlusion with macular edema effectively.[5] Bevacizumab was approved for treating metastatic colorectal cancer as an intravenous drug. In 2004, bevacizumab was used for the first time in ophthalmology. It was off-label use in neovascular AMD.[8-9] There was reduced macular edema and improved visual acuity significantly.[8]

Some study showed that bevacizumab and ranibizumab are not different in efficacy.[10-14] Protocol T found that bevacizumab, ranibizumab and aflibercept responded to treatment with improved visual acuity and decreased number of injections in the second year of the study. In other words, the group with VA 20/32 - 20/40 visual acuity outcomes were not different. However, the group with VA was worse than 20/50, it was found that aflibercept had greater visual acuity gain and CST decreased when compared with ranibizumab and bevacizumab significantly.[15]

Moreover, bevacizumab is 30 times cheaper than ranibizumab in Thammasat university hospital. (bevacizumab costs around 1,000 + baht and ranibizumab costs around 30,000 + baht) As result, bevacizumab is the priority beyond ranibizumab and aflibercept among developing countries. The disadvantage of bevacizumab is recurrence of DME, there was increased intraretinal fluid on OCT or FA,[16] even though bevacizumab is widely used.[14, 16]

A comparative study on the effect of switching from bevacizumab to ranibizumab and aflibercept based on BCVA and CST among 18-years-old or higher patient with DM type1 and 2 with central-involved DME and had the baseline CST > 300 microns, it was found that switching from bevacizumab to ranibizumab and aflibercept resulted in significant BCVA improvements and decreased CST significantly.[17]

The primary endpoint outcomes of this study were mean changes from baseline in BCVA and CST at 1 year. This report presents the one-year results of switching treatment to ranibizumab or aflibercept in diabetic macular edema patients, refractory to bevacizumab.

Methods

This study was a retrospective chart review and selected the samples by searching patients who received the treatment from the Electronic medical record system and collecting data from a group of patients receiving retinal

examinations at the ophthalmology department, Thammasat University Hospital. The medical record was searched by using ICD -10 H36: Proliferative diabetic retinopathy (PDR), H3601: Non-proliferative diabetic retinopathy (NPDR) with maculopathy. The objectives of this study were to select a group of patients who were unresponsive to DME treatment with bevacizumab for at least 3 months. In other words, BCVA increased lower than 5 letters and CST decreased by less than 10% from baseline OCT. The patient group was divided into 2 groups: The group switched to ranibizumab and the group switched to aflibercept. The results of treatment were mean changes from baseline in BCVA and CST at 1 year after switching. There were analyzed and the authors compared mean changes BCVA and CST and then compared between 2 groups.

Inclusion criteria

- Patients who were unresponsive to DME treatment with bevacizumab for at least 3 consecutive months, both BCVA increased lower than 5 letters and CST decreased by less than 10% from baseline OCT.
- Patients with type 1 or 2 diabetes who are 18 years old or above.
- Patients with diabetes and PDR or NPDR.
- DME patients with CST > 300 microns on OCT baseline
- Patients with baseline VA > 20/40
- Patients with FBS < 300 mg/dl or HbA1C < 11 mg%

Exclusion criteria

- Patients with other diseases such as HIVs or cancer
- Patients with a previous history of LASER treatment 3 months ago
- Patients with a previous history of retinal surgery
- Patients with a previous history of macular surgery
- Patients with a history of other macular diseases such as aged-macular degeneration
- Patients with a history of intraocular inflammation
- Patients with a history of occlusive vessels such as CRAO, BRAO, CRVO, BRVO
- Patients with a previous history of systemic and topical steroid in past 3 months

Results

- Among patients at the retina clinic, the ophthalmology department, Thammasat University Hospital in 2020, 40 participants were included and divided into 2 groups. There were 19 patients who did not respond to bevacizumab treatment for at least 3 consecutive months and switched to ranibizumab. There were 21 patients who did not respond to bevacizumab treatment for at least 3 consecutive months and switched to aflibercept. The patients were treated with pro re nata basis which aflibercept or ranibizumab will be injected if the patients who were not stable in terms of both BCVA increased lower than 5 letters and CST decreased by less than 10% from baseline OCT. The results are shown in Table 1.

