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Effect of anti-vascular endothelial growth factor on early-stage post-vitrectomy macular edema in patients with proliferative diabetic retinopathy

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Abstract

Purpose To investigate the effectiveness of anti-vascular endothelial growth factor (VEGF) therapy on post-vitrectomy macular edema (PVME) and determine the risk factors for PVME recovery.

Methods This retrospective study included 179 eyes of 179 patients who underwent pars plana vitrectomy for proliferative diabetic retinopathy and developed PVME within 3 months after surgery. Eyes were grouped according to postoperative anti-VEGF treatment.

Results Central retinal thickness (CRT) decreased significantly from baseline to 3-month follow-up in groups with (509.9 ± 157.2 μm vs. 401.2 ± 172.1 μm, $P < 0.001$) or without (406.1 ± 96.1 μm vs. 355.1 ± 126.0 μm, $P = 0.008$) postoperative anti-VEGF treatment. Best-corrected visual acuity (BCVA) did not differ between the two groups during follow-up. In the group not receiving anti-VEGF therapy, BCVA was significantly improved at 1, 2, and 3 months ($P = 0.007$, $P < 0.001$, and $P < 0.001$, respectively), while in the anti-VEGF group, BCVA was significantly improved at 1 and 3 months ($P = 0.03$ and $P < 0.001$). A thicker baseline CRT ($\beta = 0.44$; 95% confidence interval, 0.26–0.61; $P < 0.001$) was significantly associated with decreasing CRT.

Conclusion PVME tends to spontaneously resolve in the early postoperative period. The effect of anti-VEGF therapy in the first 3 months after diagnosis appears to be limited.

Keywords Diabetic macular edema, Proliferative diabetic retinopathy, Vitrectomy, Postoperative, Anti–vascular endothelial growth factor

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Introduction

Nearly all patients with diabetes mellitus eventually develop diabetic retinopathy, a microvascular disease of the retina [1, 2]. Two diabetic retinopathy complications cause vision loss: diabetic macular edema (DME) and proliferative diabetic retinopathy (PDR).

DME is characterized by accumulation of exudative fluid in the macula. Although its mechanism has not been completely elucidated, blood–retina barrier disruption and increased vascular permeability caused by upregulation of vascular endothelial growth factor (VEGF) and inflammatory cytokines as well as accumulation of advanced glycation end products are thought to be involved [3, 4]. When diabetic retinopathy progresses to PDR, pars plana vitrectomy (PPV) may be required to remove vitreous opacities, fibrovascular proliferation and retinal traction; separate and excise the thickened posterior hyaloid; treat retinal detachment; and improve retinal ischemia [5, 6]. Despite recent advances in PPV, post-vitrectomy macular edema (PVME) is common and may hinder postoperative visual recovery in patients with PDR. One retrospective cohort study of 100 patients with PDR who underwent primary PPV reported that 11 developed PVME and received additional treatment [7]. A secondary analysis of this cohort showed a significant association between insulin treatment and reduced risk of PVME [8].

Development of PVME is associated with elevated levels of various cytokines, including interleukins, TNF-α, CXCL9, G-CSF, MCP-1, and RANTES [9, 10]. PVME after PPV for PDR is treated in the same way as DME clinically: intravitreal injection of anti-VEGF in conjunction with optimizing control of blood glucose, blood pressure, and blood lipids. However, the effect of anti-VEGF may be limited in certain cases [11–15].

Few studies have examined the effectiveness of anti-VEGF therapy on PVME. Therefore, this study aimed to do so. Moreover, we investigated potential risk factors for PVME recovery.

Methods

This retrospective study included patients who underwent PPV for PDR from January 2018 to March 2022 in the Eye Hospital of Wenzhou Medical University and developed PVME within 3 months of surgery. Patient data were obtained from archived electronic medical records. Patients with a history of PPV, penetrating ocular trauma, or any other ocular conditions which are associated with ME formation were excluded. We also excluded patients with less than 3 months of follow-up or non-gradable ME on optical coherence tomography and those who underwent silicone oil tamponade or any intraocular surgery within 3 months of PPV. Patients who experienced a serious postoperative complication, such as neovascular glaucoma, retinal artery occlusion, or endophthalmitis were excluded as well. Eyes were grouped according to postoperative anti-VEGF treatment status. The study only enrolled the right eye if a patient had both eyes that matched the criteria. The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Human Ethics Committee Institutional Review Board of the Eye Hospital of Wenzhou Medical University before commencement (approval number: 2022-J-117). Informed consent was waived since the data analyzed in this study were deidentified.

