Clinical Ophthalmology

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

Effectiveness and Safety of Intravitreal Brolucizumab for Diabetic Macular Edema After Vitrectomy: A Before-and-After Study at a Specialized Center in Japan

Kazuma Saito, Hideo Akiyama

Department of Ophthalmology, Gunma University Graduate School of Medicine, Gunma, 371-8511, Japan

Correspondence: Kazuma Saito, Department of Ophthalmology, Gunma University Graduate School of Medicine, 3-39-15 Showa-machi, Maebashi, Gunma, 371-8511, Japan, Tel +81-27-220-8338, Fax +81-27-220-3841, Email kazuma3110@gunma-u.ac.jp

Purpose: To evaluate the efficacy and safety of intravitreal brolucizumab (IVBr), a vascular endothelial growth factor inhibitor, for injections in vitrectomized eyes with diabetic macular edema (DME) over 1 year.

Patients and Methods: This retrospective before-and-after study analyzed 23 eyes of 20 patients with DME after vitrectomy. Outcomes assessed over 1 year included best-corrected visual acuity (BCVA), central subfield retinal thickness (CST), and the number of IVBr injections administered. The treatment protocol consisted of an initial IVBr injection followed by a pro re nata regimen. If CST did not improve after the last IVBr injection, treatment was switched to intravitreal triamcinolone acetonide injection (IVTA), sub-Tenon's triamcinolone acetonide (STTA) injection, or intravitreal faricimab (IVFa).

Results: Seven eyes (30.4%) completed one-year IVBr treatment. There was no significant change in BCVA during the treatment period (LogMAR BCVA [mean±standard error]: baseline, 0.44±0.10; 6 months, 0.35±0.12 [P=0.22]; at 1 year, 0.37±0.11 [P=0.24]). However, CST (mean±standard error) significantly improved from baseline (558±36.3 μm) to 6 months (338±27.1 μm [P<0.05]) and 1 year (307±20.4 μm [P<0.05]). The mean number of IVBr injections was 3.6±1.3 (mean±standard deviation). Of the 16 eyes (69.6%) from 14 patients who did not complete one-year IVBr treatment, 11 eyes showed no CST improvement following the last IVBr injection, prompting a switch to IVTA, STTA, or IVFa in seven, one, or three eyes, respectively. Additionally, IVBr treatment was discontinued in one eye due to intraocular inflammation, while four patients (four eyes) dropped out within 1 year after starting treatment.

Conclusion: Our findings demonstrated partial efficacy of IVBr in managing DME in vitrectomized eyes. However, variable responses often necessitate supplementary treatments to achieve therapeutic goals.

Keywords: anti-vascular endothelial growth factor, diabetes, intraretinal edema, vitrectomy, best-corrected visual acuity, central subfield retinal thickness

Introduction

Diabetic macular edema (DME) is a leading cause of vision loss in patients with diabetes mellitus. A meta-analysis spanning 35 countries since 2000 indicates that the prevalence of diabetic retinopathy in the global diabetic population aged 20–79 years is 24.79%, with DME accounting for 5.46%.[1] Treatments for DME include intravitreal injections of anti-vascular endothelial growth factor (anti-VEGF) drugs, steroid injection, retinal photocoagulation, and vitrectomy. Vitrectomy is typically reserved for DME cases that are refractory to drug therapy and retinal photocoagulation or for those with complications such as epiretinal membrane or vitreomacular traction syndrome.[2] However, DME can persist even after vitrectomy. Mukai et al[3] reported that approximately 40% of patients with DME refractory to drug therapy showed no improvement in edema 1 year after undergoing vitrectomy. The vitrectomized eyes with DME are often

Received: 26 January 2025
Accepted: 13 June 2025
Published: 23 June 2025

treated with local steroid injection therapy for eyes or intravitreal injections of anti-VEGF agents. However, the absence of the vitreous in vitrectomized eyes can increase drug clearance, potentially reducing the efficacy of anti-VEGF drugs.[4]

Nevertheless, ranibizumab and aflibercept have been reported to be effective in real-world applications for vitrectomized eyes with DME.[5,6] Brolucizumab, a humanized anti-VEGF monoclonal antibody single-chain Fv fragment, has a smaller molecular weight and a molar equivalent per dose that is 12 times higher than that of aflibercept and approximately 22 times higher than that of ranibizumab.[7] Brolucizumab is therefore considered to have greater anti-VEGF activity. However, no studies have yet investigated the efficacy of brolucizumab in vitrectomized eyes with DME, and its safety profile remains to be determined. In the present study, we investigated the efficacy and safety of brolucizumab in vitrectomized eyes with DME.