From table 1, a total of forty eyes from 40 patients were included in the study. There were 57.5% of male and 42.5% of female. The most types of diabetic retinopathy were severe NPDR (37.5%) followed by moderate NPDR (35.0%) and PDR (27.5%). The mean visual acuity levels in the baseline period and the visits that did not respond to the treatment are 48.20 ± 14.48 and 45.80 ± 14.81 letter scores, respectively. Central subfield thickness levels in baseline and the visit that did not respond to treatment are 429.05 ± 105.99 and 456.25 ± 117.74 microns, respectively. The median number of bevacizumab injections was 4.5 (range

Table 1: Baseline characteristics

Baseline characteristics	n = 40
Sex n (%)	
Male	23 (57.5)
Female	17 (42.5)
Age (years) mean ± SD	58.08 ± 8.40
FBS (mg/dL) mean ± SD	155.20 ± 65.36
HbA1C (mg%) mean ± SD	7.60 ± 1.07
Type of diabetic retinopathy n (%)	
Mild NPDR	0 (0.0)
Moderate NPDR	14 (35.0)
Severe NPDR	15 (37.5)
PDR	11 (27.5)
VA at baseline (letter score) n (%)	
20 - 40	11 (27.5)
41 - 60	20 (50.0)
61 - 70	9 (22.5)
Mean ± SD	48.20 ± 14.48
VA at nonresponsive to bevacizumab (letter score) n (%)	
20 - 40	15 (37.5)
41 - 60	19 (47.5)
61 - 70	6 (15.0)
Mean ± SD	45.80 ± 14.81
Central subfield thickness at baseline (microns) n (%)	
300 - 400	22 (55.0)
401 - 500	11 (27.5)
> 501	7 (17.5)
Mean ± SD	429.05 ± 105.99
Central subfield thickness at nonresponsive to bevacizumab (microns) n (%)	
300 - 400	16 (40.0)
401 - 500	12 (30.0)
> 501	12 (30.0)
Mean ± SD	456.25 ± 117.74
Number injection of bevacizumab	
Median (IQR)	4.5 (3, 6)
Mean ± SD	4.8 ± 2.03
Lens status n (%)	
Phakic	34 (85.0)
Pseudophakic	6 (15.0)

Switching to n (%)	
ranibizumab	19 (47.5)
aflibercept	21 (52.5)

VA: Visual Acuity, CST: Central subfield thickness, NPDR: Non-proliferative diabetic retinopathy

3-6 months) injections. After no response to treatment, they were switched to aflibercept (52.5 %) and ranibizumab (47.5 %) respectively.

Visual acuity

In the group that switched to ranibizumab, the BCVA (letter score) levels at unresponsive visit, 3 months after switching and 1 year after switching showed 48.89 ± 12.26, 53.42 ± 11.96 and 51.74 ± 16.53 letters scores, respectively. There were no statistically significant changes. (P = 0.178) (Table 2) In the group that switched to aflibercept, the BCVA (letter score) levels at unresponsive visit, 3 months after switching and 1 year after switching showed 43.00 ± 16.59, 43.86 ± 20.08 and 44.57 ± 19.95 letter scores, respectively. There were no statistically significant changes. (P = 0.704) (Table 2)

When comparing the visual acuity levels between the patients who switched to ranibizumab and aflibercept, it showed that there were no statistically significant differences in all treatment stages. (P > 0.05) (Table 2). Also, comparing the improvement of visual acuity levels between ranibizumab and aflibercept, it was found that there were no statistically significant differences in all treatment stages. (P > 0.05) (Figure 1)

