



Impact of Aflibercept vs Dexamethasone Treatment on Epiretinal Membrane Formation in Eyes with Diabetic Macular Edema

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Received: September 4, 2024 / Accepted: October 11, 2024 / Published online: October 25, 2024
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ABSTRACT

Introduction: This study aimed to investigate the impact of aflibercept and dexamethasone (DEX) on the formation of epiretinal membrane (ERM) and their treatment outcomes in eyes with diabetic macular edema (DME).

Methods: In this retrospective cohort study, medical records of 124 eyes from 429 patients diagnosed with DME were reviewed between June 2017 and June 2019. Patients were categorized into two groups: the aflibercept group (67 eyes) and the DEX group (57 eyes). The primary endpoint was the secondary ERM incidence following intravitreal treatments and its correlation across different medications. Secondary endpoints included longitudinal changes in

best-corrected visual acuity (BCVA) and central macular thickness (CMT).

Results: Over a 24-month follow-up, eyes treated with DEX had approximately a fourfold higher incidence of ERM development compared to aflibercept [hazard ratio (HR)=3.97, $p=0.02$]. These eyes also showed worse BCVA ($p=0.059$) and increased CMT ($p=0.004$), despite requiring fewer total injections ($p=0.000$) in the survival analysis model. The cumulative probability of ERM formation was 13.7%. Additionally, DME eyes exhibited poor functional and anatomical outcomes after developing ERM, while age, A1c level, DR severity, initial BCVA and CMT, lens status, and previous laser treatment were not associated with an elevated incidence of ERM formation.

Conclusion: Intravitreal DEX implantation in DME eyes resulted in a higher incidence of secondary ERM formation compared to aflibercept over a 2-year period. The therapeutic efficacy for DME was diminished following ERM development, leading to worse anatomical outcomes. New therapeutic approaches should be explored to prevent ERM formation while maintaining both anatomical and functional outcomes in DME treatment.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s40123-024-01057-z>.

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Keywords: Aflibercept; Dexamethasone; Diabetic macular edema; Epiretinal membrane

Key Summary Points

Why carry out this study?

Patients with diabetic retinopathy are at a higher risk of developing epiretinal membrane (ERM) in the future, and its formation has been associated with vision impairment and reduced efficacy of intravitreal therapies.

Therefore, this study aims to explore ERM incidence and treatment outcomes with different intravitreal medications.

What was learned from the study?

Intravitreal dexamethasone (DEX) implantation is associated with a higher incidence of ERM formation compared to aflibercept injections. ERM development reduces the therapeutic efficacy on diabetic macular edema (DME), regardless of the medication used.

The hypothesis that steroids reduce inflammatory cytokines and prevent ERM formation was refuted in the case of DEX implantation, likely because of its formulation design and its tendency to cause structural changes in the posterior chamber.

Awareness of ERM formation following intravitreal treatments is crucial in patients with DME.

implantation are considered the standard management of DME [4–7].

Epiretinal membrane (ERM) is a pathologic fibrocellular membrane located at the vitreo-retinal interface, depositing extracellular matrix on the internal limiting membrane and exerting a contractile force [8]. While most ERM are idiopathic, common secondary causes include ocular surgery, retinal vascular disease, uveitis, and laser photocoagulation [9–11]. In patients with DR, secondary ERM occurs approximately 1.8–2.5 times more frequently than idiopathic ERM [10]. Once ERM develops, it may act as a physical barrier and reduce the effectiveness of intravitreal treatments [11–13]. The exact cause of secondary ERM formation is not fully understood, but it may be associated with intravitreal treatments for DME, possibly due to repeated procedures or the medication per se over time. Previous studies have indicated an increased risk of ERM formation following DEX implantations. However, many were constrained by short follow-up periods, small sample sizes, and a lack of comprehensive assessments of time-to-event data and post-treatment disease progression [13, 14].

