Original Article

Short-Term Outcomes of Switching Therapy from Bevacizumab Non-Responder to Ranibizumab in Diabetic Macular Edema

Wipada Laovirojjanakul MD[1], Watcharaporn Thongme MD[1], Navapol Kanchanaranya MD[2], Sritatath Vongkulsiri MD[3], Pichai Jirarattanasopa MD[4], Nawat Watanachai MD[5], Tanapat Ratanapakorn MD[1], Chavakij Bhoomibunchoo MD[1], Thuss Sanguansak MD[1], Suthasinee Sinawat MD[1]

[1] KKU Eye Center, Department of Ophthalmology, Khon Kaen University, Khon Kaen, Thailand

[2] Thammasart Eye Center, Department of Ophthalmology, Faculty of Medicine, Thammasat University, Pathum Thani, Thailand

[3] Department of Ophthalmology, Phramongkutklao Hospital, Phramongkutklao College of Medicine, Bangkok Thailand

[4] Department of Ophthalmology, Faculty of Medicine, Prince of Songkla University, Songkhla, Thailand

[5] Department of Ophthalmology, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand

Objective: To evaluate the short-term efficacy of ranibizumab therapy in terms of visual function and retinal thickness in patients with diabetic macular edema (DME) who failed to respond to treatment with repeated bevacizumab injections. Additionally, parameters affecting outcomes after switching were investigated.

Materials and Methods: The present study was a multicenter, retrospective study of 70 eyes with DME non-responding to bevacizumab. All patients were initially treated with at least three consecutive injections of bevacizumab then switched to at least one injection of ranibizumab. A monthly follow-up after the first ranibizumab injection to the last injection within six months was monitored. Primary outcomes included mean change in best-corrected visual acuity (BCVA) and central subfield thickness (CSFT) changes from baseline. Exploratory outcomes included parameters affecting prognosis after switching.

Results: Seventy eyes with DME were included in the present study. The mean change of BCVA (logMAR) was 0.075±0.375 (95% CI 0.014 to 0.164, p=0.098). The mean change of CSFT was 58.85±110.37 µm (95% CI 32.54 to 85.17, p<0.001). Forty-two percent of patients had BCVA improvement and 75.71% had CSFT improvement after switching to ranibizumab. Factors associated with BCVA and CSFT improvement were baseline BCVA, baseline CSFT, and older than 50 years old.

Conclusion: Switching to ranibizumab therapy in DME patients unresponsive to repeated bevacizumab injection provides better anatomical outcomes than visual acuity improvement. This will help ophthalmologists better understand the benefits on switching therapy to ranibizumab in terms of visual function and retinal thickness in patients with DME in the real-world setting.

Keywords: Diabetes, macular edema; Anti-vascular endothelial growth factor (VEGF); Intravitreal injection; Non-responder; Persistent diabetic macular edema

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Macular edema is the most common cause of vision loss in diabetes[1]. Anti-vascular endothelial growth factor (VEGF) therapy has become the first-line choice for center involved in diabetic macular edema (DME) treatment. Currently, three anti-VEGF drugs are routinely used in DME treatment, bevacizumab (Avastin; Genentech, South San Francisco, CA), ranibizumab (Lucentis; Genentech, South San Francisco, CA), and aflibercept (Eylea; Regeneron, Tarrytown, NY). In 2015, the Diabetic Retinopathy Clinical Research Network published a 2-year comparative effectiveness of these agents for the treatment of DME (protocol T)[2]. Despite the intensive intravitreal injection schedules used in clinical trials, persistent DME (pDME) at 24 weeks after anti-VEGF therapy and chronic, persistent DME (cpDME) two years after initiation of treatment was

Correspondence to:

Laovirojjanakul W.

Vitreoretinal and Uveitis Service, KKU Eye Center, Srinagarind Hospital, Department of Ophthalmology, Khon Kaen University, Khon Kaen 40000, Thailand.

Phone: +66-81-6494442, **Fax**: +66-43-363010

Email: Wipala@kku.ac.th

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still a significant problem[3].

When a patient does not respond to the initial agent after several monthly injections, many ophthalmologists switch to another anti-VEGF agent, especially if the initial treatment agent was bevacizumab. The choice of initial anti-VEGF agent for DME treatment is based on availability, efficacy, and cost. Switching between the available anti-VEGF drugs is the most common approach in clinical practice in these persistent cases, and most physicians switch after two to three injections[4,5].

