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Original Research Article

Posterior Subtenon Interferon Alpha-2b with Intravitreal Bevacizumab: An Evolving Novel Approach for Macular Edema Treatment

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Abstract:

Purpose: To evaluate the efficacy of posterior subtenon interferon alpha-2b (IFN-α2b) combined with intravitreal bevacizumab (IVB) on central macular thickness (CMT) and best-corrected visual acuity (BCVA) in patients with macular edema.

Methods: This observational analytical study included 40 eyes diagnosed with macular edema secondary to diabetic macular edema (DME), retinal vein occlusion (RVO), or age-related macular degeneration (ARMD). All patients received a single session of intravitreal bevacizumab (1.25mg/0.05ml) with posterior subtenon IFN-α2b (1mlU/ml). Outcomes were evaluated through CMT using spectral-domain optical coherence tomography (OCT) and BCVA on the LogMAR scale at baseline and post-injection follow-up.

Results: Mean CMT decreased significantly from 507.9 ± 162.8 µm to 286.5 ± 78.6 µm (mean change −221.4 µm, $p < 0.001$) changes seen on October one month post injection. Mean BCVA improved from 1.13 ± 0.36 to 0.78 ± 0.25 LogMAR (mean gain −0.35 LogMAR, $p < 0.001$). All etiological groups (DME, RVO, and ARMD) showed significant anatomical and visual improvement. Severe macular edema (>500 µm) showed the largest CMT reduction (−354.4 µm) and BCVA improvement (−0.46 LogMAR). CMT reduction correlated strongly with visual improvement ($\rho = 0.689$, $p < 0.001$).

Conclusion: Posterior subtenon IFN-α2b combined with intravitreal bevacizumab significantly reduces macular edema and improves visual outcomes. It is a promising steroid-sparing adjunct especially in severe or refractory cases.

Keywords: Macular Edema, Interferon alpha-2b, Bevacizumab, OCT, BCVA, Posterior Subtenon Injection.
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Introduction

Macular edema (ME) remains one of the leading causes of visual impairment worldwide, occurring in a variety of retinal vascular and degenerative conditions including diabetic retinopathy, retinal vein occlusion (RVO), and age-related macular degeneration (ARMD)[1-6]. The pathogenesis of macular edema primarily involves the breakdown of the blood-retinal barrier (BRB), increased vascular permeability, and accumulation of intraretinal or subretinal fluid, largely driven by vascular endothelial growth factor (VEGF) and inflammatory cytokines [1-5,7,8]. VEGF induces phosphorylation of tight-junction proteins in retinal endothelial cells, resulting in fluid extravasation and central macular thickening [9]. In addition to VEGF-driven leakage, inflammatory mediators including interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and interleukin-8 (IL-8) contribute to BRB disruption, leukocyte adhesion, and persistent edema [2,3,7,8].

Anti-VEGF therapy has emerged as the standard of care for most causes of macular edema [6,9-16]. Bevacizumab, a full-length monoclonal antibody against VEGF-A, has demonstrated significant efficacy in reducing central macular thickness and improving visual acuity in DME, RVO, and neovascular ARMD [10-12,16]. Large randomized clinical trials have shown that intravitreal bevacizumab provides meaningful visual improvement and anatomical resolution, comparable to ranibizumab and aflibercept in many clinical scenarios [11-13,15]. Despite this, approximately 20–40% of patients show an incomplete or suboptimal response to anti-VEGF monotherapy, indicating that inflammation and VEGF-independent mechanisms play an important

role in many cases [1,3,5,7,8,17,18]. Interferon alpha-2b (IFN-α2b), a type I interferon, possesses potent anti-inflammatory, antiangiogenic, and immunomodulatory properties [7,19,20]. It downregulates IL-6, IL-8, TNF-α, and VEGF expression, stabilizes the BRB, and reduces vascular permeability [1-4,7,8,19]. Its ability to modulate multiple inflammatory and angiogenic pathways makes it an attractive adjunct therapy for macular edema, particularly when the response to anti-VEGF agents alone is inadequate [1,3,7,17]. IFN-α2b has been studied in various ocular conditions including macular edema, ocular surface neoplasia, and uveitis, using topical, intralesional, and subtenon routes [1-4,7,8,19,20].

