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The impact of aflibercept combined with dexamethasone intravitreal implant on visual function and aqueous humor inflammatory responses in diabetic macular edema

Dan Luo*
Department of Ophthalmology, The First Affiliated Hospital of Hunan University of Chinese Medicine, Changsha, Hunan, China

Abstract: **Background**: Diabetic macular edema (DME) is a predominant cause of visual impairment among patients. The concurrent administration of anti-vascular endothelial growth factor (VEGF) agents and corticosteroids may yield synergistic therapeutic benefits. **Objective**: In this study, we evaluated the efficacy and safety of aflibercept (AFL) in combination with dexamethasone (DEX) intravitreal implant for the treatment of DME. **Methods**: A total of 80 patients with DME admitted to a hospital from June 2022 to June 2024 were enrolled. 42 patients in the AFL group received monotherapy, and 38 patients in the AFL+DEX group received combination therapy. The best corrected visual acuity (BCVA), central macular thickness (CMT), intraocular pressure (IOP) and aqueous humor inflammatory factors (IL-1β, MCP-1, IL-6, VEGF) were evaluated monthly. Efficacy was graded according to criteria at 4 months after treatment, and adverse events were recorded. **Results**: The findings revealed no statistically significant difference in the overall clinical efficacy rate between the AFL+DEX group and the AFL group ($P>0.05$). However, the AFL+DEX group demonstrated superior best-corrected visual acuity (BCVA) at 1, 3 and 6 months post-treatment, alongwith a significant reduction in central macular thickness (CMT) compared to the AFL group ($P<0.05$). Furthermore, aqueous humor analysis indicated markedly lower levels of inflammatory cytokines in the AFL+DEX group following treatment ($P<0.05$). In terms of safety profiles, the AFL+DEX group required fewer intravitreal injections ($P<0.05$). **Conclusion**: These findings underscore the potential of AFL combined with DEX intravitreal implant to enhance visual outcomes and modulate intraocular inflammation in DME patients, highlighting its substantial clinical utility.

Keywords: Aflibercept; Diabetic macular edema; Dexamethasone; Inflammatory responses; Visual function.

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INTRODUCTION

Diabetic macular edema (DME), a prevalent and vision-threatening complication of diabetic retinopathy, represents a significant cause of visual impairment among diabetic patients (Lai *et al.*, 2023). A 2020 epidemiological study reported that the risk of DME development in individuals with diabetes mellitus (DM) is as high as 10.1% (Michelson & Forst, 2020). Over the past 15 years, the advent of intravitreal anti-vascular endothelial growth factor (VEGF) therapies has fundamentally transformed the therapeutic landscape for DME (Wirkkala *et al.*, 2022). However, the clinical effect of these treatments is often limited by the necessity for frequent injections, the invasive nature of the procedure and the substantial economic burden (Ruamviboonsuk *et al.*, 2025). Corticosteroids have been proposed as an adjunctive therapy to enhance visual outcomes and reduce retinal thickness, yet their use is associated with an elevated risk of cataract formation and intraocular pressure (IOP) elevation (Gao *et al.*, 2021). Thus, the development of a DME treatment strategy that optimizes visual gains, extends therapeutic durability and reduces treatment frequency remains a pivotal challenge in ophthalmic research.

The distinct mechanistic pathways of anti-VEGF agents and corticosteroids have prompted investigations into their potential synergistic effects when used in combination (Furino *et al.*, 2021). Accumulating evidence has demonstrated the efficacy of this dual-therapy approach in addressing conditions such as macular edema secondary to retinal vein occlusion (Sanders *et al.*, 2023) and retinal edema (Salvetat *et al.*, 2024). Notably, a recent study published in *International Ophthalmology* evaluated the combined use of dexamethasone (DEX) implants and aflibercept (AFL) in DME patients. Their findings revealed significant reductions in central macular thickness (CMT) and total macular volume (TMV) in the combination therapy group (Ozsaygili & Bayram, 2024), highlighting the potential therapeutic advantages of integrating anti-VEGF agents with corticosteroids in DME management.

Despite the growing body of literature comparing the efficacy of AFL and DEX as monotherapies for DME (Chakraborty *et al.*, 2024), data on their combined use remain scarce. The study by Ozsaygılı *et al*. primarily focused on post-treatment anatomical outcomes, such as CMT and TMV, as well as cataract incidence (Ozsaygili & Bayram, 2024), leaving a critical gap in comprehensive clinical evidence. This study looked at the therapeutic effect of AFL combined with DEX intravitreal implantation on DME with a view to providing an evidence-based basis for future treatment options.