Patients and Methods

Patients and Study Approval

This study was approved by the Institutional Review Board of Gunma University Hospital and adhered to the guidelines of the Declaration of Helsinki (HS2002-252). Informed consent was obtained from all participants. This retrospective before-and-after study included patients with DME after vitrectomy who received intravitreal injections of brolucizumab (IVBr) between July 2022 and October 2023 at Gunma University Hospital.

Inclusion Criteria and Treatment Protocol

Inclusion criteria were as follows: eyes with DME, a history of vitrectomy, and central subfield retinal thickness (CST) >300 μm. The eyes were treated with IVBr (6 mg/0.05 mL). After the initial IVBr administration, treatment followed a pro re nata (PRN) regimen. In the present study, the protocol reflected real-world clinical practice, and since the accompanying text permits administration at 6-week intervals for up to 5 doses, the minimum 6-week interval was used, and after the 5th dose, the minimum 8-week interval was used in accordance with the accompanying text. Readministration was based on the treating physician's assessment, and additional IVBr was administered if DME worsened or if intraretinal edema persisted. Brolucizumab treatment was discontinued if non-infectious intraocular inflammation (IOI) occurred. If there was no reduction in CST after IVBr administration, even if it is the first dose, alternative treatments were administered, including intravitreal faricimab injection (IVFa) (6 mg/0.05 mL), sub-Tenon's triamcinolone acetonide injection (STTA) (30 mg/0.75 mL), or intravitreal triamcinolone acetonide injection (IVTA) (4 mg/0.1 mL). Focal retinal photocoagulation was also performed if focal edema from microaneurysms was observed.

Ophthalmologic Assessments

At each visit, all patients underwent the following: best-corrected visual acuity (BCVA) assessment, intraocular pressure (IOP) measurement, slit-lamp biomicroscopy (conducted with a non-contact fundus lens), color fundus photography (conducted using Canon CX-1; Canon Medtech Supply Corporation), and optical coherence tomography (OCT) (carried out using either DRI OCT-1 Triton [Topcon] or Xephilio OCT-S1 [Canon]). The CST was defined as the mean retinal thickness within a 1-mm diameter area centered on the fovea and was automatically calculated using the OCT software. BCVA was determined using manifest refraction, and recorded as decimal values, then converted to the logarithm of the minimal angle of resolution (logMAR) units.

Safety Assessment

We also investigated adverse events related to brolucizumab. This investigation covered both ocular and extraocular adverse events.

Statistical Analysis

The Wilcoxon signed-rank test was used to compare differences in BCVA and CST between baseline and subsequent time points. Data were analyzed using Microsoft Excel and the Bell Curve for Excel add-in software (Social Survey

Research Information Co., Ltd). A *P*-value of <0.05 was considered statistically significant. BCVA and CST data are presented as mean ± standard error (SE), while other data are expressed as mean ± standard deviation (SD).

Results

The study included 23 eyes from 20 patients with DME following vitrectomy, comprising 10 men and 10 women, with a mean age of 63.5 ± 14.3 years. Baseline demographic and clinical characteristics are shown in Table 1. All 23 eyes had proliferative diabetic retinopathy and had undergone post-panretinal photocoagulation. The reasons for vitrectomy included DME complicated by the epiretinal membrane (nine eyes), macular hole (one eye), DME refractory to drug and laser therapy (six eyes), and vitreous hemorrhage (seven eyes). All patients had undergone internal limiting membrane peeling during vitrectomy. There were no eyes injected with silicone oil. DME first developed after vitrectomy in six of the 23 eyes; of these, five had vitreous hemorrhage, and one had a macular hole. Of the 23 eyes treated with IVBr, 11 had received prior treatment with other anti-VEGF agents, 18 had been treated with STTA or IVTA., and one had undergone retinal photocoagulation after vitrectomy.