Recent randomized trials have explored the addition of topical IFN-α2b to intravitreal bevacizumab in diabetic macular edema. Karimi et al. reported significantly greater improvements in both CMT and BCVA with combination therapy compared to bevacizumab alone [1]. Afarid et al. similarly demonstrated enhanced outcomes with the addition of topical interferon in DME [3]. Farzan et al. also reported reduced macular thickness in a pilot study of topical interferon in DME [9]. Subtenon injection, however, may provide superior posterior segment penetration compared to topical therapy. Modarres et al. showed that posterior subtenon IFN-α2b produced significant anatomical improvement in refractory DME [4]. A case report by Cellini et al. demonstrated marked resolution of macular edema following subtenon interferon [2].

Posterior subtenon injections are considered safe, extraocular procedures that avoid risks associated with intravitreal injections, such as endophthalmitis and vitreous haemorrhage [5,21,22]. Unlike corticosteroids, interferon does not cause intraocular pressure elevation or cataract progression, making it a favourable steroid-sparing alternative [4,5,7,8,10]. Given these mechanistic and early clinical insights, the combination of posterior subtenon IFN-α2b with intravitreal bevacizumab offers a compelling multimodal therapeutic approach by targeting both the VEGF pathway and inflammatory cytokines. However, real-world data remain limited, and further clinical evaluation is needed. This study evaluated the anatomical and visual outcomes following combined intravitreal bevacizumab and posterior subtenon interferon alpha-2b in macular edema due to diabetic retinopathy, RVO, and ARMD, with special attention to severe edema and correlation between structural and functional improvement.

Methods

This observational analytical study was conducted in the Postgraduate Department of Ophthalmology at a tertiary care institution. It was approved by the Institutional review board and Institutional ethics committee and conformed to the guidelines of the Declaration of Helsinki.

Forty eyes of forty patients diagnosed with macular edema due to diabetic macular edema (DME), retinal vein occlusion (RVO), or age-related macular degeneration (ARMD) were included. Written informed consent was obtained prior to participation. All patients underwent detailed medical and ocular history taking, including systemic illnesses, prior ocular treatments, and duration of symptoms. A comprehensive ophthalmic evaluation was performed, including best-corrected visual acuity using standardized LogMAR charts, slit-lamp biomicroscopy, intraocular pressure measurement, and dilated fundus examination. Spectral-domain optical coherence tomography (OCT) was performed to document central macular thickness and retinal morphology (Figure 1).

Treatment consisted of intravitreal bevacizumab administered under aseptic conditions, followed in the same sitting by posterior subtenon injection of interferon alpha-2b given through a blunt cannula directed toward the macular area. No additional treatments were administered during the observation interval. Patients were followed up at a uniform post-injection time point, at which BCVA and CMT were reassessed using the same standardized methods (Figure 2). Statistical analysis included Wilcoxon signed-rank test for within-group comparisons, Kruskal–Wallis test for baseline differences between etiological groups, and Spearman correlation coefficient to evaluate the relationship between CMT reduction and BCVA improvement.

