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Original Article/นิพนธ์ต้นฉบับ

Efficacy and Safety of Intravitreal Ziv-Aflibercept for the Treatment of Patient with Diabetic Macula Edema Refractory to Intravitreal Bevacizumab: A Case Series

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Abstract

Purpose: To evaluate the safety and efficacy of intravitreal ziv-aflibercept (IVZ) injection in Thai patients with diabetic macular edema (DME) refractory to intravitreal bevacizumab (IVB).

Materials and Methods: Consecutive patients with refractory DME were treated with three monthly IVZ (1.25 mg/0.05 ml) injections. For patients who responded, a pro-re-nata protocol was used for recurrence or persistent DME, defined as central macular thickness (CMT) > 300 um. Outcome measures included best corrected visual acuity (BCVA), CMT and adverse events at 6 months. Comprehensive ophthalmic exams and optical coherence tomography (OCT) were performed at baseline and follow-up visits.

Results: Seven type 2 diabetic patients, mean age 56.71 ± 5.34 years, were included. The mean number of previous IVB injections was 5.71 ± 2.43. Patients were switched to IVZ 4-5 weeks after their last IVB injection. Mean BCVA improved from 0.46 ± 0.27 logMAR to 0.32 ± 0.17 logMAR (p = 0.018) at 3 months and 0.32 ± 0.13 logMAR (p = 0.001) at 6 months. Mean baseline CMT decreased from 512.71 ± 158.41 μm to 347.86 ± 122.61 μm (p = 0.012) at 3 months and 351.60 ± 117.71 μm (p = 0.029) at 6 months. After three loading injections, 2 eyes were non-responders. The mean number of IVZ injections was 4.6 ± 1.2. No intraocular inflammation, lens opacity progression, elevated IOP, or retinal detachment was observed. No serious systemic complications were detected.

Conclusions: Intravitreal ziv-aflibercept is a safe and cost-effective treatment for DME refractory to IVB. It offers a valuable alternative, especially in resource-limited settings, but further large-scale, prospective studies are needed to confirm its efficacy and long-term safety

Keywords: bevacizumab, diabetic macular edema, persistent, refractory, ziv-aflibercept

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Introduction

In 2020, the global prevalence of diabetic retinopathy (DR) and diabetic macular edema (DME) was estimated at 22.27% and 4.07%, respectively[1]. DME, a major cause of visual impairment, is usually treated with anti-vascular endothelial growth factor (anti-VEGF) agents. Aflibercept has shown superior outcomes compared to bevacizumab for certain baseline conditions[2], and switching to aflibercept can benefit persistent DME resistant to bevacizumab or ranibizumab.[3,4] However, its high cost limits its use in developing countries.[5]

Ziv-aflibercept, originally developed as a systemic anti-VEGF agent for metastatic colorectal cancer, shares a similar molecular structure with aflibercept and may offer a more cost-effective alternative6. Intravitreal ziv-aflibercept (IVZ) has demonstrated good efficacy and safety in naïve DME cases[7–15]. This study evaluates its effectiveness for DME refractory to bevacizumab.

Materials and methods

The study was a single-center, prospective clinical trial at KKU Eye Center, Srinagarind hospital, Khon Kaen University, Khon Kaen, Thailand. The procedures adhered to the tenets of the Declaration of Helsinki. Prospective ethical approval was obtained Khon Kaen University Ethics Committees in Human Research (IRB no. 00001189). The study was registered at Thai Clinical Trials Registry (identifier: TCTR20191130001). The Invitation Research Fund had no role in this study.

Patient eligibility

Patients with diabetic macular edema refractory to at least 3 monthly intravitreal bevacizumab (IVB) injections were recruited between June 2019 and July 2020. Refractory DME was defined as the decrease in central macular thickness (CMT) of less than 10% from baseline during the last 3 monthly IVB injections and CMT was still more than 300 μm. For patients with bilateral DME, only one eye was randomly enrolled. Written informed consent was obtained from all patients before screening and after an explanation of study protocol and possible consequences of participation.