**Corresponding author:* e-mail: giftknow@163.com

MATERIALS AND METHODS

Study design

This retrospective study was conducted with a waiver of informed consent. The study population comprised DME patients who were admitted to The First Affiliated Hospital of Hunan University of Chinese Medicine between June 2022 and June 2024. A total of 80 patients were enrolled after applying predefined (GPower 3.1 software) inclusion and exclusion criteria, with an effect size of 0.4, α=0.05and power (1-β) set at 0.8 based on preliminary data from similar studies (Sedziak-Marcinek *et al*., 2021). A total of 194 patients were admitted during the study period. A total of 134 patients were screened according to the inclusion criteria, 54 patients were excluded according to the exclusion criteria, and 80 patients were finally left. Of these, 42 patients were assigned to the AFL group and received AFL monotherapy, while 38 patients were assigned to the AFL+DEX group and underwent combination therapy with AFL and DEX intravitreal implant. The patient screening and allocation process is depicted in fig. 1.

Inclusion criteria

(1) Confirmed diagnosis of DME using optical coherence tomography (OCT); (2) Demonstrated tolerance to pharmacological interventions; (3) CMT > 250 μm and glycated hemoglobin (HbA1c) levels ≤ 8%; (4) Baseline IOP<21 mmHg; (5) monocular disease.

Exclusion criteria

(1) Previous history of laser therapy or intraocular surgery; (2) Macular edema due to non-diabetic etiologies; (3) Inability to provide informed consent or communicate effectively; (4) Significant media opacities affecting retinal visualization; (5) History of severe cardiovascular or cerebrovascular diseases, or chronic renal failure; (6) Diagnosis of glaucoma or ocular hypertension; (7) Presence of proliferative diabetic retinopathy; (8) Administration of AFL or DEX within the preceding 6 months. This study has been approved by the ethics committee of The First Affiliated Hospital of Hunan University of Chinese Medicine (No. HN-LL-GZR-2025-06) and all aqueous humor samples were obtained from the remaining samples collected by routine clinical anterior chamber paracentesis.

Treatment protocol

All patients underwent intravitreal implantation therapy. Preoperatively, patients self-administered levofloxacin eye drops to the operative eye for three consecutive days. Both groups received preoperative mydriasis using compound tropicamide eye drops and topical anesthesia with oxybuprocaine eye drops. Following standard aseptic preparation and draping, a needle was inserted perpendicular to the scleral surface at a distance of 3.5 or 4.0 mm from the corneal limbus in the inferotemporal quadrant. AFL+DEX group: intravitreal injection of 0.05 mL AFL (Vetter Pharma-Fertigung GmbH & Co. KG, SJ20180010), followed by an injection of 0.7 mg DEX (Allergan Pharmaceuticals Ireland, H20170377) into a separate quadrant. AFL group: intravitreal injection of 0.05 mL AFL alone. Postoperatively, tobramycin-DEX eye ointment was applied, 7 consecutive days.

Follow-up protocol

Patients in both groups were followed up (re-examination) monthly for 6 months following the initial injection. Additional injections were administered if a patient exhibited a decline in best-corrected visual acuity (BCVA) of more than two lines and/or an increase in CMT exceeding 100 μm.

Clinical efficacy assessment

Clinical efficacy was evaluated 4 months post-treatment according to predefined criteria (Tatsumi, 2023). (1) Pharmacokinetic studies of AFL (half-life of about 5-7 days) and DEX (half-life of about 30 days) show that the efficacy of combination therapy tends to stabilize at 4 months; (2) Clinical guidelines recommend initial evaluation of DME treatment at 3 to 4 months after treatment.

- Markedly Effective: Complete resolution of macular edema accompanied by improvement in visual acuity.
- Effective: Partial resolution of macular edema with associated improvement in visual acuity.
- Ineffective: Failure to meet the above criteria.