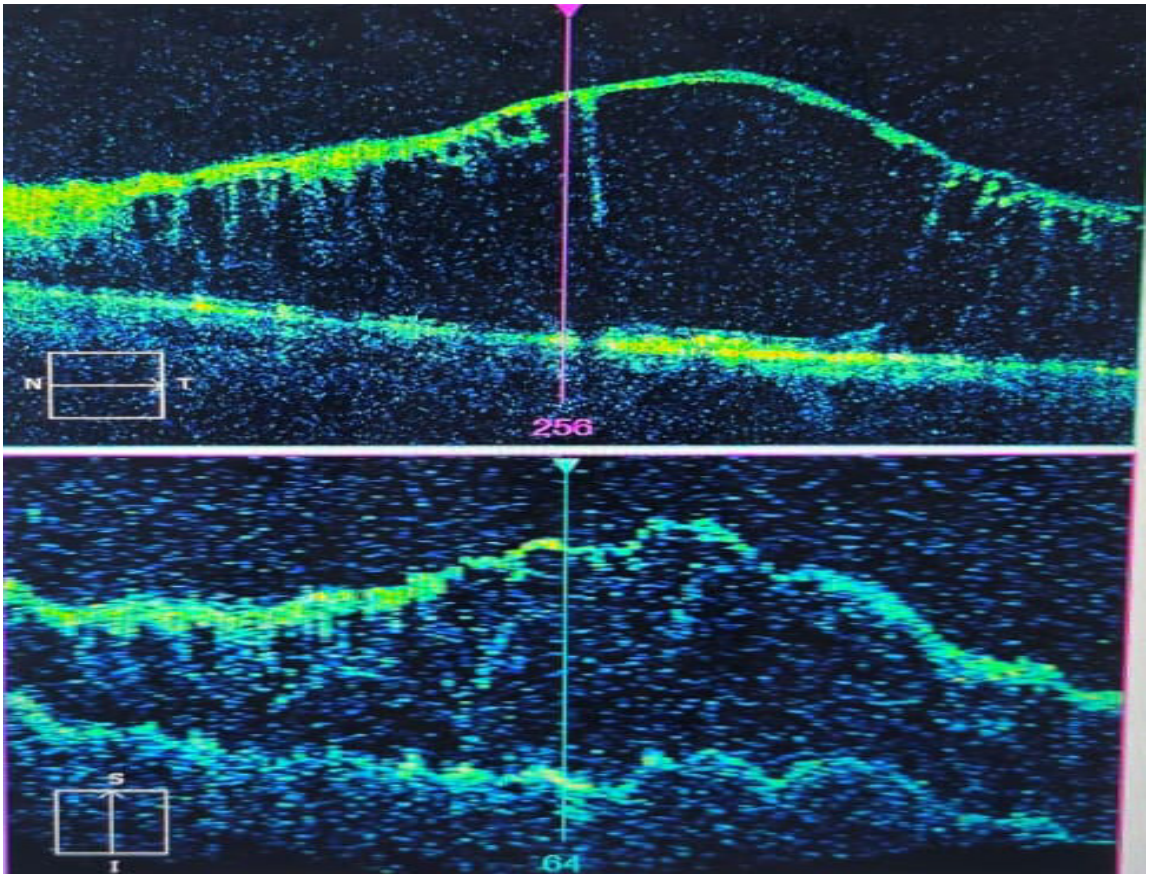

Figure 1: Spectral domain-OCT of the right eye shows macular edema measured pre-injection