The 23- or 25-gauge PPVs were performed under retrobulbar (50% mixture of 2% lidocaine and 0.75% bupivacaine) or general anesthesia using a Stellaris PC (Bausch & Lomb, Bridgewater Township, NJ, USA) or Constellation Vision System (Alcon Laboratories, Fort Worth, TX, USA) vitrectomy machine. Peeling of the internal limiting membrane (ILM) or epiretinal membrane and any other additional procedures were performed at the surgeon's discretion. Moreover, the choice of anti-VEGF agents and treatment decision was left to the physician's discretion.

Spectral-domain optical coherence tomography (Spectralis; Heidelberg Engineering, Heidelberg, Germany) was performed with a 30° scanning angle (9×9 mm) at the central macula for image acquisition and analysis. Central retinal thickness (CRT) was measured at the central 1-mm region of the standard Early Treatment Diabetic Retinopathy Study subfield. The diagnosis of PVME was confirmed if the CRT was over 300 μm [16, 17]. PVME was categorized in to three subgroups: diffuse retinal thickening (DRT), a sponge-like retinal swelling of the macula with reduced intraretinal reflectivity; cystoid macular edema (CME), intraretinal cystoid spaces of low reflectivity and highly reflective septa separating cystoid-like cavities in the macular area; and serous retinal detachment (SRD), a shallow elevation of the retina and an optically clear space between the neurosensory retina and retinal pigment epithelium [18]. CRT and best corrected visual acuity (BCVA) were recorded at baseline (time of PVME diagnosis) and during follow-up. Change in CRT was calculated as the difference between the baseline and 3-month follow-up CRT values. PDR was categorized as follows: stage 1, neovascularization of the retina, vitreous hemorrhage, or preretinal hemorrhage; stage 2, stage 1 criteria plus the presence of fibrovascular membranes; and stage 3, stage 2 criteria plus the presence of tractional retinal detachment [19].

Statistical analyses were performed using SPSS software version 25.0 (IBM Corp., Armonk, NY, USA) and R software (version 4.2.2, R Foundation for Statistical Computing, Vienna, Austria). Visual acuities in the decimal system were converted to logarithm of the minimum angle of resolution (logMAR) values. A

BCVA value < 0.01 was recorded as logMAR 2.0. Categorical variables were compared using the chi-square or Fisher exact test as appropriate. Continuous variables with a non-normal distribution were compared using the Wilcoxon rank-sum test; those with a normal distribution were compared using the independent t-test. Baseline and follow-up CRT values were compared using repeated measures analysis of variance followed by Bonferroni multiple comparison testing. BCVA was compared between the groups using the Wilcoxon rank-sum test. Baseline and follow-up BCVA values were compared using the Kruskal–Wallis test. All variables with a P-value < 0.1 in univariate liner regression analysis or variables considered clinically meaningful were entered into multivariate liner regression analysis to examine risk factors influencing the change in CRT. Propensity score matching analysis was performed to balance the heterogeneity. $P < 0.05$ was considered significant.