Assessment methods

Visual function evaluations were conducted at four time points: baseline (T0), 1 month (T1), 3 months (T2) and 6 months (T3) after treatment. BCVA [logarithm of the minimum angle of resolution (LogMAR)] was assessed using a standard logarithmic visual acuity chart at a testing distance of 5 meters, with the 1.0 line of the chart aligned at the patient's eye level under standardized illumination conditions (Virgili, *et al*., 2023). Examinations were performed monocularly, beginning with the right eye followed by the left eye, with uncorrected visual acuity measured prior to corrected visual acuity. CMT was measured for all patients using the SPECTRALIS-OCT system (Heidelberg Engineering, Germany) by a single ophthalmologist to ensure consistency. Prior to OCT imaging, patients underwent complete pupil dilation. Three consecutive scans were acquired for each eye and the average value of scans with a signal strength >5 was utilized for analysis. IOP was measured using a non-contact tonometer, with the mean of three consecutive measurements recorded. Additionally, aqueous humor samples were collected via anterior chamber paracentesis at baseline and 6 months post-treatment. Approximately 0.1 mL of aqueous humor was aspirated from the corneal limbus at a depth of 1 mm. Concentrations of monocyte chemotactic protein 1 (MCP-1), interleukin (IL)-1β, IL-6 and VEGF were quantified using ELISA.

Outcome measures

The study outcomes included the following parameters: (1)

Baseline demographic and clinical characteristics (e.g., age, gender); (2) Clinical efficacy based on predefined criteria; (3) Visual function metrics, including LogMAR, CMT and IOP; (4) Inflammatory biomarkers in aqueous humor; (5) Safety, including the frequency of intravitreal injections and the incidence of adverse events such as vitreous hemorrhage and cataract formation.

Statistical analysis

Statistical analyses were performed using SPSS version 26.0. Continuous variables following a normal distribution were expressed as mean ± SD, and independent sample t-tests or paired t-tests were selected according to the specific circumstances. Categorical variables were compared using chi-square tests or Fisher's exact probability test, as appropriate. Statistical significance was established when the P-value was less than 0.05.

RESULTS

Intergroup comparability

Baseline characteristics, including age, gender, duration of DM and affected eye, were compared between the two groups. Statistical analysis demonstrated no significant differences in these parameters ($P>0.05$), confirming that the groups were well-matched and comparable (Table 1).

Clinical efficacy analysis

The overall treatment efficacy rates were 92.11% in the AFL+DEX group and 85.71% in the AFL group. Despite the numerical difference, statistical analysis revealed no significant disparity between the two groups ($P>0.05$) (Table 2).

Visual function analysis

Changes in LogMAR, CMT and IOP throughout the treatment period were monitored. At baseline (T0), no significant differences in these visual function parameters were observed between the two groups ($P>0.05$). At 1 month (T1), 3 months (T2) and 6 months (T3) post-treatment, IOP levels remained comparable between the groups ($P>0.05$); however, the AFL+DEX group exhibited significantly better LogMAR and lower CMT compared to the AFL group at these time points ($P<0.05$). Within-group analyses revealed that IOP remained stable from T0 to T3 in both groups ($P>0.05$). LogMAR in both groups showed a decline at T1, which further progressed by T2 ($P<0.05$), but no additional changes were observed between T2 and T3 ($P>0.05$). In contrast, CMT displayed a progressive reduction starting at T1, reaching its nadir at T3 ($P<0.05$) (Table 3).

Inflammatory response analysis

Analysis of aqueous humor inflammatory markers showed no significant intergroup differences at baseline ($P>0.05$). Following treatment, both groups experienced significant reductions in IL-1β, MCP-1, IL-6 and VEGF levels ($P<0.05$). Importantly, the AFL+DEX group achieved significantly lower posttreatment levels of IL-1β, MCP-1 and IL-6 compared to the AFL group ($P<0.05$) (Table 4).

Safety analysis

During the follow-up period, the AFL+DEX group required fewer intravitreal injections than the AFL group (1.84±0.75 vs. 2.38±0.85, $P<0.05$). Cataract formation was reported in one patient from each group. However, there was no difference in the incidence of adverse reactions between the two groups ($P>0.05$) (Table 5).