Five retrospective studies[6-10] and two prospective study[11,12] looked at switching from bevacizumab to ranibizumab. Four studies reported no visual improvement despite a significant universal reduction in the central subfield thickness (CSFT). Three studies showed significant visual improvement after switching to ranibizumab[10-12].

However, the published data on the efficacy of ranibizumab for the treatment of DME patients with refractory cases to bevacizumab are limited, especially in the Asian context. Therefore, the authors evaluated the short-term efficacy of ranibizumab therapy in terms of visual function and retinal thickness in patients with DME who failed to respond to treatment with repeated bevacizumab injections. In addition, the authors aimed to identify any parameters associated with improved prognosis after switching.

Materials and Methods

SALD (switching therapy for non-responders from bevacizumab (Avastin) to ranibizumab (Lucentis) in diabetic macular edema) study group, consisting of five clinical sites in Thailand, retrospectively investigated the clinical benefits of switching therapy from bevacizumab to ranibizumab in patients with DME. The present study was approved by the local ethics committee of all study sites. Applicable institutional and governmental regulations concerning the ethical use of patient data collection were followed during the present research. The data were collected between September 2019 and June 2020.

The authors retrospectively reviewed the medical records and optical coherence tomography (OCT) images of DME cases that were initially treated with at least three consecutive injections of bevacizumab and met the criteria for "non-responders" before switching to ranibizumab between January 2014 and July 2019 from five sites in Thailand. During this period, all patients who met the criteria were enrolled in the present study. One eye from one patient was included. If the patient experienced DME in both eyes, the worse eye was included for the analysis. The criteria for "non-responders" consisted of no improvement or worsening of best-corrected visual acuity (BCVA) by Snellen chart (converted subsequently to equivalent logarithm of the minimum angle of resolution [logMAR]) or persistent or less than 10% reduction of CSFT of macular edema. CSFT was defined as the average thickness of the macula in the central 1 mm ETDRS grid, whereas CSFT of 320 μm or more in male and 305 μm or more in female were considered macular edema[13]. The duration from baseline measurement to first ranibizumab injection must not exceed six weeks. The duration from last bevacizumab injection to the first follow-up visit after ranibizumab injection must be more than eight weeks for the wash out effect. Eyes that received intravitreal or periocular steroid therapy, focal laser, or panretinal photocoagulation during anti-VEGF injection period were excluded.

Each patient received a monthly consecutive injection of ranibizumab at a dose of 0.5 mg 0.05 mL (Lucentis, Genentech; Inc., South San Francisco, CA; co-developed by Genentech, Inc., and Novartis) and repeated injections were administered on an as-needed basis when spectral-domain OCT revealed any evidence of intra-retinal or subretinal fluid or an increase in the CSFT. A monthly follow-up after the first ranibizumab injection to the last injection was monitored. Final follow up was six months or less depending on the number of ranibizumab injections. Outcomes will be assessed by mean change of BCVA and CSFT at final follow up compared to baseline. The authors defined BCVA improvement as any improvement of visual acuity after the last ranibizumab injection compared to baseline and anatomic or CSFT improvement as patients exhibiting a dry macula or any reduction in CSFT at that time point.

Sample size calculation and statistical analysis

The authors calculated that enrollment of 66 eyes would provide the study with 80% power to detect a difference in mean BCVA logMAR of 0.13[11], using paired t-test at a two-sided alpha level of 0.05. Since there was no previous report on standard deviation (SD) of mean difference, the authors use SD from the present study instead.

Categorical data were summarized using proportions and percentages and were analyzed using a chi-square test or Fisher's exact test, as appropriate. Continuous data were summarized using mean with SD and median with range for baseline BCVA in logMAR due to non-normal distribution of the data.

The mean difference of BCVA and CSFT between pre- and post-ranibizumab injection was analyzed using paired t-test. Univariate and multivariate logistic regression analyses were used to evaluate prognostic factors for BCVA improvement and CSFT improvement after switching to ranibizumab treatment. Snellen visual acuity records were converted to the logMAR for statistical analysis. BCVA of counting fingers (CF), hand motion, light perception, and no light perception were converted to 2.6, 2.7, 2.8, and 2.9 logMAR, respectively. Statistical analyses were performed using Stata Statistical Software, version 16.0 (StataCorp LLC, College Station, TX, USA). Two-sided p-value of less than 0.05 was considered statistically significant.

Results

Seventy eyes from 70 patients switched from bevacizumab therapy to ranibizumab between January 2014 and July 2019 were included in the present study. Among all patients, mean age was 59±8.49 years old. The mean CSFT and median of BCVA (logMAR) were 420.57±116.28 µm and 0.6, with a range of 0.1 to 2.6, Snellen equivalent of 20/80 at baseline. Mean number of bevacizumab injection before switching was 3.45±1.35. The mean follow-up time was 3.60±1.57 months. The baseline characteristics of these eyes are demonstrated in Table 1.