Eyes Completing 1 Year of IVBr Treatment

Seven of the 23 eyes were successfully treated with IVBr for 1 year. The baseline demographic and clinical characteristics of these patients are shown in Table 2. Of the seven eyes, five had a history of prior anti-VEGF therapies, and six had received local steroid injection therapy after vitrectomy. BCVA, measured as LogMAR, showed no significant improvement during the treatment period. Baseline LogMAR was 0.44 ± 0.1, which decreased to 0.35 ± 0.12 at 6 months (P = 0.22) and 0.37 ± 0.11 at 1 year (P = 0.24) (Figure 1). However, CST showed significant improvement after treatment. The mean baseline CST was 558 ± 36.3 μm, which decreased to 338 ± 27.1 μm at 6 months (P<0.05) and 307

Table 1 Baseline Demographic and Clinical Characteristics of All Patients with DME After Vitrectomy

Number of eyes		23
Number of patients		20
Age (years), median [Q1–Q3]		67 [19–72]
Men		10 (50%)
Best-corrected visual acuity (logMAR), mean±SD		0.49±0.26
Central subfield thickness (μm), mean±SD		519±143
IOP (mmHg), mean±SD		15.1±3.1
Phakic/IOL		4/19
Type of DM(Type1/Type2)		0/20
Duration of diabetes (years), median [Q1–Q3]		6 [5–11]
HbA1c (%), mean±SD		6.9±1.0
Duration of DME (M), median [Q1–Q3]		59 [12–64]
Duration between DME onset to PPV (M), mean±SD		23.1±22.9
Duration between PPV to first IVBr (M), median [Q1–Q3]		19 [6–32]
Anti-VEGF	After PPV, median [Q1–Q3]	3 [1–7]
	Before PPV, median [Q1–Q3]	0 [0–2]
Steroid	After PPV, median [Q1-Q3]	0 [0–0]
	Before PPV, median [Q1-Q3]	2 [1–8]
Type of DME	Cystoid	20 (87%)
	Retinal swelling	11 (49%)
	Subretinal fluid	5 (22%)

Abbreviations: DME, diabetic macular edema; logMAR, the logarithm of the minimal angle of resolution; SD, standard deviation; IOP, intraocular pressure; IOL, intraocular lens; DM, diabetes mellitus; HbA1c, Hemoglobin A1c; PPV, pars plana vitrectomy; IVBr, intravitreal brolucizumab; VEGF, vascular endothelial growth factor.

https://doi.org/10.2147/OPTH.S519313

Table 2 Baseline Demographic and Clinical Characteristics of Patients with DME After Vitrectomy Who Completed 1 year of Brolucizumab Treatment

Number of eyes		7
Number of patients		7
Age (years), median [Q1–Q3]		54.7±16.1
Men		6 (86%)
Best-corrected visual acuity (logMAR), mean±SD		0.44±0.28
Central subfield thickness (μm), mean±SD		558±96
IOP (mmHg), mean±SD		14.6±3.7
Phakic/IOL		4/3
Duration of diabetes (years), median [Q1–Q3]		7.6±3.2
HbA1c (%), mean±SD		7.3±1.0
Duration of DME (M), median [Q1–Q3]		37±23
Duration between DME onset to PPV (M), mean±SD		18±23
Duration between PPV to first IVBr (M), median [Q1–Q3]		19±9.5
Anti-VEGF	After PPV, mean±SE	4.7±4.6
	Before PPV, mean±SE	2.1±2.0
Steroid,	After PPV, median [Q1-Q3] min, max	0 [0–0] 0,1
	Before PPV, mean±SE	3.4±1.3
Type of DME	Cystoid	5 (71%)
	Retinal swelling	4 (57%)
	Subretinal fluid	1 (14%)

Abbreviations: DME, diabetic macular edema; logMAR, the logarithm of the minimal angle of resolution; IOP, intraocular pressure; IOL, intraocular lens; SE, standard error; HbA1c, Hemoglobin A1c; PPV, pars plana vitrectomy; IVBr, intravitreal brolucizumab; VEGF, vascular endothelial growth factor.

± 20.4 μm at 1 year (P<0.05) (Figure 2). The average (mean ± SD) number of IVBr injections during the one-year treatment was 3.6 ± 1.3. One of the seven eyes required focal photocoagulation for microaneurysms causing focal DME.