Therefore, in our study, we investigated the incidence of ERM in eyes with DME that underwent intravitreal injections of aflibercept or DEX implantations. We also assessed the impact of ERM on both functional and anatomical outcomes and analyzed the parameters contributing to ERM formation following treatments for DME.

INTRODUCTION

Diabetic macular edema (DME) is a leading cause of vision loss in patients with diabetic retinopathy (DR) [1]. Its pathophysiology involves hyperglycemia-induced oxidative stress, which triggers inflammation. This process damages vascular endothelial cells and pericytes, leading to impaired retinal blood flow and resulting in retinal hypoxia. This cascade disrupts the blood–retina barrier, increases vascular permeability, elevates vascular endothelial growth factor (VEGF) levels, and releases inflammatory cytokines [2, 3]. Consequently, intravitreal injections of anti-VEGF and dexamethasone (DEX)

METHODS

This retrospective cohort study adhered to the principles of the Declaration of Helsinki and was approved by the Institutional Review Board at Taipei Veterans General Hospital (No 2019-11-001BC). Informed consent was waived because of the retrospective nature of the study and the use of anonymized data, in accordance with institutional and national guidelines.

We enrolled patients diagnosed with DR accompanied by DME who received intravitreal injections of aflibercept or DEX implantations

from June 2017 to June 2019. Follow-up assessments were conducted every month, with a minimum observation period of 24 months after the initial treatment.

A total of 429 patients were initially enrolled, and their medical charts were comprehensively reviewed. DME was defined as retinal thickening with intraretinal fluid accumulation and presence of cystoid macular edema on optical coherence tomography (OCT) using the Optovue RTVue (Optovue Inc., Fremont, CA, USA). Central macular thickness (CMT) exceeding 300 μm and macular leakage confirmed via fluorescein angiography (FA) were also criteria for inclusion. DME was further categorized into central involvement and non-central involvement DME on the basis of the involvement of the fovea. DR severity was classified as mild, moderate, severe non-proliferative diabetic retinopathy (NPDR), or proliferative diabetic retinopathy (PDR) on the basis of dilated funduscopy exam and FA. ERM was defined as an irregular, hyperreflective layer on the internal limiting membrane within the central 1-mm area in our study.

We excluded patients meeting the following criteria: (1) presence of ERM at the initial visit, (2) coexistence of central or branch retinal vessel occlusion, (3) concurrent neovascular age-related macular degeneration, (4) presentation with tractional retinal detachment or vitreous hemorrhage obscuring detailed macular conditions, (5) underwent phacoemulsification surgery, intravitreal injection, ocular surgery within 3 months prior to the first treatment, (6) received intravitreal injections of other agents such as bevacizumab, ranibizumab, or triamcinolone during follow-up, (7) received panretinal laser photocoagulation (PRP) or focal/grid laser photocoagulation within 3 months, or (8) had poorly controlled diabetes mellitus with HbA1c levels exceeding 10%.

Ophthalmologic evaluations were conducted before and after the initial treatment, at 1-month intervals thereafter, and at month 24. These assessments included best-corrected visual acuity (BCVA), intraocular pressure, slit-lamp biomicroscope, dilated fundus evaluation with photography, and spectral-domain OCT. ERM formation and grading of DR severity were evaluated collaboratively by two physicians (TCL

and HHC). Additionally, demographic characteristics including age, gender, A1c levels, history of previous cataract surgery, and previous PRP were collected for all participants.

All intravitreal injections/implantations were administered by experienced retinal specialists. Aflibercept (Eylea[®], Regeneron, Tarrytown, NY, USA) and DEX implants (Ozurdex, Allergan, Irvine, CA, USA) were delivered 3.5–4 mm posterior to the limbus.

Participants were divided into two groups: the aflibercept group and the DEX group. In the aflibercept group, participants exclusively received aflibercept injections over the 24-month follow-up period. This regimen involved three loading doses, followed by injections adhering to the pro re nata principle. In the DEX group, participants initially received DEX implantation and subsequently had repeated DEX implantations. Additionally, rescue aflibercept injections could be administered throughout the study period.