Table 1. Baseline demographic and clinical characteristics of the study population

Number of patients/eyes	70/70
Age (years); mean±SD	59±8.49
Sex; n (%)	
Male	33 (47.14)
Female	37 (52.86)
Baseline BCVA in logMAR; median (range)	0.6 (0.1 to 2.6)
Baseline CSFT (µm); mean±SD	420.57±116.28
Follow up time (months); mean±SD	3.60±1.57
Baseline CSFT (µm); mean±SD	420.57±116.28
Number of bevacizumab injections (times); mean±SD	3.45±1.35
Number of ranibizumab injections (times); mean±SD	3.62±1.61
Associated systemic diseases; n of eyes (%)	
Hypertension	32 (45.7)
Dyslipidemia	24 (34.3)
Chronic kidney disease	3 (4.3)
Cardiovascular disease	3 (4.3)
Others	4 (5.7)

BCVA=best-corrected visual acuity; logMAR=logarithm of the minimum angle of resolution; CSFT=central subfield thickness; SD=standard deviation

Primary outcomes: efficacy of ranibizumab

Visual acuity: The mean change of BCVA for the 70 eyes was 0.075±0.375 (95% CI 0.014 to 0.164, p=0.098), equivalent to 3.75±18.5 letter score. Thirty eyes (42.9%) had BCVA improvement after switching to ranibizumab injection. Difference in proportion of eyes with visual acuity of 20/200 or less between baseline and after switching to ranibizumab was 1.42% (95% CI –10.33 to 7.48, p=0.75). A summary of the treatment outcomes of BCVA is given in Table 2.

Central subfield thickness: Mean change of CSFT was 58.85±110.37 µm (95% CI 32.54 to 85.17, p<0.001). Fifty-three eyes (75.71%) had CSFT improvement after switching to ranibizumab. The difference in proportion of eyes with CSFT of 400 µm or more between baseline and after switching to ranibizumab was 25.71% (95% CI 10.05 to 41.37, p=0.002). The summary of the treatment outcomes of CSFT is shown in Table 2.

Secondary outcomes: factors effecting BCVA and CSFT

The authors identified the factors effecting BCVA improvement as shown in Table 3. Baseline BCVA (OR 4.41, 95% CI 1.04 to 18.76, p=0.045) and baseline BCVA of more than 0.8 logMAR (OR 3.61, 95% CI 1.21 to 10.72, p=0.021) were the significant prognostic factors for BCVA improvement by univariate analysis. Baseline BCVA was also a significant prognostic factors for BCVA improvement by multivariate analysis (OR 5.28, 95% CI 1.11 to 25.07, p=0.036). The baseline of CSFT (OR 1.01, 95% CI 1.00 to 1.02, p=0.002) and the age of 50 years old or older (OR 10.89, 95% CI 2.70 to 43.93, p=0.005) were prognostic factors for improvement of CSFT by multivariate analysis (Table 4).

Discussion

The authors presented a retrospective observational study of the clinical benefits of switching therapy to ranibizumab in patients with DME who did not respond to at least three consecutively bevacizumab injections. Mean CSFT showed statistically significant reduction by 58.85±110.37 µm and 75.71% of DME eyes, which were classified as anatomical improvement. However, there was no significant difference in mean change of BCVA and those who had BCVA improvement in DME.

Visual acuity had improved in all previous studies after switching from bevacizumab to ranibizumab.

Table 2. Anatomical and functional outcomes after switching to ranibizumab treatment in diabetic macula edema patients

Outcome measures	n=70 eyes		Difference (95% CI)	p-value
	Baseline	Final follow up		
BCVA in logMAR; median (min, max)	0.6 (0.1, 2.6)	0.6 (0, 1.6)	0.075 (–0.014 to 0.164)	0.098
CSFT (μm); mean±SD	420.57±116.28	361.7±101.2	58.85±110.37 (32.54 to 85.17)	<0.001*
Proportion of patients with BCVA ≤20/200; n of eyes (%)	11 (15.71)	10 (14.29)	1.42% (–10.33 to 7.48)	0.75
Proportion of patients with CSFT ≥400 um; n of eyes (%)	37 (52.86)	19 (27.14)	25.71% (10.05 to 41.37)	0.002*

BCVA=best-corrected visual acuity; CSFT=central subfield thickness; SD=standard deviation; CI=confidence interval