Inclusion criteria included (1) age ≥ 18 years, (2) type 2 diabetes mellitus (DM), (3) refractory DME to IVB, and (4) CMT > 300 um confirmed by spectral-domain optical coherent tomography (SD-OCT) device.

Exclusion criteria included (1) one-eyed patient, (2) history of stroke, (3) history of kidney transplantation or hemodialysis, (4) previous treatment with intravitreal ranibizumab or aflibercept injections, (5) history of intravitreal corticosteroid injection within 6 months, (6) history of focal/grid or panretinal photocoagulation (PRP) within 3 months prior to enrollment, (7) history of pars plana vitrectomy, (8) autoimmune disorders or connective tissue diseases, (9) vitreoretinal diseases such as retinal vascular occlusion and uveitis, (10) intraocular pressure (IOP) > 25 mmHg, (11) vitreomacular traction or epimacular membrane with traction on SD-OCT images, (12) media opacities that cause poor image quality such as diabetic vitreous hemorrhage, (13) Systolic blood pressure > 180 mmHg or diastolic blood pressure > 110 mmHg, (14) Serum glycosylated hemoglobin (HbA1c) level > 12 %, (15) could not be investigated by SD-OCT such as nystagmus, and (16) patients could not be followed up for 6 months.

Withdrawal criteria included (1) decrease in Early Treatment Diabetic Retinopathy Study (ETDRS) > 5 letters after intravitreal injections and decrease in CMT < 10% from baseline after receiving 3 monthly loading injections, defined as non-responder; (2) severe adverse events such as endophthalmitis, retinal detachment, stroke and myocardial infarction; (3) patients decided to withdraw from the study.

Surgical intervention

All participants received 3 monthly IVZ (Zaltrap; Sanofi-Aventis, Bridgewater, NJ, USA/Regeneron, Tarrytown, NY, USA) injections under standard sterile technique. The first IVZ injection was performed 4-5 weeks after the last IVB injection. If the participants responded to ziv-aflibercept, then pro-re nata (PRN) protocol was used for persistent or recurrent DME (residual fluid with a CMT > 300 μm on OCT). Ziv-aflibercept 0.05 ml was prepared under sterile condition by pharmacy division of Srinagarind hospital using 1 ml syringes. Sterile vials of 100 mg per 4 ml were punctured only once. After each drug preparation, all syringes with 1.25 mg ziv-aflibercept per 0.05 ml were stored at 40 °C and used within 4 weeks. Patients were disinfected the periocular skin and eyelid with 10% povidone iodine. After topical anesthesia, 5% povidone iodine was instilled and left for at least 3 minutes. Ziv-aflibercept 1.25 mg/0.05 ml was injected at 3-4 mm posterior to temporal limbus with a 30-gauge needle. A mild pressure was applied using a cotton tip at the injection site, followed by the application of antibiotic drops.

Patient evaluation and outcome measures

All patients underwent monthly follow-up evaluations for a period of 6 months following the initial IVZ injection. Best corrected visual acuity (BCVA) was measured using the ETDRS chart, and subsequently converted to the logarithm of minimum angle of resolution (logMAR). A comprehensive ocular examination was performed at baseline and during each follow-up visit. The macula was evaluated by SD-OCT device (Spectralis, Heidelberg Engineering, Heidelberg, Germany). Functional outcome measures included BCVA and changes in BCVA. Anatomical outcomes were evaluated based on of CMT and changes in qualitative and quantitative OCT parameters, including the presence of intraretinal fluid (IRF) and subretinal fluid (SRF), changes in CMT, and vitreomacular interface (VMI) abnormalities. Safety parameters were ocular and systemic adverse events.

Statistical analysis

All statistical analyses were performed with STATA version 10.0 (StataCorp, College Station, TX, USA). Continuous variables were described using mean ± standard deviation (SD), while categorical variables were expressed as percentages. Paired t test was employed to determine the significant differences between variables. A P-value of < 0.05 was considered indicative of statistical significance.