DISCUSSION

As a retrospective analysis, the study's relatively limited sample size may introduce potential bias, necessitating careful consideration of the reliability of the findings. To address this, we rigorously compared baseline clinical characteristics and confirmed the comparability of the two groups. Although the efficacy was similar between the two groups, a detailed analysis of visual function parameters revealed that the combination therapy achieved superior LogMAR and greater reductions in CMT compared to the control. In other words, AFL+DEX has a clear advantage in improving visual outcomes for DME patients, aligning with the results reported previously (Ozsaygili & Bayram, 2024). AFL and DEX, as representative agents of anti-VEGF and corticosteroid therapies, respectively, have been extensively studied in the management of DME (Xie *et al.*, 2023; Madamsetty *et al.*, 2022). AFL is a novel fusion protein (Sun *et al.*, 2023; Xiao *et al.*, 2020). By binding tightly to VEGF, AFL reduces vascular permeability, mitigates fluid leakage and edema and alleviates macular thickening (Dascalu *et al.*, 2022). Additionally, a study showed that AFL exerts neuroprotective effects, reducing apoptosis in retinal neural cells and contributing to visual recovery (Uslubas *et al.*, 2021). The therapeutic benefits of AFL for DME have been further validated by the research conducted by Wykoff CC *et al*. (Wykoff *et al.*, 2023). DEX, in contrast, is formulated as a biodegradable sustained-release implant, consisting of micronized DEX (0.7 mg) embedded within a poly lactic-co-glycolic acid (PLGA) copolymer matrix. Following intravitreal implantation, it facilitates a controlled and prolonged release of the active agent, effectively suppressing the release of various inflammatory mediators within the ocular environment. This action reduces vascular permeability, stabilizes the blood-retinal barrier and alleviates macular edema, all while minimizing systemic adverse effects (Wilkins *et al.*, 2022; Pillai *et al.*, 2023). Supporting this, Ozcalıskan S *et al*. demonstrated that intravitreal DEX implantation significantly ameliorates macular ischemia in patients with DME (Ozcaliskan *et al.*, 2022). Consequently, we speculate that the visual function outcomes in both groups at the 4-month follow-up likely met the criteria for marked or moderate clinical efficacy, potentially explaining the absence of significant differences in overall treatment efficacy between the two groups. However, a chance result due to the small number of cases cannot be ruled out. The synergistic combination of AFL and DEX not only targets vascular leakage but also optimizes the inflammatory microenvironment within the eye, leading to more substantial improvements in visual function.