Table 3. Univariate analysis for prognostic factors for BCVA improvement after switching

Prognostic factors	Univariate			Multivariate		
	OR	95% CI	p-value	Adjusted OR	95% CI	p-value
Baseline BCVA (logMAR)	4.41	1.04 to 18.76	0.045	5.28	1.11 to 25.07	0.036
Baseline BCVA that more than 0.8 logMAR	3.61	1.21 to 10.72	0.021			
Age (years)	1.04	0.98 to 1.10	0.203			
Age >50 years	1.63	0.44 to 6.00	0.467			
Baseline CSFT (μm)	1.00	0.99 to 1.01	0.593			
Number of bevacizumab injections (times)	1.07	0.69 to 1.65	0.774			
Number of ranabizumab injections (times)	1.26	0.93 to 1.71	0.131	1.32	0.96 to 1.81	0.092

BCVA=best-corrected visual acuity; logMAR=logarithm of the minimum angle of resolution; CSFT=central subfield thickness; OR=odds ratio; CI=confidence interval

Table 4. Univariate and multivariate analysis for prognostic factors for CSFT improvement

Prognostic factors	Univariate			Multivariate		
	OR	95% CI	p-value	Adjusted OR	95% CI	p-value
Baseline BCVA (logMAR)	0.99	0.29 to 3.36	0.987			
Age (years)	1.09	1.00 to 1.18	0.038			
Age >50 years	10.89	2.70 to 43.93	0.001	15.13	2.28 to 100.18	0.005
Baseline CSFT (μm)	1.01	1.01 to 1.02	0.001	1.01	1.01 to 1.02	0.002
Number of Bevacizumab injections (times)	1.17	0.68 to 2.01	0.577			
Number of Ranabizumab injections (times)	0.90	0.64 to 1.27	0.566	0.76	0.49 to 1.16	0.203

BCVA=best-corrected visual acuity; logMAR=logarithm of the minimum angle of resolution; CSFT=central subfield thickness; OR=odds ratio; CI=confidence interval

Mean BCVA improvement from those studies varied between 0.13 to 0.04 logMAR. The present study visual acuity outcome is comparable to the previous studies with 0.075 logMAR improvement. However, only three studies showed significant visual improvement[10-12]. Most studies reported non statistically significant change in visual improvement despite a significant reduction in CSFT, including the present report. Patients with chronic DME may already have significant photoreceptor damage and may not achieve visual improvement after anatomical improvement. It is well established that delayed resolution of DME has a negative effect on the visual gains ultimately achieved[14]. This confirms the non-association between OCT derived early anatomical response and long-term BCVA improvement[15,16]. Theories about this functional impairment have been suggested, including microstructural defects in the photoreceptors and external limiting membrane occurring in the fovea after a DME episode, neural apoptosis, glial reactivity, malfunction due to ischemia, or reduction in the thickness of the inner retinal layers[17].

Several factors were identified to be predictive factors of the response after switching such as pre-switch visual acuity[6], decreasing vision before the switch[8], and a partial response to bevacizumab[9], which were reported to be associated with response after switching, whereas others did not find the pre-switch changes in vision and CSFT to be predictive

of the response after switching[7,10]. The association between the number of post-switch injections of ranibizumab and better outcomes was positive in one study[6] and negative in the other[8]. In the present study, the authors found baseline BCVA and baseline BCVA more than 0.8 logMAR such as worse than 20/125, were prognostic factors for improvement of visual outcome.

An anatomic benefit of switching to ranibizumab was significant in the present study. This can be attributed to the pharmacokinetic/pharmacodynamic differences of the drugs and the potential of tachyphylaxis associated with prior bevacizumab treatment. Ranibizumab has a higher affinity for VEGF-A and smaller size than bevacizumab. The latter is believed to enhance its diffusion from the vitreous into the retina and the choroid[18,19]. These differences may translate into different clinical efficacy between the two medications. Tachyphylaxis, also well documented in a previous study on nAMD patients[20], is another potential explanation for the results observed in the current study. Although the attenuated response occurs after repeated administration of a drug, little is known about the minimum time or number of treatments before the development of tachyphylaxis[21].