Results

Thirteen patients with DME refractory to IVB injection were recruited, but 6 patients were excluded for the following reasons: 3 patients were lost to follow-up during the COVID-19 outbreak, one patient had HbA1c more than 12%, one patient had wide epimacular membrane (EMM) with traction and one patient had a macular scar. Ultimately, 3 males and 4 females were included in the study. The average age of participants was 56.72 ± 5.34 years. All patients had type 2 diabetes, mean duration of DM was 12.29 ± 5.62 years and mean HbA1c was 8.34 ± 1.25 %. Most patients were diagnosed proliferative diabetic retinopathy. Six out of seven cases had bilateral DME. Mean duration of symptom was 18.14 ± 8.34 months. Mean number of previous IVB injections was 5.71 ± 2.43. One patient had history of intravitreal triamcinolone acetonide (IVTA) and 4 patients had ever been treated with laser photocoagulation, all laser treatments had been performed more than 3 months before enrollment. Patients' demographic data and baseline data are showed in Table 1. Intraretinal fluid was demonstrated as cystoid macular edema in all eyes and subretinal fluid was also observed in 2 eyes. Vitreomacular detachment was showed on OCT at the

initial examination in 2 eyes which one eye of these also had thin EMM without traction.

Table 1 Demographic and baseline data

No.	Age	Sex	Type 2 DM			Lens	Symptom duration (months)	Previous treatments		
			Duration (years)	A1C (%)	DR Laser			IVB	IV	TA
1	60	M	20	9.7	PDR	Phakic	21	6	-	-
2	57	F	20	7	PDR	IOL	21	11	2	PRP
3	61	F	10	8.3	PDR	Phakic	6	4	-	-
4	47	F	7	6.3	PDR	Phakic	12	6	-	PRP
5	52	F	13	9.3	PDR	Phakic	27	3	-	Focal
6	56	M	4	8	NPDR	Phakic	30	6	-	PRP
7	64	M	12	9.8	PDR	Phakic	10	4	-	-

DM = Diabetes mellitus; IVB = intravitreal bevacizumab; IVTA = intravitreal triamcinolone acetonide; IOL = intraocular lens; DR = diabetic retinopathy; PDR = proliferative diabetic retinopathy; NPDR = non- proliferative diabetic retinopathy; BCVA = best corrected visual acuity; logMAR = logarithm of the minimum angle of resolution; CST = central subfield thickness; VMI = vitreomacular interface; VMA = vitreomacular adhesion; EMM = epimacular membrane; PVD = posterior vitreous detachment.

The clinical characteristics and outcomes after switching to ziv-aflibercept are detailed in Table 2. Mean baseline BCVA was 0.46 ± 0.27 logMAR which improved significantly to 0.32 ± 0.17 logMAR at 3 months (p = 0.018). At the 6-month follow-up, mean BCVA was 0.32 ± 0.13 logMAR. This reflects a significant visual improvement, with a mean visual acuity gain of 0.27 ± 0.15 logMAR (95%CI 0.09-0.26; p = 0.001) as shown in Table 3. Visual improvement and CMT reduction were sustained throughout the follow-up period (Figure 1). Mean baseline CMT was 512.71 ± 158.41 μm which significantly decreased to 351.60 ± 117.71 μm at 6 month (p = 0.012). The reduction in CMT was significant, with a mean decrease of 191 ± 161.11 μm (95%CI 16.67-301.63; p = 0.029).

Table 2 Clinical characteristics and outcomes after switching to intravitreal ziv-aflibercept.