Table 1 Patient characteristics according to group

Category	No anti-VEGF group ($n = 100$)	Anti-VEGF group ($n = 79$)	*P*-value
Age (mean ± SD, years)	57.4 ± 10.7	56.6 ± 10.4	0.64
Gender (n, %)	62 (62.0)	49 (62.0)	0.99
Male	38 (38.0)	30 (38.0)	
Female			
Laterality (n, %)	50 (50.0)	42 (53.2)	0.67
Right	50 (50.0)	37 (46.8)	
Left			
Grade of PDR (n, %)	33 (33.0)	32 (40.5)	**0.03**
Stage 1	34 (34.0)	36 (45.6)	
Stage 2	33 (33.0)	11 (13.9)	
Stage 3			
Duration of DM (n, %)	26 (26.0)	24 (30.4)	0.31
< 10 years	47 (47.0)	39 (49.4)	
10 ~ 20 years	27 (27.0)	16 (20.3)	
≥20 years			
HbA1c (mean ± SD, %)	8.0 ± 1.5	8.1 ± 1.7	0.96
FPG (mean ± SD, mmol/L)	8.2 ± 2.9	8.3 ± 2.5	0.77
ILM peeling during vitrectomy (n, %)	26 (26.0)	22 (27.8)	0.78
No	74 (74.0)	57 (72.2)	
Yes			
Combined cataract surgery during vitrectomy (n, %)	19 (19.0)	10 (12.7)	0.25
No	81 (81.0)	69 (87.3)	
Yes			
DME before vitrectomy (n, %)	20 (30.8)	30 (53.6)	**0.01**
No	45 (69.2)	26 (46.4)	
Yes			
Time for diagnosis of PVME (mean ± SD, days)	13.6 ± 14.4	19.3 ± 18.2	**0.02**
CRT (mean ± SD, μm)	406.1 ± 96.1	509.9 ± 157.2	**< 0.001**
BCVA (logMAR) *	0.8 (0.5, 1.5)	0.8 (0.5, 1.3)	0.71
Pattern of PVME (n, %)	36 (36.0)	40 (50.6)	**0.007**
CME	57 (57.0)	27 (34.2)	
DRT	7 (7.0)	12 (15.2)	
SRD			
Number of injections	-	2.2 ± 0.7	-

VEGF, vascular endothelial growth factor; SD, standard deviation; PDR, proliferative diabetic retinopathy; DM, diabetes mellitus; FPG: fasting plasma glucose; ILM, internal limiting membrane; DME, diabetic macular edema; PVME, post-vitrectomy macular edema; CRT, central retinal thickness; BCVA, best corrected visual acuity; CME, cystoid macular edema; DRT, diffuse retinal thickening; SRD, serous retinal detachment

*Presented as medians (interquartile range) and tested using the Wilcoxon rank-sum test

Results

A total of 179 eyes from 179 patients were included for analysis. The mean patient age was 57.1 ± 10.5 years. One hundred eleven patients were men (62.0%). Patient characteristics in the anti-VEGF and no anti-VEGF groups are shown in Table 1. The groups significantly differed in terms of PDR grade ($P = 0.03$), DME before PPV ($P = 0.01$), time for diagnosis of PVME ($P = 0.02$), and pattern of PVME ($P = 0.007$). Baseline CRT was significantly greater in the anti-VEGF group (509.9 ± 157.2 μm vs. 406.1 ± 96.1 μm; $P < 0.001$). The mean number of injections per patient in the anti-VEGF group was 2.2 ± 0.7 within 3 months follow-up.

Figure 1 shows the changes in CRT over time in both groups during follow-up. In the no anti-VEGF group, CRT decreased from 406.1 ± 96.1 μm at baseline to 383.9 ± 116.9 μm at 1 month ($P = 0.57$), 375.6 ± 137.0 μm at 2 months ($P = 0.22$), and 355.1 ± 126.0 μm at 3 months ($P = 0.008$). In contrast, CRT in the anti-VEGF group significantly decreased from 509.9 ± 157.2 μm at baseline to 436.3 ± 164.1 μm at 1 month ($P = 0.02$), 432.8 ± 166.6 μm at 2 months ($P = 0.01$), and 401.2 ± 172.1 μm at 3 months ($P < 0.001$).

BCVA values over time are shown in Table 2. BCVA did not significantly differ between the groups at any point. In the no anti-VEGF group, BCVA was significantly improved over baseline at 1, 2 and 3 months ($P = 0.007$, $P < 0.001$, and $P < 0.001$, respectively). In the anti-VEGF group, BCVA was significantly improved at 1 and 3 months ($P = 0.03$ and $P < 0.001$).

Thicker baseline CRT ($\beta = 0.44$; 95% confidence interval, 0.26–0.61; $P < 0.001$) was significantly associated with decreasing CRT; anti-VEGF therapy was not (Table 3).

Propensity score matching resulted in 50 matched pairs of patients. Patient characteristics of the matched pairs are shown in Supplementary Table 1. CRT did not significantly differ between the two groups during the follow-up period after matching (Supplementary Fig. 1).