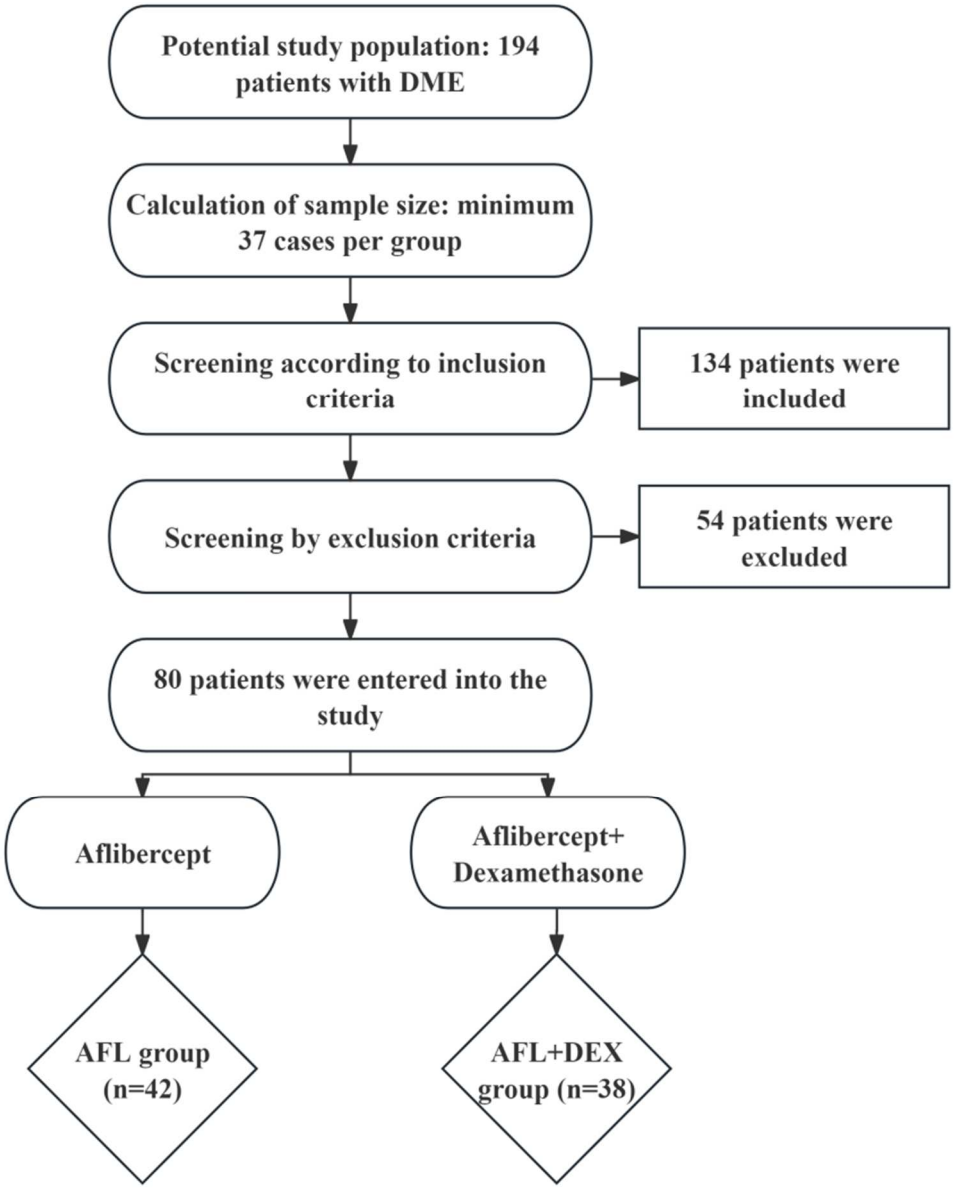

Fig. 1: Screening process for the study population. Final 80 patients with DME entered the study.

Table 1: Comparison of clinical data

Projects		AFL group (n=42)	AFL+DEX group (n=38)	Statistical	P
Age (years old)		57.17±9.29	57.53±12.10	t=0.150	0.881
Sex	Male Female	29 (69.05) 13 (30.95)	22 (57.89) 16 (42.11)	χ^2=1.074	0.300
Duration of DM (years)		8.45±3.01	7.63±1.82	t=1.455	0.150
Hypertension		11 (26.19)	9 (23.68)	χ^2=0.067	0.796
Prevalent eye	Left Eye Right eye	22 (52.38) 20 (47.62)	17 (44.74) 21 (55.26)	χ^2=0.467	0.495
HbA1c (%)		7.01±0.42	7.06±0.36	t=0.564	0.574
Duration of vision loss (months)		5.67±2.37	6.26±3.17	t=0.960	0.340
Smoking		25 (59.52)	20 (52.63)	χ^2=0.385	0.535
Drinking		14 (33.33)	12 (31.58)	χ^2=0.028	0.867

Table 2: Comparison of clinical efficacy.

	AFL group (n=42)	AFL+DEX group (n=38)	χ^2	P
Markedly Effective	16 (38.10)	21 (55.26)		
Effective	20 (47.62)	14 (36.84)		
Ineffective	6 (14.29)	3 (7.89)		
Overall treatment efficacy rate	36 (85.71)	35 (92.11)	0.816	0.366

Note: Overall treatment efficacy rate= (Markedly Effective+Effective)/n*100%.

Table 3: Comparison of visual function.

		AFL group (n=42)	AFL+DEX group (n=38)	t	P
LogMAR	T0	0.69±0.30	0.68±0.33	0.089	0.929
	T1	0.58±0.26*	0.42±0.29*	2.455	0.016
	T2	0.43±0.18$^{*\#}$	0.29±0.17$^{*\#}$	3.523	<0.001
	T3	0.43±0.21$^{*\#}$	0.32±0.18$^{*\#}$	2.421	0.018
	F	11.443	18.721		
	P	<0.001	<0.001		
CMT (μm)	T0	459.47±96.55	456.62±81.66	0.142	0.888
	T1	389.45±107.24*	345.29±66.08*	2.189	0.032
	T2	322.85±83.55$^{*\#}$	286.75±77.55$^{*\#}$	1.997	0.049
	T3	315.15±84.55$^{*\#\&}$	276.09±86.23$^{*\#\&}$	2.044	0.044
	F	21.804	42.513		
	P	<0.001	<0.001		
IOP (mmHg)	T0	17.90±1.81	17.43±2.41	0.990	0.325
	T1	17.60±2.16	17.33±2.51	0.524	0.602
	T2	17.53±2.13	17.31±2.13	0.463	0.645
	T3	17.42±2.16	17.72±2.52	0.572	0.569
	F	0.417	0.238		
	P	0.741	0.870		

Note: vs. T0 *P<0.05, vs. T1 $^{\#}$P<0.05, vs. T2 $^{\&}$P<0.05.

Table 4: Comparison of inflammatory response of aqueous humor.