Table 2: Visual Acuity

	Total (n = 40)	ranibizumab (n = 19)	aflibercept (n = 21)	P value (a)
Visual Acuity (letter score), mean ± SD				
1. Baseline	48.20 ± 14.48	51.32 ± 13.23	45.38 ± 15.29	0.199
2. Nonresponsive to bevacizumab	45.80 ± 14.81	48.89 ± 12.26	43.00 ± 16.59	0.213
3. At 3 months after switching	48.40 ± 17.21	53.42 ± 11.96	43.86 ± 20.08	0.073
4. At 1 year after switching	47.98 ± 18.53	51.74 ± 16.53	44.57 ± 19.95	0.226
P value (b)		0.178	0.704	
Visual acuity changes from baseline (letter score), mean ± SD				
1. Nonresponsive to bevacizumab	-4.75 ± 2.09	-3.87 ± 2.39	-5.55 ± 3.40	0.695
2. At 3 months after switching	8.66 ± 5.60	12.68 ± 5.96	5.02 ± 9.29	0.502
3. At 1 year after switching	5.67 ± 4.59	4.84 ± 4.33	6.43 ± 7.94	0.866

Data were analyzed with Independent t-test (a), Repeated measure ANOVA (b)

Central subfield thickness

Central subfield thickness levels were compared between the patients who switched to ranibizumab and aflibercept. In the group that switched to ranibizumab had the CST levels at unresponsive visit, 3 months after switching and 1 year after switching showed 428.63 ± 96.45, 346.16 ± 70.35 and 334.53 ± 59.47 microns, respectively with a statistically significant difference at the 0.05 level. (P < 0.001) (Table 3)

In the group that switched to aflibercept, central subfield thickness levels at unresponsive visit, 3 months after switching and 1 year

after switching showed 481.24 ± 131.45, 372.43 ± 129.91 and 351.71 ± 120.79 microns, respectively. There was a statistically significant difference at the 0.05 level. (P < 0.001) When comparing CST improvement levels between ranibizumab and aflibercept, it was found that there were no statistically significant differences in all treatment stages. (P > 0.05) (Table 3)

In the group that switched to ranibizumab, the mean change in CST levels from baseline to unresponsive visit, 3 months after switching and 1 year after switching treatment was 4.23 ± 3.71%, decreased 17.51 ± 3.59% and decreased 19.68 ± 3.93%, respectively. In the group that switched to aflibercept, the mean change in CST levels from baseline to unresponsive visit, 3 months after switching

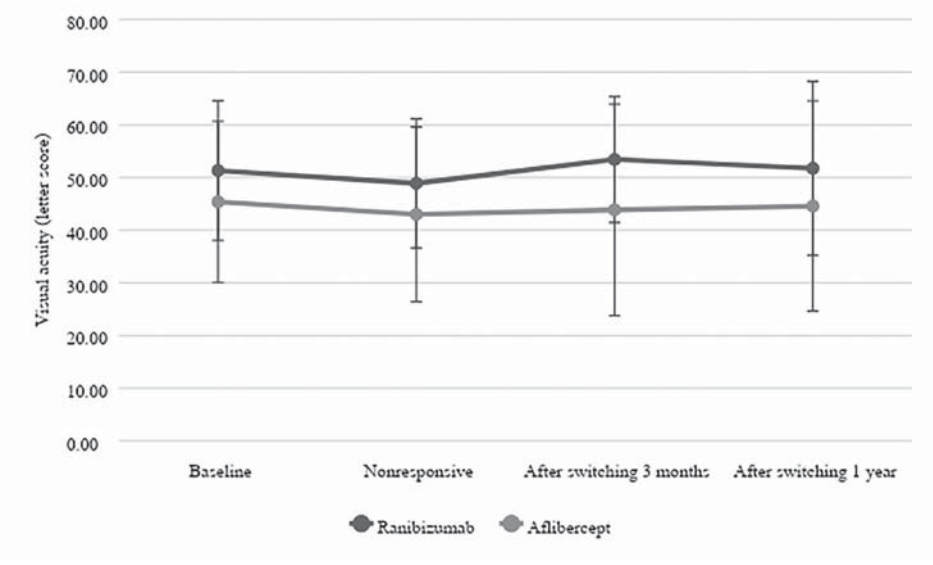

Figure 1: Visual Acuity (letter score)