No.	Initial characteristics		VMI	At 3 months		At 6 months		
	BCVA (logMAR)	CMT (μm)		BCVA (logMAR)	CMT (μm)	BCVA (logMAR)	CMT (μm)	No of injections
1	0.60	422	VMA*	0.20	222	0.20	220	3 IVZ
2	0.84	797	EMM+PVD†	0.50	302	0.40	300	5 IVZ
3	0.34	322	PVD	0.30	293	0.16	273	3 IVZ
4	0.80	636	VMA	0.60	237	0.50	549	4 IVZ
5	0.36	536	VMA	0.36	473	0.34	416‡	6 IVZ
6	0.10	330	VMA	0.10	324	0.10	333	3IVZ 2IVA§
7	0.20	546	VMA	0.20	584	0.30	614	3IVZ 1IVA§

BCVA = best corrected visual acuity; logMAR = logarithm of the minimum angle of resolution; CST = central subfield thickness; IRF = intraretinal fluid; SRF = subretinal fluid; VMI = vitreomacular interface; VMA = vitreomacular adhesion; EMM = epimacular membrane; PVD = posterior vitreous detachment; IVZ = intravitreal ziv-aflibercept; IVA = intravitreal aflibercept; HE = hard exudates.

*Patient had PVD after IVZ, †patient had stable EMM, ‡patient had significantly decreased in hard exudates, §patients were classified as IVZ non-responder, IVT aflibercept was used as a rescue therapy.

Table 3 Changes in best corrected visual acuity and central subfield thickness at 3 months and 6 months of follow-up.

	Baseline	At 3 months				At 6 months			
		Mean (SD)	Mean Change (SD)	95% CI	*P*-value	Mean (SD)	Mean Change (SD)	95% CI	*P*-value
BCVA (logMAR)	0.46 ± 0.27	0.32 (0.17)	0.14 (0.16)	0.02, 0.26	0.018	0.32 (0.13)	0.27 (0.15)	0.09,0.36	0.001
CST (um)	512.71 ± 158.41	347.8 (122.61)	164.86 (192.82)	3.45, 293.26	0.012	351.60 (117.71)	191 (161.11)	16.67, 301.63	0.029

BCVA = best corrected visual acuity; logMAR = logarithm of the minimum angle of resolution; CST = central subfield thickness; SD = standard deviation; CI = confidence interval.

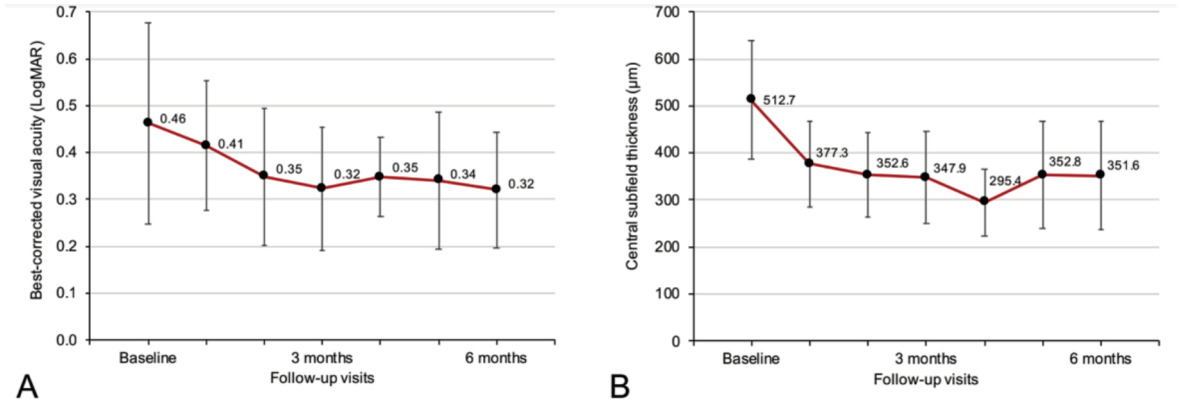


Figure 1 Mean best corrected visual acuity (A) and mean central macular thickness (B) with 95% confidence interval according to time assessment.