Statistical analysis was executed using the Statistical Package for the Social Sciences software (IBM SPSS Statistics for Windows, Version 28.0, Armonk, NY: IBM Corp). The independent sample *t* test or Mann–Whitney *U* test was applied to analyze continuous variables, while the chi-square test was used for the categorical variables. Univariate logistic regression was utilized to assess the relationship between the total number of treatments and ERM formation. Kaplan–Meier survival curves and Cox proportional hazards regression models were used to analyze the time period and possible risk factors for ERM formation. A *p* value less than 0.05 was considered statistically significant.

RESULTS

We reviewed 429 medical records of patients diagnosed with DME between June 2017 and June 2019. Of these, 124 patients met the inclusion criteria. Most exclusions were due to insufficient follow-up (less than 24 months) or receiving intravitreal injections other than aflibercept or DEX. The aflibercept group consisted of 67 patients (54%), who were exclusively treated

with aflibercept throughout the entire 2-year period. The DEX group included 57 patients (46%) who received an initial DEX implantation, followed by repeated DEX implants with or without rescue aflibercept treatments. In the DEX group, 10.5% of patients (6 out of 57) required rescue aflibercept during the 2-year follow-up.

The comparison of demographic characteristics between these two groups is shown in Table 1. There were no significant differences between the two groups in age, gender, baseline BCVA, CMT, lens status, A1c level, or DR severity. However, the DEX group had a higher proportion of central-involved DME ($p=0.022$) and previous PRP treatment compared to the aflibercept group ($p=0.002$).

Incidence of ERM Formation

In our study, the cumulative probability of ERM formation was 13.7% over a mean follow-up period of 24 months, translating to a mean annual incidence of 7.5%. Among patients in the DEX group, 12 out of 57 (21%) developed ERM which was significantly higher compared to those in the aflibercept group [5 out of 67 patients (7%)] ($p=0.008$) (Table 1).

Potential Risk Factors for ERM Formation in DME Eyes

In Cox proportional hazards regression models, eyes treated with DEX had approximately a

Table 1 Comparison of demographic characteristics of patients with DME between aflibercept group and DEX group at baseline

Characteristics ($n = 124$)	All	Aflibercept group ($n = 67$)	DEX group ($n = 57$)	p value
Age (years, mean \pm SD)	61.3 \pm 10.7	60.5 \pm 9.9	62.3 \pm 11.5	0.37
Sex (female, %)	50 (41%)	34 (49.3%)	16 (28.1%)	0.09
Serum A1C level (mean \pm SD)	7.7 \pm 1.5	7.7 \pm 1.5	7.7 \pm 1.7	0.93
Baseline BCVA (logMAR, median)	0.64 \pm 0.41	0.52	0.7	0.16
Baseline CMT (μ m, mean \pm SD)	420 \pm 144	412 \pm 141	425 \pm 147	0.63
Lens status (phakic, %)	86 (69%)	48 (72%)	38 (67%)	0.48
Macular edema pattern (n , %)				
Central-involved DME	111 (90%)	56 (84%)	55 (96%)	0.022*
Non-central involved DME	13 (10%)	11 (16%)	2 (4%)	
Previous PRP (n , %)	51 (41%)	19 (28%)	32 (56%)	0.002*
DR status (n , %)				
NPDR	78 (61%)	47 (70%)	31 (54%)	0.07
PDR	46 (37%)	20 (30%)	26 (46%)	
ERM formation (n , %)	17 (13.7%)	5 (7%)	12 (21%)	0.008*

The categorical variables were analyzed by chi-square test; the continuous variables were analyzed by independent t test or Mann–Whitney U test

BCVA best-corrected visual acuity, CMT central macular thickness, DEX dexamethasone, DME diabetic macular edema, DR diabetic retinopathy, ERM epiretinal membrane, NPDR non-proliferative diabetic retinopathy, PDR proliferative diabetic retinopathy, PRP panretinal photocoagulation, SD standard deviation

*A p value less than 0.05 was considered significant when comparing the aflibercept groups

fourfold higher incidence of ERM development compared to those receiving aflibercept injections ($p=0.02$, $HR=3.97$) (Table 2). Kaplan–Meier survival analysis is shown in Fig. 1. The mean time for ERM development was 313 days, with a median of 291 days.