		AFL group (n=42)	AFL+DEX group (n=38)	t	P
IL-1β (ng/L)	Before treatment	21.04±3.87	21.20±3.05	0.199	0.843
	After treatment	12.75±1.49	10.49±2.36	5.172	<0.001
	t	12.947	17.093		
	P	<0.001	<0.001		
IL-6 (ng/L)	Before treatment	153.02±17.22	150.04±13.97	0.846	0.400
	After treatment	93.03±8.76	85.03±8.16	4.215	<0.001
	t	20.121	24.772		
	P	<0.001	<0.001		
MCP-1 (ng/L)	Before treatment	242.68±20.21	245.19±24.13	0.505	0.615
	After treatment	151.74±13.58	144.44±11.02	2.648	0.010
	t	27.657	20.810		
	P	<0.001	<0.001		
VEGF (pg/mL)	Before treatment	73.71±11.46	76.08±12.32	0.892	0.375
	After treatment	46.23±8.35	44.57±8.39	0.882	0.380
	t	12.562	13.034		
	P	<0.001	<0.001		

This is corroborated by our findings that the AFL+DEX group exhibited significantly lower levels of inflammatory factors in the aqueous humor compared to the AFL group. The robust anti-inflammatory properties of DEX have been extensively validated in prior studies (Mannes *et al.*, 2023; Dechamps *et al.*, 2023). In the pathogenesis of DME, hyperglycemia activates multiple inflammatory pathways, resulting in the excessive release of inflammatory cytokines into the aqueous humor.

Table 5: Comparison of prognostic safety.

		AFL group (n=42)	AFL+DEX group (n=38)	t	P
Number of injections		2.38±0.85	1.84±0.75	2.987	0.004
Adverse reaction	Cataracts	1 (2.38)	1 (2.63)		
	Vitreous hemorrhage	1 (2.38)	0 (0.00)		
	Conjunctivitis	2 (4.76)	1 (2.63)		
	Eye discomfort	4 (9.52)	3 (7.89)		
	Subconjunctival hemorrhage	3 (7.14)	1 (2.63)		
	Total	11 (26.19)	6 (15.79)	1.290	0.256

This cascade increases vascular endothelial permeability, disrupts the blood-retinal barrier and promotes the leakage of fluid and proteins into the macular region, ultimately causing edema (Minaker *et al.*, 2022). Thus, the adjunctive use of DEX with anti-VEGF therapy enables more effective modulation and improvement of the intraocular microenvironment, thereby reducing optic nerve damage associated with DME. Of note, although AFL acts by blocking the VEGF pathway, there was no significant difference in the level of VEGF in the aqueous humor between the two groups after treatment (P>0.05), which may be due to the sufficient inhibition of VEGF by AFL in the single-agent group, while DEX acts mainly on inflammatory pathways rather than directly regulating VEGF.

Finally, the AFL+DEX group required fewer intravitreal injections compared to the AFL group, further highlighting the superior therapeutic efficacy of the combined AFL and DEX regimen. This reduction in injection frequency not only enhances patient compliance but also minimizes the potential risks associated with repeated ocular penetration, such as intraocular tissue damage and infection. The consistency of safety between the two treatment groups further strengthens the favorable safety profile of this combination and is consistent with that reported by Ozsaygılı C *et al*. (Ozsaygili & Bayram, 2024). Nevertheless, the small number of cases may introduce variability and limit the generalizability of the results. To address this, future studies with larger, more diverse patient cohorts are essential to validate these findings. In the future, a larger sample size and longer follow-up (≥12 months) are needed to evaluate long-term safety indicators such as the durability of visual gain, cataract progression and delayed intraocular pressure elevation. Additionally, the short follow-up duration precludes the assessment of long-term outcomes, including sustained efficacy and potential late-onset adverse effects. In addition, the mechanism of action of AFL and DEX in DEM deserves further investigation. These limitations will serve as critical areas of focus in subsequent research endeavors.

CONCLUSION

The combination of AFL and DEX intravitreal implant demonstrates significant efficacy in improving visual function, attenuating aqueous humor inflammatory responses and reducing the need for frequent intravitreal injections in patients with DME. Coupled with its favorable safety profile, this combined therapeutic approach is strongly recommended for clinical adoption. It represents a promising strategy to optimize visual outcomes and enhance the overall ocular health and quality of life for patients with DME.

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Authors' contributions
All the work for this study was performed by Dan Luo.

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Data availability statement
Original data in this study are available from the corresponding author on reasonable requests.

Ethical approval
The study protocol was approved by the Ethics Committee of The First Affiliated Hospital of Hunan University of Chinese Medicine (No.HN-LL-GZR-2025-06).

Conflict of interest
Authors have no conflict of interest to declare.

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