Vitreomacular detachment was observed in one patient following three loading doses of ziv-aflibercept, with no recurrence of DME. Patient No. 4 responded positively to the initial IVZ injection; however, recurrent DME was noted at 5 months of follow-up. Notably, this patient required up to three additional IVZ injections to achieve a subsequent response. In Patient No. 5, SRF persisted throughout the study period, although there was a significant reduction in both SRF and hard exudates. The chronic nature of DME in this patient was identified as a major factor contributing to the limited visual improvement observed. The mean number of IVZ injections administered was 4.2 ± 1.17. At the 3-month follow-up, 2 eyes (16.67%) were classified as non-responders, and they did not respond to further intravitreal aflibercept after switching. Ultimately, one patient with persistent IRF was treated with IVTA, and another patient with refractory DME complicated by EMM and progressive traction was scheduled for pars plana vitrectomy (PPV).

Throughout the study, there were no sign of intraocular inflammation, lens opacity progression, elevation of IOP or retinal detachment. An epiretinal membrane emerged as an ocular adverse event in one eye (14.29%). EMM with vitreomacular detachment at baseline in one patient had no progression whereas the new EMM in a non-responder rapidly progressed with traction (Figure 2). No systemic complications were observed during the follow-up period.

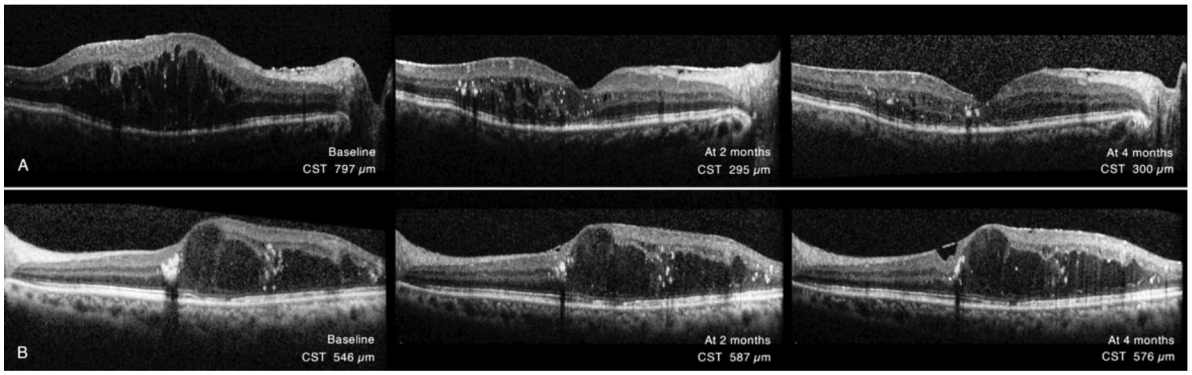


Figure 2 Epimacular membrane (EMM) was observed in 2 eyes. (A) Stable EMM from baseline (B) EMM development with progressive traction after intravitreal ziv-aflibercept injections.

Discussion

Historically, DME was categorized as clinically significant macular edema (CSME) according to the ETDRS. Today, the terminology has evolved to 'center-involving DME' is when the central 1 mm of the macula shows thickening on OCT. The diagnosis is typically based on a specific threshold value of central macular thickness (CMT). In the early stages of DME, retinal thickening leads to reduced retinal transparency and alteration in refractive index. With chronic DME, there is neural damage that disrupts and degrades photoreceptors. Even after DME resolves, issues such as macular ischemia and disorganization of inner retina may persist.[19]

Anti-VEGF medications are the first-line treatment for DME, with intravitreal bevacizumab (IVB) being the only anti-VEGF listed in Thailand's National list of essential medicines. Consequently, IVB is commonly used as the initial therapy in Thailand. Accordingly, we defined refractory DME a lack of response to at least three monthly IVB injections. However, some patients do not respond well to this treatment, highlighting the need for cost-effective alternatives in resource-limited settings.