Age and gender did not exhibit a significant correlation with ERM formation. The severity of diabetes mellitus, assessed by A1c level, yielded a mean of 7.7% in the entire cohort. A higher A1c level was not associated with an increased risk of developing ERM ($p=0.43$).

The mean initial BCVA was 0.64 ± 0.41 log-MAR units, and the mean baseline CMT was 420 ± 144 μm . Our analysis revealed no correlation between baseline BCVA or CMT and ERM formation ($p=0.17$ and 0.83 , respectively). Among the 124 eyes, 69% (86/124) were phakic, and 31% (38/124) were pseudophakic. Additionally, 90% (111/124) had central-involved DME, while 10% (13/124) had non-central involved DME. In all patients, 63% had NPDR and 37% had PDR, with 41% having undergone previous PRP treatments. Neither lens status, DR severity, types of DME, nor prior PRP treatments were

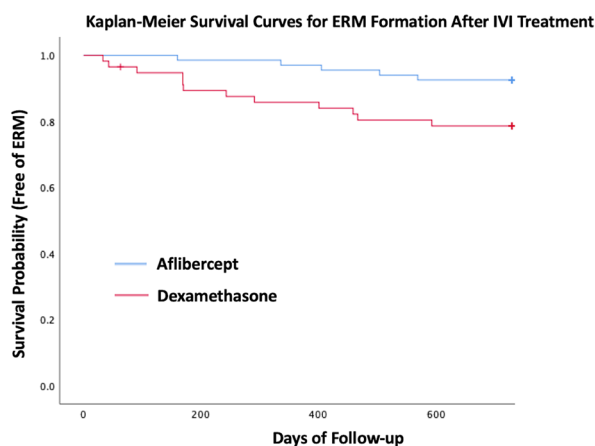


Fig. 1 Kaplan–Meier survival curves comparing the incidence of epiretinal membrane (ERM) formation following intravitreal injection of DEX vs aflibercept. Eyes treated with DEX exhibited a higher incidence of ERM formation compared to those receiving aflibercept injections ($p=0.02$). *DEX* dexamethasone, *IVI* intravitreal injections/implantations

Table 2 Potential risk factors for ERM formation in univariate Cox proportional hazards regression model

Variables	Value with great hazard	HR	HR 95% CI	<i>p</i> value
Treatment	DEX	3.97	1.21–9.53	0.02*
Age (years)	Lower	0.96	0.92–1.01	0.1
Sex	Female	1.04	0.40–2.70	0.93
Serum A1c level	Higher	1.12	0.84–1.51	0.43
Baseline BCVA (logMAR)	Higher	2.12	0.72–6.23	0.17
Baseline CMT (μm)	–	1.00	0.99–1.00	0.83
Lens status	Pseudophakic	0.75	0.29–1.95	0.56
DME type	Central DME	0.47	0.06–3.53	0.46
Previous PRP	Previous PRP	2.4	0.94–6.25	0.07
DR status	PDR	1.24	0.47–3.27	0.66

Survival analysis was performed by using univariate Cox proportional hazards regression models

BCVA best-corrected visual acuity, *CI* confidence interval, *CMT* central macular thickness, *DEX* dexamethasone, *DME* diabetic macular edema, *DR* diabetic retinopathy, *ERM* epiretinal membrane, *HR* hazard ratio, *PDR* proliferative diabetic retinopathy, *PRP* panretinal photocoagulation

*A *p* value less than 0.05 was considered significant when comparing groups

correlated with ERM formation ($p=0.56$, 0.46 , 0.07 , respectively). The multivariate Cox proportional hazards model demonstrated that DEX implantation independently correlated with an increased incidence of ERM, after adjusting for other covariates like previous PRP and central-involved DME ($p=0.037$, $HR=3.31$).