Eyes Discontinuing IVBr Treatment and Adverse Events

Of the 16 eyes (69.6%) from 14 patients who did not complete 1-year of IVBr treatment, 11 did not show a reduction in CST after the last IVBr injection. Consequently, treatment switch was initiated. Seven eyes were switched to IVTA, one to STTA, and three to IVFa. IVBr treatment was discontinued in one eye due to IOI. Additionally, four patients (four eyes) dropped out within 1 year after starting brolucizumab treatment.Eight of the 11 eyes in which CST did not decrease after the last IVBr injection had previously received IVTA or STTA between vitrectomy and the first IVBr, including five eyes that responded to IVTA or STTA. The CST (mean ± SE) in the eyes where treatment was switched from IVBr to IVTA was 527 ± 57 μm before the switch and 323 ± 86 μm, 1 month after the switch, showing a significant improvement (P < 0.05, Wilcoxon signed-rank test). Two-thirds of the eyes where treatment was switched from IVBr to IVFa also exhibited decreased edema after the switch. One eye, where IVBr treatment was discontinued due to IOI, developed anterior chamber inflammation with posterior corneal deposits after the second IVBr injection (9 weeks after the first IVBr). The IOI was treated with a conjunctival injection of dexamethasone sodium phosphate (1.3 mg/0.3 mL) and 0.1% betamethasone eye drops, leading to improvement without loss of vision. No cases of vitritis, retinal vasculitis, or retinal vascular occlusion were observed. No extraocular complications occurred.

Discussion

The purpose of this study was to investigate the efficacy and safety of IVBr for DME after vitrectomy. In our study, among the seven out of 23 (30.4%) eyes treated with IVBr therapy for 1 year, there was no significant difference in visual acuity, but the CST improved significantly from baseline to 1 year after treatment. These findings strongly suggest the

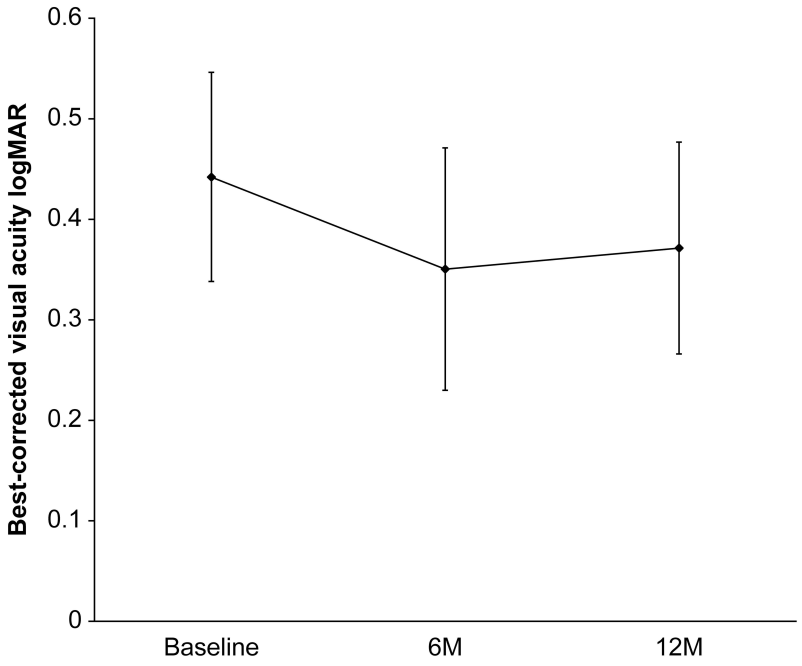

Figure 1 Changes in average BCVA in seven eyes with DME after vitrectomy followed by 1 year of brolucizumab treatment. There was no significant difference in visual acuity. Data are expressed as mean±SE.
Abbreviations: BCVA, best-corrected visual acuity; DME, diabetic macular edema; M, months; logMAR, the logarithm of the minimal angle of resolution; SE, standard error.