Aflibercept, an anti-VEGF drug with higher binding affinity to VEGF-A and additional targets such as placental growth factor and VEGF-B20, has shown promise in treating refractory DME. DRCR Protocol T study indicated that 41% of patients receiving bevacizumab had treatment failure, characterized by persistent central macular thickening or a loss of 10 ETDRS letters in vision following 6 monthly intravitreal injections[2]. Multiple visits can impose substantial economic and logistical burdens, particularly for patients in remote areas. A systematic review and meta-analysis suggest that switching to intravitreal aflibercept may improve outcomes for persistent or refractory DME, offering significant benefits for vision recovery[4]. Additionally, the DRCR Protocol AC study found no statistically significant difference in visual outcomes between aflibercept monotherapy and a regimen starting with bevacizumab followed by aflibercept for suboptimal responders over two years[3]. However, despite its efficacy, aflibercept are less cost-effective compared to bevacizumab,[5] making them less accessible under Thailand's current healthcare system. This system, which aims to provide healthcare to all citizens, faces budget constraints that limit the inclusion of more expensive medications.

Ziv-aflibercept (Zaltrap; Sanofi-Aventis, Bridgewater, NJ/Regeneron, New York, USA) was approved by the Food and Drug Administration for

the treatment of metastatic colorectal carcinoma.[5] Ziv-aflibercept has the identical molecular structure and action mechanism with aflibercept. Because of the different buffer, hyperosmotic sucrose, ziv-aflibercept has 3-times higher osmolarity than aflibercept. Despite concerns about hyperosmolarity, a large retrospective study of 5914 IVZ (1.25 mg/0.5 ml) injections demonstrated an acceptable safety profiles.[21]

The efficacy and safety of IVZ in the treatment of DME has been previously published, but most studies have examined IVZ in naïve DME.[7-15] One-year results of a 3-armed double–blind randomized clinical trial, no significant difference in outcomes was shown between the 2 ziv-aflibercept groups (1.25 mg and 2.5 mg). Visual improvement was significantly better in both ziv-aflibercept groups compared with bevacizumab group in eyes with baseline BCVA ≤ 20/50, however, there was no significant difference in CMT reduction between groups.[12]

Three studies have explored the use of IVZ for treating refractory DME. Ashraf et al retrospectively reviewed patients with DME unresponsive to various intravitreal anti-VEGF treatments, using a pro-re nata strategy for IVZ[16]. They found a mean of 2.03 ± 0.75 injections led to a significant visual and CMT improvements in 10 eyes at 3 months. Although their baseline data and clinical characteristics were similar to our study, our results showed better outcomes likely due to a more intensive treatment regimen. Ebrahimiadib et al conducted a prospective study with 38 patients who had refractory DME to IVB. All patients received three monthly IVZ injections. At 12 weeks, significant visual improvement was observed in eyes with baseline VA < 20/50.[17] When considering the baseline data and clinical characteristics, their patients had more severity and chronicity of DME than those in our study. Their patients had older ages, a greater number of previous IVB injections and worse baseline VA. While the visual acuity changes in patients with baseline VA < 20/50 were comparable to our study (0.28 ± 0.34 vs. 0.31 ± 0.08 logMAR), the CMT reduction was greater in our study (365 ± 123 μm vs. 145 ± 175 μm) due to their lower baseline CMT (452 ± 60 μm vs. 618 ± 154 μm). Nawar et al. evaluated the efficacy of ziv-aflibercept in cases of diabetic macular edema (DME) resistant to a three-month course of ranibizumab. Their study, conducted in Egypt, demonstrated significant improvements in both functional and anatomical outcomes, reinforcing ziv-aflibercept's potential as an effective alternative for patients not responding to initial ranibizumab treatment.[18]

Switching therapy to ziv-aflibercept for persistent DME likely had comparable outcomes to aflibercept conversion from a systematic review and meta-analyses, the mean visual improvement after switching to aflibercept was 0.24 logMAR and mean CMT reduction was 113.88 μm at 3 months[4]. Therefore, ziv-aflibercept potentially could offer comparable benefits to aflibercept at a significantly lower cost, making it a potentially effective option for patients with refractory DME.