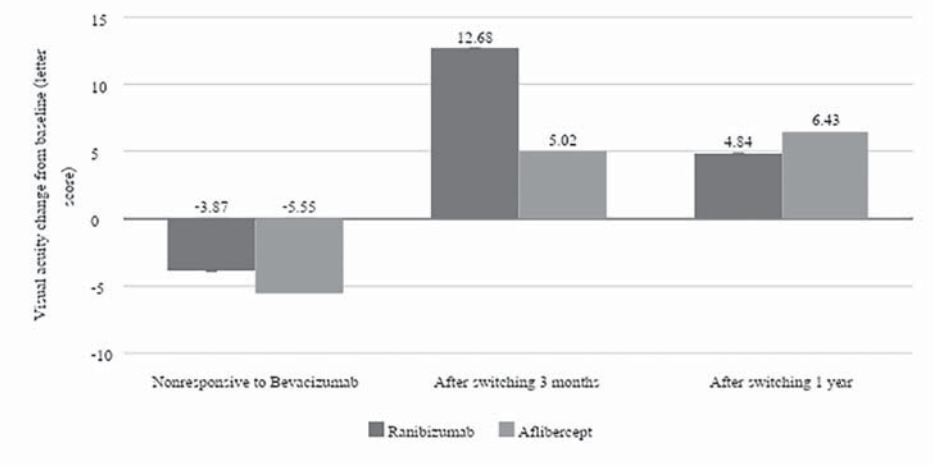

Figure 2: Visual acuity change from baseline visual acuity (letter score) was compared with nonresponsive to Bevacizumab, at 3 months and 1 year after switching.

Table 3: Central subfield thickness (microns)

	Total (n = 40)	ranibizumab (n = 19)	aflibercept (n = 21)	P value (a)
Central subfield thickness (microns), mean ± SD				
1. Baseline	429.05 ± 105.99	417.42 ± 109.73	439.57 ± 104.06	0.516
2. Nonresponsive	456.25 ± 117.74	428.63 ± 96.45	481.24 ± 131.45	0.155
3. At 3 months after switching	359.95 ± 105.43	346.16 ± 70.35	372.43 ± 129.91	0.427
4. At 1 year after switching	343.55 ± 95.86	334.53 ± 59.47	351.71 ± 120.79	0.567
P value (b)		<0.001*	<0.001*	
OCT Central subfield thickness change from baseline (microns), mean ± SD				
1. Nonresponsive to bevacizumab	7.63 ± 3.46	4.23 ± 3.71	10.70 ± 5.69	0.357
2. At 3 months after switching	-18.75 ± 3.68	-17.51 ± 3.59	-19.88 ± 6.29	0.753
3. At 1 year after switching	-22.56 ± 3.03	-19.68 ± 3.93	-25.16 ± 4.55	0.373

Data were analyzed with Independent t-test (a), Repeated measure ANOVA (b)
The same characters represent mean difference is significant at the 0.05 level
* Statistically significant at the 0.05 level