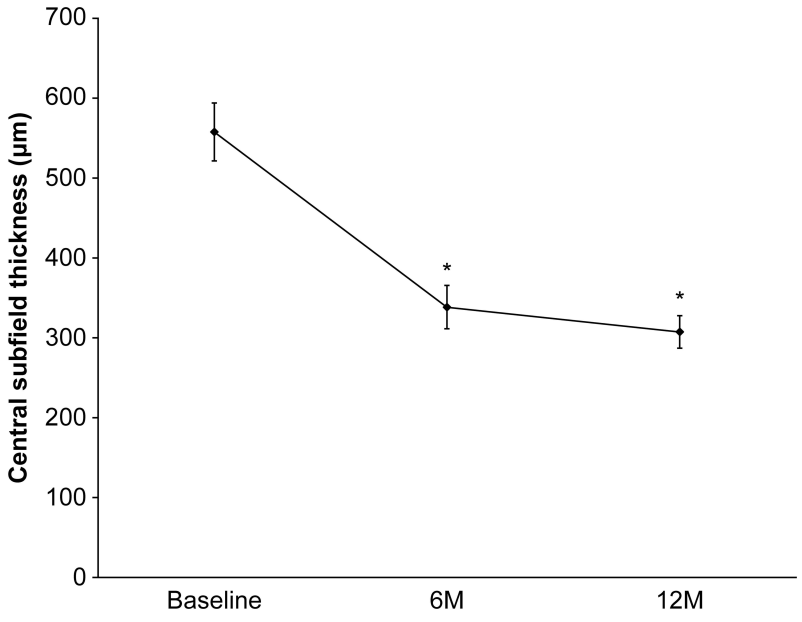

Figure 2 Changes in average CST in seven eyes with DME after vitrectomy followed by 1 year of brolucizumab treatment. There were significant improvements in CST after the first injection of brolucizumab (*$P < 0.05$). Data are expressed as mean±SE.
Abbreviations: CST, subfield retinal thickness; DME, diabetic macular edema; M, months; SE, standard error.

potential utility of brolucizumab for treating DME after vitrectomy in terms of retinal fluid control. One case of IOI occurred as a side effect of IVBr. Even after vitrectomy, caution is required regarding the onset of IOI.

In our study, we observed a mean improvement of approximately 3.5 letters in Early Treatment Diabetic Retinopathy Study (ETDRS) scores in eyes completing 1 year of IVBr treatment. The KESTREL/KITE Phase III trial of brolucizumab for DME reported an improvement in BCVA of +9.2 letters/+10.6 letters at 1 year post-treatment.[8] It has been

https://doi.org/10.2147/OPTH.S519313

suggested that the absence of vitreous in a vitrectomized eye may increase drug clearance and decrease the efficacy of anti-VEGF drugs.[8] However, it is unclear from our study whether vitrectomy played a role in the lack of visual gain with IVBr treatment for DME. Chen et al[9] reported an improvement in LogMAR BCVA from 0.78±0.36 at baseline to 0.49 ±0.35 ($P < 0.001$) at 6 months after three consecutive doses of ranibizumab followed by a PRN regimen. Similarly, Tran et al[6] observed that PRN treatment of postoperative DME following five consecutive doses of aflibercept led to an improvement of +6 letters in ETDRS scores (baseline 53.5±14.7, $P < 0.001$) at 1 year. In comparison, the visual acuity improvement observed in the current study was smaller.

It is well-known that poor baseline visual acuity is a strong predictor of visual acuity improvement with anti-VEGF therapy in DME.[10,11] The relatively better baseline visual acuity in our study, compared to previous reports,[6,9] may explain why there was no significant difference in visual acuity improvement. On the other hand, the CST in our study was −219 ± 148 μm (39.2% decrease) at 6 months and −250 ± 139 μm (44.8% decrease) at 1 year after treatment. Chen et al[9] reported a CST change of −111 ± 98 μm at 6 months, while Tran et al[6] reported a median CST reduction of 15% (−65 μm, 95% confidence interval [CI]: [−107, −22.7]) at 6 months and 25% (−108 μm, CI [−67, −149]) at 1 year. The CST reduction observed in our study was greater than that reported by Chen et al[9] and Tran et al.[6] Moreover, the number of IVBr injections in our study was 3.6 ± 1.3 per year, compared to 4.12 ± 0.58 for IVR at 6 months[9] and 9.3 ± 1.8 for intravitreal Aflibercept (IVA) at 12 months[6] in the other studies. The number of anti-VEGF drug administrations in our study was lower. These findings suggest that IVBr for vitrectomized eyes with DME may reduce edema with fewer injections compared to IVR and IVA. Direct comparisons with other anti-VEGF agents and local steroid injection therapy for eyes are needed to assess the effect of brolucizumab on DME after vitrectomy. The small number of DME cases after vitrectomy, however, limits single-center, multidrug comparative studies. We believe that a collaborative study with a larger number of patients at multiple centers is needed to investigate the effect of brolucizumab on DME after vitrectomy.