Several prognostic predictors have been studied in large clinical trials. History of PRP, long duration of DM, poor baseline VA, more severe DME, EMM, foveal atrophy and foveal pigmentation were associated with worse visual outcome[22]. Despite the presence of multiple adverse prognostic factors in our study cohort, ziv-aflibercept still achieved notable visual improvements. Criteria for retreatment and non-responses varied among studies. For instance, while the DRCR.net Protocol I and Protocol T required a CMT > 250 μm for reinjection, our study, along with Ebrahimiadib's applied a threshold of CMT > 300 μm for retreatment. Ebrahimiadib et al reported a non-response rate of 15%, which is comparable to the 16.67% observed in our study[17].

Persistent DME can cause ultrastructural changes and neural damage within the retina, leading to

permanent visual impairment and limiting the potential for vision recovery. The DRCR.net Protocol I study highlighted that initial VA response after 3 injections was a significant prognostic indicator of long-term response and outcomes[23]. Consequently, we withdrew 2 patients who did not respond to 3 monthly IVZ injections. Patients who did respond to ziv-aflibercept continued to show improvements in best-corrected visual acuity (BCVA) throughout the study period

The common complications of IVZ in treatment of DME were subconjunctival hemorrhage (7.89-18.64%) and transient mild anterior chamber reaction (16.48%).[12,16,17] EMM without traction had been reported in one eye[9]. In this study, EMM developed as ocular adverse event in one eye (14.29%) which unfortunately progressed with traction.

The patients with DME may exhibit a lack of response to either specific anti-VEGF agents or to the entire class of medication. Currently, there are no standardized treatment guidelines for refractory DME that does not respond to bevacizumab. Although aflibercept, ranibizumab and dexamethasone implants have proven effective, their high cost limit their accessibility within the public sector[3,4,24,25]. In the real-world perspective, the available treatment options and adjunctive treatments include laser treatment, off-label IVZ, off-label triamcinolone acetonide (TA), and pars plana vitrectomy (PPV). As recent laser therapy may affect retinal thickness and visual outcomes, we excluded patients who had undergone laser treatment within 3 months prior to enrollment to reduce potential confounding.

Focal/grid macular photocoagulation has been employed as a rescue treatment in many clinical trials. However, a study utilizing microperimetry to assess retinal function suggest that focal/grid laser photocoagulation may be associated with worsening of macular function[26]. Data indicated that subthreshold diode micropulse laser photocoagulation may offer superior outcomes compared to conventional and multi-spot laser approaches[27]. Therefore, subthreshold micropulse laser therapy should be considered a valuable adjunctive treatment alongside anti-VEGF.

Switching to off-label intravitreal triamcinolone (IVTA) can provide short-term visual acuity improvements but may be associated with potential complications such as increased IOP and cataract progression, particularly in phakic eyes[28]. Yolcu et al. demonstrated the advantages of combined IVTA and IVB for patients with refractory DME to bevacizumab with CMT > 500 μm, showing benefits at one year of follow-up[29]. The DRCR.net protocol U compared the efficacy of ranibizumab monotherapy with combined ranibizumab and dexamethasone implant in patients with refractory DME. There was no significant difference in visual outcomes[30]. While PPV is a well-established treatment for tractional DME, its role in non-tractional DME remains under investigation. These findings pose significant questions for ophthalmologists, patients, and policymakers regarding the most cost-effective treatments for refractory DME unresponsive to bevacizumab.

The prospective study design and extended follow-up period than previous studies are the strengths of this study. However, there are some limitations including the small sample size, inhomogeneous population and one-armed open-label design.

Conclusions

Refractory DME to bevacizumab remains a significant clinical challenge in real-world practice. Our study demonstrated that off-label use of intravitreal ziv-aflibercept over 6-month period appeared to be a safe and effective treatment for refractory DME to bevacizumab. These results make ziv-aflibercept a potential substitute to aflibercept at a much lower cost. Further studies should assess the safety and long-term outcomes of 1.25 and 2.5 mg ziv-aflibercept in

recalcitrant DME. Large randomized clinical trials with long-term follow-up period are needed to compare ziv-aflibercept and aflibercept.