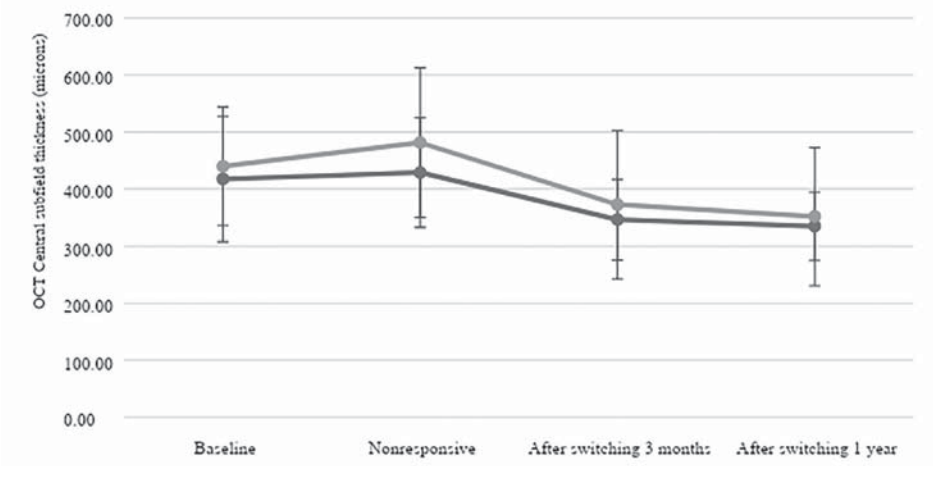

Figure 3: central subfield thicknesses (microns) before and after switching to ranibizumab or aflibercept.

and 1 year after switching treatment was 10.70 ± 5.69%, decreased 19.88 ± 6.29% and decreased 25.16 ± 4.55%, respectively. (Figure 4)

When comparing the percentage change of central subfield thickness levels between ranibizumab and aflibercept, it was found that there were no statistically significant differences in all treatment stages. (P > 0.05) (Table 3)

From table 4, The number injection after switching to ranibizumab had the median 4 (range 3-4 months) times and number injection after switching to aflibercept had the median 3 (range 3-7 months) times. There were no statistically significant differences. (P = 0.957)

Adverse Events

Among 40 patients were included in the study. In the group that switched to ranibizumab was found in 1 (5.3%) with epiretinal membrane and 2 (10.5%) with retreatment of DME. In the group that switched to aflibercept was found in 2 (9.5%) with epiretinal membrane and

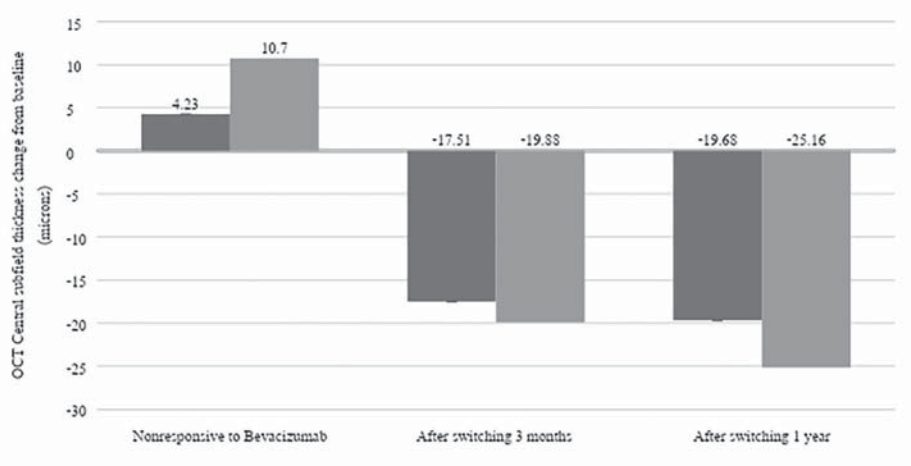

Figure 4: OCT Central subfield thickness change from baseline (microns) was compared with nonresponsive to Bevacizumab, at 3 months and 1 year after switching.

Table 4: Number of injections after switching and complication

	ranibizumab (n = 19)	aflibercept (n = 21)	P value
Number injection after switching			
Median (IQR)	4 (3, 4)	3 (3, 7)	0.957
Mean ± SD	4.05 ± 1.58	5.00 ± 3.11	0.228
Adverse Events, n (%)			
None	16 (84.2)	16 (76.2)	0.805
Epiretinal membrane	1 (5.3)	2 (9.5)	
Retreat	2 (10.5)	3 (14.3)	

Data were analyzed with Mann-Whitney U test and Chi-square test

3 (14.3%) with retreatment of DME. Other serious adverse events such as endophthalmitis, vitreous hemorrhage, retinal detachment were not found from both ranibizumab and aflibercept groups. The results, intravitreal injection of both groups showed no serious adverse events and no difference statistically. (P = 0.805) (Table 4)

Discussion

For DME treatments, the previous popular treatments were LASER treatment and grid macular photocoagulation investigated by the Early Treatment Diabetic Retinopathy Study (ETDRS).[3] However, contemporary DME treatment has changed to the injection of vascular endothelial growth factor inhibitors (VEGF-inhibitors) which is categorized as first line treatment in patients with central-involved diabetic macular edema.