Discussion

In this study of patients who developed ME early after PPV for PDR, CRT showed a decreasing trend in the first 3 months after the diagnosis of ME regardless of anti-VEGF treatment. Furthermore, BCVA did not

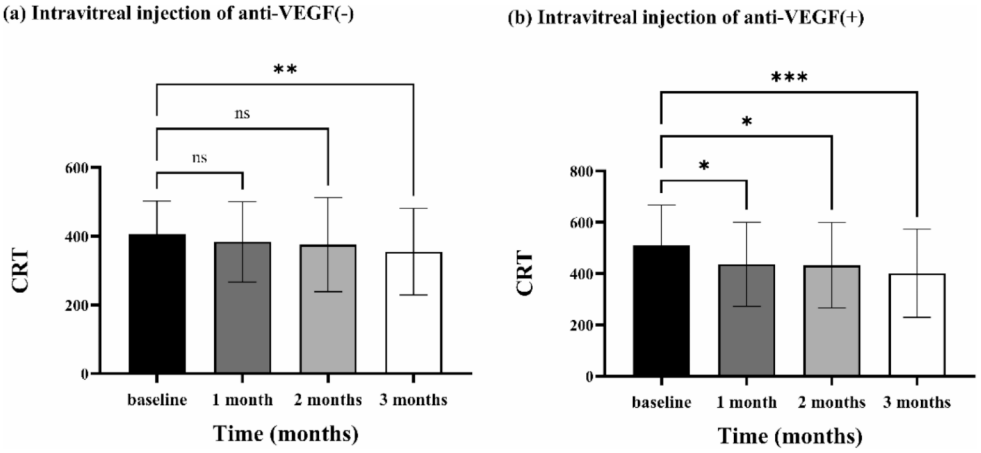

Fig. 1 Central retinal thickness (CRT) values in the (**a**) no anti-vascular endothelial growth factor (VEGF) group and (**b**) anti-VEGF group at baseline and during follow-up. ns, not significant; *P<0.05; **P<0.01; ***P<0.001

Table 2 Visual acuity over time

BCVA (IQR, logMAR)	No anti-VEGF group	Anti-VEGF group	*P*-value
Baseline	0.8 (0.5, 1.5)	0.8 (0.5, 1.3)	0.71
1 month	0.6 (0.4, 1.0) *	0.6 (0.3, 1.0) *	0.96
2 months	0.5 (0.3, 1.0) *	0.7 (0.4, 1.0)	0.09
3 months	0.5 (0.2, 0.8) *	0.5 (0.3, 0.8) *	0.75

BCVA, best corrected visual acuity; IQR, interquartile range; VEGF, vascular endothelial growth factor

*Significant difference compared to baseline ($P<0.05$)

Table 3 Multivariate linear regression analysis of risk factors influencing change in central retinal thickness

Category	Multi-factor analysis	
	β (95% CI)	*P*-value
Age (years)	-0.47 (-2.68 to 1.74)	0.68
Gender (male vs. female)	39.37 (-6.44 to 85.19)	0.09
Grade of PDR	Ref	0.56
Stage 1	-15.91 (-70.25 to 38.43)	0.53
Stage 2	-19.71 (-81.67 to 42.26)	
Stage 3		
HbA1c (%)	2.81 (-13.10 to 18.73)	0.73
FPG (mmol/L)	3.00 (-6.24 to 12.25)	0.52
Baseline CRT (μm)	0.44 (0.26 to 0.61)	**< 0.001**
Baseline BCVA (logMAR)	14.35 (-22.39 to 51.08)	0.44
Intravitreal injection of anti-VEGF	-2.54 (-51.00 to 45.92)	0.92

CI, confidence interval; PDR, proliferative diabetic retinopathy; FPG: fasting plasma glucose; CRT, central retinal thickness; BCVA, best corrected visual acuity; logMAR, logarithm of the minimum angle of resolution; VEGF, vascular endothelial growth factor

significantly differ between patients who received anti-VEGF treatment and those who did not. Thicker CRT at the time of PVME diagnosis was significantly associated with decreasing CRT in the follow-up period.