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ประสิทธิผลและความปลอดภัยของการฉีดยา Ziv-aflibercept เข้าวุ้นตา ในการรักษาผู้ป่วยเบาหวานจอตาบวมน้ำที่ไม่ตอบสนองต่อยา bevacizumab



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บทคัดย่อ:

วัตถุประสงค์: เพื่อประเมินความปลอดภัยและประสิทธิผลของการฉีดยา ziv-aflibercept เข้าวุ้นตา ในผู้ป่วยชาวไทยที่มีภาวะจุดรับภาพชัดบวมน้ำจากเบาหวาน (Diabetic macular edema; DME) ซึ่งไม่ตอบสนองต่อการฉีดยา bevacizumab เข้าวุ้นตา

วิธีการศึกษา: ผู้ป่วยที่มีภาวะ DME ที่ดื้อต่อการรักษา ได้รับการฉีดยา ziv-aflibercept (1.25 mg/0.05 ml) ทุก 1 เดือน จำนวน 3 ครั้ง ในผู้ป่วยที่ตอบสนองต่อการรักษา ได้ใช้แนวทางการรักษาตามความจำเป็นต่อ (pro re nata) ในกรณีที่มีการกลับเป็นซ้ำหรือการบวมน้ำคงอยู่ โดยนิยามจากความหนาบริเวณจุดรับภาพชัด (central macular thickness; CMT) มากกว่า 300 ไมครอน ตัวชี้วัดผลลัพธ์ ได้แก่ ค่าการมองเห็น BCVA ค่า CMT และเหตุการณ์ไม่พึงประสงค์ที่ 6 เดือน ผู้ป่วยทุกรายได้รับการตรวจตาและตรวจด้วย OCT ก่อนเริ่มรักษาและระหว่างการนัดติดตามผลทุกครั้ง

ผลการศึกษา: ผู้ป่วยเบาหวานชนิดที่ 2 จำนวน 7 ราย อายุเฉลี่ย 56.71 ± 5.34 ปี ได้เข้าร่วมการศึกษา จำนวนครั้งเฉลี่ยของการฉีด IVT Bevacizumab ก่อนหน้าเท่ากับ 5.71 ± 2.43 ครั้ง ผู้ป่วยได้รับการเปลี่ยนมาใช้ IVT ziv-aflibercept ภายใน 4–5 สัปดาห์หลังการฉีด IVT Bevacizumab ครั้งสุดท้าย ค่าเฉลี่ย BCVA ดีขึ้นจาก 0.46 ± 0.27 logMAR เป็น 0.32 ± 0.17 logMAR (p = 0.018) ที่ 3 เดือน และ 0.32 ± 0.13 logMAR (p = 0.001) ที่ 6 เดือน ค่า CMT ลดลงจาก 512.71 ± 158.41 ไมโครเมตร เป็น 347.86 ± 122.61 ไมครอน (p = 0.012) ที่ 3 เดือน และ 351.60 ± 117.71 ไมครอน (p = 0.029) ที่ 6 เดือน พบการดื้อต่อการรักษาด้วย ziv-aflibercept 2 ราย จากการศึกษาไม่พบการอักเสบในลูกตา การขุ่นของเลนส์ที่มากขึ้น ความดันลูกตาสูง หรือการเกิดจอประสาทตาลอกหลุดที่เพิ่มขึ้น และไม่พบภาวะแทรกซ้อนทางร่างกายที่รุนแรง

สรุป: การฉีด ziv-aflibercept เข้าวุ้นตาเป็นวิธีการรักษาที่ปลอดภัยในผู้ป่วย DME ที่ดื้อต่อยา bevacizumab และเป็นทางเลือกที่น่าสนใจ โดยเฉพาะในพื้นที่ซึ่งมีทรัพยากรจำกัด อย่างไรก็ตาม ควรมีการศึกษาเพิ่มเติมเพื่อยืนยันประสิทธิผลและความปลอดภัยในระยะยาว

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