A subgroup analysis of eyes without prior PRP treatment revealed that eyes treated with DEX had a higher incidence of ERM formation compared to those treated with aflibercept (16% vs 6%, $p=0.000$) (see Supplementary Materials Table S1). Additionally, we performed a subgroup analysis for both NPDR and PDR eyes, which indicated a higher incidence of ERM formation in the PDR group, although this difference was not statistically significant (see Supplementary Materials Table S2).

Relationship Between Number of Injections and ERM

A greater total number of intravitreal treatments was not correlated with a higher incidence of ERM ($p=0.61$). In the aflibercept group, eyes that developed ERM had an average of 7.29 injections, compared to 6.61 injections in those without ERM ($p=0.66$). In the DEX group, eyes with ERM received an average of 2.26 implantations, while eyes without ERM had an average of 2.41 implantations ($p=0.71$) (Table 3).

Comparison of Therapeutic Effects in Relation to ERM

Eyes with secondary ERM had significantly higher final CMT ($468\ \mu\text{m}$) compared to those without ERM ($296\ \mu\text{m}$) ($p=0.000$). These eyes showed no CMT improvement after 24 months, unlike those without ERM, which saw a significant reduction. Though not statistically significant, eyes with ERM had poorer final BCVA and less VA improvement ($p=0.25$ and 0.49) (Table 3).

Comparison of Treatment Results Between Aflibercept and DEX Groups

Regarding total treatment numbers, eyes in the aflibercept group received an average of 6.69 injections, significantly more than the 4.2 treatments in the DEX group ($p<0.001$). After 24 months of treatment, eyes in the DEX group showed significantly poorer mean BCVA ($p=0.001$) and thicker average CMT ($p<0.001$) despite receiving fewer injections compared to those in the aflibercept group. In addition, eyes in the aflibercept group exhibited a significantly greater reduction in CMT from baseline than those in the DEX group ($138\ \mu\text{m}$ vs $48\ \mu\text{m}$, $p=0.004$) (Table 4).

When functional and anatomical outcomes were compared relative to lens status,

Table 3 Therapeutic outcomes in eyes with and without ERM formation after 24 months

	ERM group ($n=17$)	Non-ERM group ($n=107$)	p value
24-month BCVA (BCVA change)	0.71 (− 0.008)	0.56 (− 0.084)	0.25 (0.49)
24-month CMT (CMT change)	468 (+45)	296 (− 126)	< 0.001* (0.001*)
Total injections of aflibercept	7.29	6.61	0.66
Total treatments of DEX	2.26	2.41	0.71
Total treatments of aflibercept + DEX	9.55	9.02	0.61

The comparison of continuous variables was analyzed by independent t test. The changes of BCVA and CMT between baseline and 24-month were analyzed by paired t test

BCVA best-corrected visual acuity, CMT central macular thickness, DEX dexamethasone, ERM epiretinal membrane

*A p value less than 0.05 was considered significant when comparing groups

Table 4 Comparison of treatment outcomes between Aflibercept group and DEX group after 24 months treatment

	Aflibercept group (<i>n</i> = 67)	DEX group (<i>n</i> = 57)	<i>p</i> value
In all DME eyes (<i>n</i> = 124)			
Final mean BCVA (logMAR) (BCVA change)	0.44 (− 0.13)	0.75 (+ 0.01)	0.001* (0.059*)
Final mean CMT (μm) (CMT change)	280 (− 138)	378 (− 48)	< 0.001* (0.004*)
Total treatments of aflibercept and DEX	6.69	4.2	< 0.001*
Total treatments of DEX	0	2.34	0.001*
ERM formation	5 (7%)	12 (21%)	0.008*
In pseudophakic eyes (<i>n</i> = 38)			
Final mean BCVA (logMAR)	0.26	0.60	0.007*
Final mean CMT (μm)	279	374	0.02*

The comparison of continuous variables was analyzed by independent *t* test. The changes of BCVA and CMT between baseline and 24-month were analyzed by paired *t* test

BCVA best-corrected visual acuity, CMT central macular thickness, DEX dexamethasone, ERM epiretinal membrane

**p* < 0.05 (considered significant when comparing groups)

pseudophakic eyes in the DEX group consistently had worse final BCVA and thicker CMT than those in the aflibercept group (*p*=0.007 and 0.02, respectively).