In our study, DME did not improve with IVBr in 11 of the 23 eyes. Among these, DME decreased after switching to steroid injection treatments in all seven eyes that were switched from IVBr to IVTA and in one eye switched from IVBr to STTA. While VEGF is a key molecule in the pathogenesis of macular edema, DME is a multifactorial disease with numerous therapeutic targets.[12] Inflammatory mediators and cascades play a significant role in the pathogenesis of diabetic retinopathy and macular edema, particularly during the chronic phase.[13,14] Corticosteroids are potent anti-inflammatory agents that inhibit VEGF activation and reduce the synthesis of inflammatory mediators associated with increased vascular permeability. Thus, corticosteroid treatment for DME is considered more comprehensive than anti-VEGF therapy, which targets only part of the inflammatory cascade.[15] In patients with chronic DME who had previously received at least three bevacizumab injections, switching to 4 mg/0.1 mL intravitreal triamcinolone acetonide resulted in significant improvements in visual acuity and reductions in retinal thickness as early as 1 month after injection, with effects maintained up to 6 months.[16] Therefore, in patients with DME resistant to anti-VEGF drugs, intravitreal steroid therapy, such as IVTA, may be effective even after vitrectomy.

IOI should be considered a potential side effect of IVBr. In the KESTREL study, IOI was reported in 4.7% (n=9), 3.7% (n=7), and 0.5% (n=1) of patients in the 3 mg brolucizumab, 6 mg brolucizumab, and aflibercept groups, respectively. In the KITE study, IOI was reported at similar rates in the 6 mg brolucizumab group (1.7% [n=3]) and the aflibercept group (1.7% [n=3]). Additionally, in the KESTREL study, retinal vasculitis/vascular occlusion was reported in one patient (0.5%) in the 6 mg brolucizumab group.[8] In our study, IOI developed in one eye following IVBr treatment; however, local steroid treatment improved the ocular inflammation without resulting in visual impairment. Mukai et al[17] identified old age, female sex, and a history of diabetes as risk factors for the development of IOI during brolucizumab treatment for age-related macular degeneration, suggesting that caution should be exercised when treating DME with brolucizumab.

This study has several limitations. First, Due to the small number of cases in this study, it was not possible to statistically analyze the clinical background and ocular findings of DME in which brolucizumab was effective. Second, IVBr treatment was not standardized as a treatment strategy, as the protocol was not uniform. After the first IVBr injection, patients were treated on a PRN basis; however, strict criteria for additional dosing were not established. In some cases, even when a physician proposed additional IVBr injections, the treatment was not administered due to economic constraints. Many patients with DME cannot receive active treatment due to

financial constraints, and the results may reflect the actual clinical outcomes of IVBr treatment. Third, patients who switched to other DME treatments during the observation period were excluded, as multiple treatment options were available for DME other than anti-VEGF agents. This forced a mid-course change in treatment, and the exclusion of refractory cases may have biased the sample toward those with relatively favorable outcomes. Fourth, local steroid injections for eyes and other anti-VEGF drugs are administered prior to IVBr treatment, and it is possible that these interventions prior to IVBr treatment may affect the outcome of the treatment.

Conclusion

This real-world retrospective study demonstrated that IVBr effectively reduced CST in some patients with DME after vitrectomy. However, improvements in visual acuity were limited, likely due to the baseline BCVA in this cohort. In terms of retinal fluid control, IVBr can be an option for the treatment of DME after vitrectomy. However, care must be taken regarding the side effect of IOI.

Abbreviations

BCVA, Best-Corrected Visual Acuity; CST, Central Subfield Thickness; DME, Diabetic Macular Edema; ETDRS, Early Treatment Diabetic Retinopathy Study; IOI, Intraocular Inflammation; IVBr, Intravitreal Brolucizumab; IVR, Intravitreal Ranibizumab; IVA, Intravitreal Aflibercept; IVTA, Intravitreal Triamcinolone Acetonide; LogMAR, Logarithm of the Minimum Angle of Resolution; PRN, Pro Re Nata (as needed); STTA, Subtenon Triamcinolone Acetonide; VEGF, Vascular Endothelial Growth Factor.

Ethics Approval and Consent to Participate

This study was approved by the Institutional Review Board of the Gunma University Hospital and adhered to the guidelines of the Declaration of Helsinki (HS2002-252). Informed consent was obtained from all participants.

Acknowledgments

The authors thank Editage for English language editing of this manuscript (www.editage.com).