Bevacizumab is considered a first-line choice for treatment of DME in Thailand, due to its listing in the on essential drug list under the national committee of Thailand. Patients under health care benefits, government officials and state enterprise employees with access to ranibizumab and aflibercept by national list of medicine because ranibizumab and aflibercept are more expensive than bevacizumab. Therefore,

many patients from the National Health Insurance system are limited in terms of cost. Because of economic considerations, in developing countries, bevacizumab is usually the first-line treatment in DME. As a result, this study is limited in the number of patients studied.

The population of interest in this study were patients who were unresponsive to DME treatment with bevacizumab for at least 3 consecutive months. Defined in this study as an improvement in BCVA of less than 5 letters and CST decreased by less than 10% from baseline OCT. The patients were divided into 2 groups: the group switched to ranibizumab and the group switched to aflibercept. The results of treatment after switching at 3 months and 1 year were analyzed and the authors compared mean changes BCVA and CST of both groups.

The DRCR.net Protocol T research in 2016 found that bevacizumab, ranibizumab and aflibercept responded to treatment with improved visual acuity and decreased number of injections in the second year of the study. In other words, the group with VA 20/32 to 20/40 visual acuity outcome was not different. However, in the group with VA worse than 20/50, it was found that aflibercept had greater visual acuity and CST decreased when compared with ranibizumab and bevacizumab significantly.[15]

In 2017, Mohammed Ashraf et al. conducted a comparative study on the effect of switching from bevacizumab to ranibizumab and aflibercept based on BCVA and CST among patients with central-involved DME and baseline CST > 300 microns, it was found that switching from bevacizumab to ranibizumab and aflibercept resulted in significant BCVA improvements ($P < 0.05$) and decreased CST significantly from 475.6 microns 118.8 microns to 416.2 microns 119 microns ($P < 0.05$).[17] In addition, there is no clear consensus on the exact timing of switching.[17]

Based on the aforementioned study, the authors conducted their own investigation and found that when followed-up for 1 year, the group switched from bevacizumab to ranibizumab or aflibercept had insignificantly increased BCVA. When comparing visual acuity between the two drug-switched groups (bevacizumab to ranibizumab or aflibercept), there was no statistical difference in at all time points of follow-up during the 1-year period. The group that switched from bevacizumab to ranibizumab or aflibercept had a decrease of CST (microns) with statistically different changes. However, when comparing CST levels between the two drug-switched groups, aflibercept had a slightly greater reduction in CST compared to ranibizumab, but there was no difference statistically in all treatment stages for 1 year.

In this study, serious adverse events such as endophthalmitis, vitreous hemorrhage, retinal detachment, ocular inflammation, including cardiovascular and hemorrhagic events were not found.

The results revealed that when anti-VEGF is used, there are differences in visual acuity improvement and decreased macular edema. However, it will be useful for ophthalmologists to select highly effective anti-VEGF to treat DME and promote these anti-VEGF into The National List of Essential Medicines in the future. However, the limitations of this study are its retrospective design, small number of each group and varying treatment philosophy. Therefore, intravitreal ranibizumab and aflibercept should be considered with concern for the DME treatment.

Conclusions

This study demonstrates the effect of switching treatment for patients with DME. The group that switched from bevacizumab to ranibizumab or aflibercept had a statistically significant decrease in the CST. In addition,

the patients who switched in both two groups had improved BCVA but there were no statistically significant changes. The results suggest intravitreal ranibizumab and aflibercept treatment at the non-responsive to bevacizumab are effective in central-involved DME patients. When comparing BCVA and CST between the two groups switched to ranibizumab and aflibercept, there was no statistical difference in all treatment follow-up periods.

Conflicts of interest:

The authors have no conflict of interest.

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