Anti-VEGF therapy is currently the first-line treatment for DME because it improves retinal hypoxia and inflammation by inhibiting both VEGF and downstream inflammatory cytokines, which suppresses leukocyte chemotaxis and adhesion in the retinal vessels [20]. However, anti-VEGF therapy is not always effective. Bressler et al. reported that DME persisted in almost 50% of patients after six monthly intravitreal injections of anti-VEGF [11]. Adding a steroid to anti-VEGF treatment in DME patients may reduce CRT, improve BCVA, and reduce anti-VEGF treatment frequency, suggesting that inflammation plays an important role in DME [12–14]. This view is consistent with our previous study which found that intraoperative injection of triamcinolone acetonide prevents PVME after PPV for PDR but preoperative and intraoperative injection of anti-VEGF does not (unpublished). In a 3-year natural history study, sham-treated DME patients with no history of PPV showed a decreasing trend in CRT [21]. Chen et al. reported that most patients with DME exhibit a stable CRT without treatment over a median duration of 8 months, providing additional evidence that DME tends to progress slowly [22]. Notably, this slow progression is not limited to non-vitrectomized eyes with DME. Behera et al. examined treatment of eyes with DME after PPV and found a statistically significant reduction in CRT regardless of DME treatment; in addition, changes in CRT and BCVA were comparable in treated patients and those who were simply observed [15].

Few studies have reported the natural history of early-stage new-onset PVME or the effectiveness of anti-VEGF therapy. Yang et al. reported that macular thickening and macular cystic change after vitrectomy for PDR was developed in 37% and 28.7% of patients, respectively, and improvement of both abnormalities spontaneously or after triamcinolone acetonide treatment was observed in some cases [23]. In a retrospective multicenter observational study in India, DME post PPV showed a significant reduction in central subfield thickness and vision gain whether treated or not, suggesting DME post PPV may not require immediate treatment [15]. It is worth

noting that the study above had a mean latency of 6.8±6.8 months of DME post PPV, while this study focused more on early post PPV period, with a mean latency of 16.1±16.3 days. In this study, a greater reduction of CRT was associated with thicker baseline CRT, probably because a thicker CRT has greater potential for reduction, regardless of anti-VEGF therapy. After adjusting for confounding factors using multivariate linear regression, use of anti-VEGF therapy did not show a significant effect on either CRT reduction or BCVA improvement. This suggests that PVME is mainly caused by postoperative inflammation and microstructural damage to a vulnerable vascular bed, poor endothelial integrity, and loss of pericytes in patients with PDR, which may recover spontaneously and gradually within 3 months of diagnosis. PPV shifts the vitreous towards a more antiangiogenic environment, as evidenced by reduced levels of angiopoietin-2, hepatocyte growth factor, and VEGF [24, 25]. However, PPV seems to be unsatisfactory for controlling intraocular inflammation [9, 10]. Even after successful PPV, elevated levels of inflammatory cytokines may persist, indicating prolonged inflammation, which may cause PVME [9, 10]. Therefore, the effect of anti-VEGF therapy seems to be limited. Moreover, the lower half-lives and increased clearance of anti-VEGF drugs in vitrectomized eyes may reduce their effects and necessitate an increase in frequency of treatments. More frequent intravitreal injections have been associated with ocular pain, ischemic retinopathy, endophthalmitis, raised intraocular pressure, glaucoma and an overall increase in the cost of treatment [26–29].

This study has several limitations. Its retrospective design is a major limitation. Furthermore, because of the short follow-up period, the assessment of the effect of anti-VEGF on PVME was incomplete. However, it is worth mentioning that this study focused more on the early postoperative period. Lastly, instead of using the ETDRS chart to present BCVA, BCVA in decimal system was converted to logMAR values. Although this strategy was widely used, it still may cause a slight bias.

Conclusion

Spontaneous recovery of PVME had a similar trend as compared to those with anti-VEGF therapy. A reduction in CRT was more apparent in patients who presented with a greater baseline CRT.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12886-024-03634-z.

Supplementary Material 1

Supplementary Material 2

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Author contributions

ZL had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: ZL and HTZ. Acquisition, analysis or interpretation of data: ZL, HTZ, JYZ, BHG, JHM, CYD, and JL. Drafting of the manuscript: ZL and HTZ. Critical revision of the manuscript for important intellectual content: all authors. Administrative, technical, or material support: ZL, QXZ, and RHW. Study supervision: ZL.

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Data availability

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

Declarations

Ethical approval

The research protocol complies with the ethical guidelines of the Declaration of Helsinki and was approved by the Human Ethics Committee Institutional Review Board of the Eye Hospital of Wenzhou Medical University (approval number: 2022-J-117). Informed consent was waived since the data analyzed in this study were deidentified.

Competing interests

The authors declare no competing interests.

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