The present study investigated prognosis factors for improvement of CSFT that affirmed the scientific knowledge on patient characteristics of DME non-responders who would benefit from switching to ranibizumab. Thicker in CSFT at baseline demonstrated more improvement of CSFT after switching. However, the odds ratio of baseline CSFT that was 1.01 with 95% CI from 1.00 to 1.02 suggested that the improvement of CSFT may be independent to baseline CSFT. Reports from large randomized clinical trials have demonstrated that eyes with CSFT of more than 400 µm at baseline showed more improvement in CSFT after ranibizumab treatment than those with CSFT of less than 400 µm[22,23]. Studies have found that VEGF concentrations in the vitreous and aqueous humor exhibit a strong correlation with the mean foveal thickness[24,25]. Therefore, the authors may assume that a switch to intravitreal ranibizumab may be considered if the anatomic response to repeated intravitreal bevacizumab was suboptimal in patients with higher baseline CSFT values. Switching to ranibizumab may lead to a further reduction in the VEGF level, which cannot be suppressed completely with bevacizumab.

In term of limitations, the present paper studied clinical response after switching from bevacizumab to ranibizumab in a single arm and did not compare visual outcome between switching and non-switching eyes. However, previous studies that investigated treatment response in pDME demonstrated that BCVA improvement could be found in eyes continuing bevacizumab[3,26,27]. Consequently, future research should consider comparison arms between switching from bevacizumab to ranibizumab and continuing treatment of bevacizumab in these patients to further strengthen the results of the present study. The present study was a retrospective study. Therefore, it may allow selection bias caused from non-randomized treatment, and potential loss to follow up. Short follow-up periods with an inadequate number of ranibizumab injections after switching may also limit gains as BCVA improvement usually lags anatomic improvement in macular edema patients[28-31]. The high proportion of loss to follow-up visits and switching to another medication resulted in varying follow-up times, hence, the present study primary endpoint was the mean change of BCVA and CSFT from baseline to the final follow-up instead of measuring an exact time point after switching. This limitation could be expected in real-world observational study. In the era of OCT, different retinal structural clues could be linked to resistant DME, such as intra-retinal high reflective foci. In addition, other retinal architectural parameters could be associated with suboptimal visual improvement, such as IS-OS junction integrity[32], outer retinal layers thickness[33], disorganization of inner retinal layers[34], and inconsistent OCT angiography findings[35]. However, the present study did not analyze the relationships between functional changes and prognostic OCT parameters.

Conclusion

In summary, the authors evaluated the short-term efficacy of ranibizumab therapy in patients with DME who failed to respond to at least three consecutively bevacizumab injections. Mean CSFT was a statistically significant reduction whereas significant visual improvement was not achieved. This is a real-world data of efficacy of switching to ranibizumab, which may be an option for pDME treatment. This will help ophthalmologists better understand the benefits on switching therapy to ranibizumab in terms of visual function and retinal thickness in patients with DME in the real-world setting.

What is already known on this topic?

Switching of anti-VEGFs results in outcome

improvement in pDME patients, but the prognostic factors were unclear, and there is a lack of this knowledge in Asian and Thai population. More specific knowledge on pDME patients' management could be used for effective treatment protocol, supporting national policy, and improving patient outcomes in real practice, especially for emerging countries initiating treatment with bevacizumab.

What this study adds?

In Asian population, which patient characteristics and socioeconomics differ from the Western countries, the early switching from bevacizumab to ranibizumab resulted in BCVA and CSFT improvement in 42.9% and 75.71% of patients, respectively. Prognostic factors for BCVA and CSFT improvement for real practice were baseline BCVA more than 0.8 logMAR with a worse than 20/125, and baseline CSFT of more than 400 μm respectively.

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Ethics approval and consent to participate

The present study was approved by 1) Khon Kaen University Ethics Committee in Human Research Panel 1, 34/2562 (Institutional Review Board Number, IRB00001189) for Khon Kaen University, 2) Human Research Ethics Committee of Thammasat University No.1 for Thammasat University, 3) Institutional Review Board of Royal Thai Army Medical Department for Phramongkutklao College of Medicine, 4) Ethics Committee in Human Research of Prince of Songkla University (Reference no. e67F-JOmL-N9jt-Jr7o) for Prince of Songkla University, and 5) Research Ethics Committee 4, Faculty of Medicine, Chiang Mai University for Chiang Mai University.

The present study was approved to conduct for all sites and a waiver of consent was granted as it was a retrospective study. Applicable institutional and governmental regulations concerning the ethical use of patient data collection were followed during the present research.

Availability of data and materials

The datasets used or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

WL initiated the study, interpreted the data, and was a major contributor in writing the manuscript. WT collected, analyzed, and interpreted the data. NK, SV, PJ, NW, TR, CB, TS, and SS collected the data and analyzed it. All authors read and approved the final manuscript.

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Conflicts of interest

The authors declare that they have no competing interests.

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