DISCUSSION

Secondary ERM is recognized for its elevated occurrence in eyes with DME, contributing to impaired vision and increased CMT [10, 15]. In our study cohort, the cumulative probability of ERM formation was 13.7% after a 24-month follow-up, resulting in an average annual incidence of 7.5%. Similarly, Kang et al. found a 9.5% incidence of secondary ERM in DME eyes following intravitreal treatments [13], while Kulikov et al. reported ERM involving the macular center in 12.3% of their cases [16].

Age, gender, A1c level, DR severity, initial visual acuity and CMT, lens status, types of macular edema, prior PRP history, and total intravitreal treatment numbers were not associated with an elevated incidence of ERM formation. However, a significantly higher incidence

of ERM was observed in eyes treated with DEX implants compared to those receiving aflibercept injections, indicating a notable association between DEX implants and increased ERM development. Previous studies have demonstrated that inflammatory processes play a central role in the pathogenesis of ERM, suggesting that steroid administration might be beneficial in suppressing inflammatory cytokines and thus reducing ERM formation [17, 18]. However, Kang et al. reported a significantly higher incidence of ERM in eyes treated with DEX implants compared to those receiving anti-VEGF injections such as bevacizumab, ranibizumab, or aflibercept [13]. They hypothesized that DEX implantation may induce mechanical stress within the vitreous cavity, leading to ERM formation. A case report highlighted that thickening and contraction of the posterior hyaloid membrane following DEX implantation may cause abnormal vitreomacular traction and ERM formation [19]. Furthermore, foreign body cell reaction caused by the DEX implant's poly lactic-co-glycolic acid matrix may contribute to ERM formation. In an animal study, a cell reaction composed mostly of

glial cells and fibroblasts was observed following intravitreal implantation of a biodegradable copolymer of lactic acid and glycolic acid [20]. Afshar et al. reported a case of secondary ERM developing in a postretinal detachment eye following DEX treatment for postoperative cystoid macular edema. The authors suggested that this could reflect a toxic effect from either the DEX itself or its degradable vehicle material, or a response to microtrauma from the implant abrading the retinal surface [21].

The impact of intravitreal injections of aflibercept on ERM formation remains uncertain [11, 22, 23]. Our study observed a 7% incidence of ERM formation in the aflibercept group during the 2-year follow-up period. Similar to our findings, previous studies have reported an incidence of secondary ERM of approximately 6–7% following intravitreal anti-VEGF injections [24, 25]. The etiology of secondary ERM may be attributed to retinal tissue fibrosis after anti-VEGF treatment and the involvement of other growth factors, such as basic fibroblast growth factor and platelet-derived growth factor [26–28].

In our study, the 2-year treatment outcomes between the aflibercept and DEX group are notable. The DEX group exhibited a higher incidence of ERM formation, thicker final CMT, and poorer final BCVA, despite receiving fewer total injections/implantations compared to the aflibercept group. Although the DEX group had a higher proportion of previous PRP treatments, our subgroup analysis among patients without PRP treatment still showed significantly higher ERM incidence ($p=0.000$) and thicker CMT ($p=0.03$) in the DEX group compared to aflibercept group.

Cataract formation following DEX implantation may result in decreased visual acuity, making it essential to consider lens status when assessing functional outcomes. Contrary to Ozsaygili and Duru, who reported that the functional superiority of aflibercept over DEX treatments became less apparent in pseudophakic eyes, our results showed that the aflibercept group continued to exhibit both functional and anatomical superiority in pseudophakic eyes [7, 29]. This suggested that the high incidence of ERM, rather than cataract formation, in the DEX group leads to inferior visual outcomes.