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

The authors did not receive support from any organization for the submitted work.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Yau JWY, Rogers SL, Kawasaki R, et al. Global prevalence and major risk factors of diabetic retinopathy. *Diabetes Care*. 2012;35(3):556–564. doi:10.2337/dc11-1909
2. Yoshida S, Murakami T, Nozaki M, et al. Review of clinical studies and recommendations for a therapeutic flowchart for diabetic macular edema. *Graefes Arch Clin Exp Ophthalmol*. 2021;259(4):815–836. doi:10.1007/s00417-020-04936-w
3. Mukai R, Matsumoto H, Akiyama H. Surgical outcomes of vitrectomy for intractable diabetic macular edema. *Graefes Arch Clin Exp Ophthalmol*. 2021;259(2):363–368. doi:10.1007/s00417-020-04898-z
4. Niwa Y, Kakinoki M, Sawada T, et al. Ranibizumab and Aflibercept: intraocular pharmacokinetics and their effects on aqueous VEGF level in vitrectomized and non-vitrectomized macaque eyes. *Invest Ophthalmol Vis Sci*. 2015;56(11):6501–6505. doi:10.1167/iovs.15-17279
5. Koyanagi Y, Yoshida S, Kobayashi Y, et al. Comparison of the effectiveness of intravitreal ranibizumab for diabetic macular edema in vitrectomized and nonvitrectomized eyes. *Ophthalmologica*. 2016;236(2):67–73. doi:10.1159/000446992

6. Tran THC, Erginay A, Verdun S, et al. One-year outcome of aflibercept intravitreal injection in vitrectomized eyes with diabetic macular edema. *Clin Ophthalmol*. 2021;15:1971–1978. doi:10.2147/OPTH.S304030
7. Tatsumi T. Current treatments for diabetic macular edema. *Int J Mol Sci*. 2023;24(11):9591. doi:10.3390/ijms24119591
8. Brown DM, Emanuelli A, Bandello F, et al. Kestrel and KITE: 52-week results from two phase III pivotal trials of brolucizumab for diabetic macular edema. *Am J Ophthalmol*. 2022;238:157–172. doi:10.1016/j.ajo.2022.01.004
9. Chen YY, Chen PY, Chen FT, Chen YJ, Wang JK. Comparison of efficacy of intravitreal ranibizumab between non-vitrectomized and vitrectomized eyes with diabetic macular edema. *Int Ophthalmol*. 2018;38(1):293–299. doi:10.1007/s10792-017-0462-1
10. Nguyen QD, Brown DM, Marcus DM, et al. Ranibizumab for diabetic macular edema: results from 2 Phase III randomized trials: RISE and RIDE. *Ophthalmology*. 2012;119(4):789–801. doi:10.1016/j.ophtha.2011.12.039
11. Diabetic Retinopathy Clinical Research Network; Wells JA, Glassman AR, Ayala AR, et al. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema. *N Engl J Med*. 2015;372(13):1193–1203. doi:10.1056/NEJMoa1414264
12. Miller K, Fortun JA. Diabetic macular edema: current understanding, pharmacologic treatment options, and developing therapies. *Asia Pac J Ophthalmol*. 2018;7(1):28–35. doi:10.22608/APO.2017529
13. Noma H, Mimura T, Yasuda K, Shimura M. Role of inflammation in diabetic macular edema. *Ophthalmologica*. 2014;232(3):127–135. doi:10.1159/000364955
14. Funatsu H, Noma H, Mimura T, Eguchi S, Hori S. Association of vitreous inflammatory factors with diabetic macular edema. *Ophthalmology*. 2009;116(1):73–79. doi:10.1016/j.ophtha.2008.09.037
15. Sohn HJ, Han DH, Kim IT, et al. Changes in aqueous concentrations of various cytokines after intravitreal triamcinolone versus bevacizumab for diabetic macular edema. *Am J Ophthalmol*. 2011;152(4):686–694. doi:10.1016/j.ajo.2011.03.033
16. Hong IH, Choi W, Han JR. The effects of intravitreal triamcinolone acetonide in diabetic macular edema refractory to anti-VEGF treatment. *Jpn J Ophthalmol*. 2020;64(2):196–202. doi:10.1007/s10384-019-00710-6
17. Mukai R, Matsumoto H, Akiyama H. Risk factors for emerging intraocular inflammation after intravitreal brolucizumab injection for age-related macular degeneration. *PLoS One*. 2021;16(12):e0259879. doi:10.1371/journal.pone.0259879