Our results showed that eyes with secondary ERM tend to have poor final functional and anatomical outcomes. Eyes without ERM showed better, albeit not statistically significant, BCVA improvement. Final CMT did not decrease in eyes with ERM but significantly reduced in those without ERM ($p=0.00$) (Table 4). Similarly, previous studies have reported diminished therapeutic effects of intravitreal anti-VEGF injections and DEX implantation in patients with DME complicated by secondary ERM, as the presence of ERM can lead to visual impairment, CMT thickening, and reduced drug penetration [11–13, 30].

Hyperreflective foci (HRF) is increasingly recognized as a biomarker in eyes with DME, and has been linked to disease severity [31, 32]. In our study, 91% of eyes exhibited HRF at baseline decreasing to 56% by the end of the 2-year follow-up. The prevalence of HRF was similar between the aflibercept and DEX groups (90% vs 92%, $p=0.75$), and both groups showed comparable reductions in HRF (54% vs 60%, $p=0.51$). Although HRF was not significantly associated with ERM formation ($p=0.07$) (data not shown), there was a trend suggesting that eyes without HRF had a lower likelihood of developing ERM.

Our study has some limitations. Firstly, the retrospective and non-randomized design introduces potential selection bias. To mitigate this, we thoroughly compared the demographic characteristics and ocular parameters of all participants at baseline. Additionally, some eyes in the DEX group received rescue aflibercept injections between DEX implantations, often due to persistent macular edema or economic considerations. While a direct comparison of DEX and aflibercept alone would be ideal, the combination treatment reflects real-world practices. Finally, a longer follow-up may show a higher prevalence of ERM. Despite these limitations, our study included a large number of cases, and the survival regression model provides a precise description of the relationship between ERM and intravitreal medications over time. Nevertheless, compared to previous studies in this field, our work offers several strengths. First, it includes a longer follow-up period and provides a head-to-head comparison between aflibercept and DEX treatment. Additionally, we employed

a survival analysis model to evaluate the influence of time on risk factors for ERM formation. Lastly, we performed a comparative analysis of treatment outcomes between the aflibercept and DEX groups.

CONCLUSION

Our study demonstrated that intravitreal DEX implantation for DME was associated with a higher incidence of secondary ERM formation compared to aflibercept over 2 years. Although the anti-inflammatory properties of steroids have been thought to prevent ERM formation, this was not observed in the context of DEX implantation, likely as a result of its vehicle design and potential structural effects in the posterior segment. The therapeutic efficacy for DME diminishes following the development of ERM, particularly evident in anatomical outcomes, irrespective of the current medication employed. Thus, new therapeutic modalities should be considered to prevent ERM formation while treating DME eyes.

Author Contributions. Hsin-Ho Chang and Tai-Chi Lin contributed to the study conception and design, as well as material preparation, data collection, and statistical analysis. The first draft of the manuscript was written by Hsin-Ho Chang, and all authors (Shih-Jen Chen, Yu-Bai Chou, Sheng-Chu Chi and Tai-Chi Lin) critically revised the manuscript at various stages. All authors read and approved the final manuscript.

Funding. The work was supported by Taipei Veterans General Hospital (V113C-220), Yen Tjing Ling Medical Foundation (CI-113-26), and Yun-Sun Ophthalmology Education Research Foundation. These funds were used to cover publication costs, including the journal's Rapid Service Fee.

Data Availability. The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of Interest. All authors including Hsin-Ho Chang, Sheng-Chu Chi, Shih-Jen Chen, Yu-Bai Chou, and Tai-Chi Lin declare that they have no conflicts of interest to disclose.

Ethical Approval. The study was approved by the Institutional Review Board (IRB) at Taipei Veterans General Hospital (IRB No. 2019–11-001BC). Informed consent was waived because of the retrospective nature of the study and the use of anonymized data, in accordance with institutional and national guidelines.

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