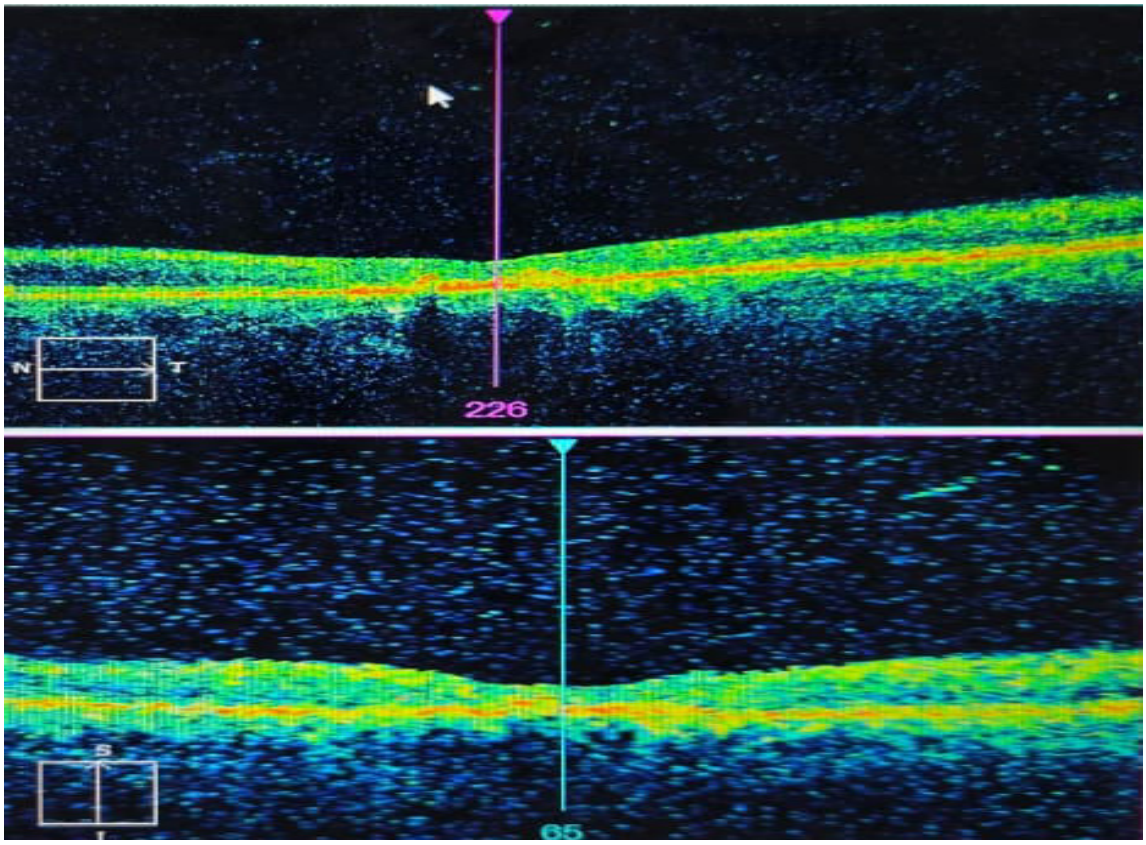

Figure 2: Spectral domain-OCT of the right eye shows reduction in the macular edema, done 1 month post-injection

Table 1: Baseline Demographic and Clinical Characteristics of the Study Population (N=40 Eyes)

Characteristic	Value
Age (Years), Mean ± SD	58.4 ± 11.7
Gender, n (%)	
Male	26 (65.0%)
Female	14 (35.0%)
Eye, n (%)	
Right	22 (55.0%)
Left	18 (45.0%)
Etiology of Macular Edema, n (%)	
Diabetic Macular Edema (DME)	14 (35.0%)
Retinal Vein Occlusion (RVO)	17 (42.5%)
Age Related Macular Degeneration (ARMD)	9 (22.5%)

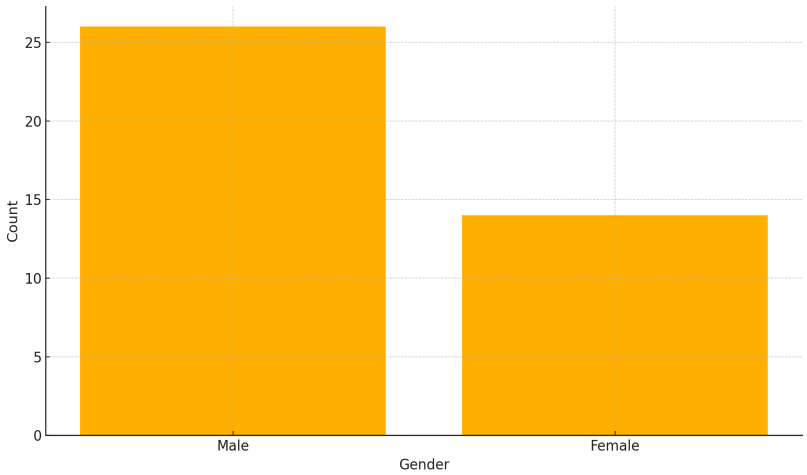

Figure 3: Gender Distribution

Table 2: Baseline Central Macular Thickness (CMT) and Visual Acuity (BCVA) by Etiology

Etiology Group	n	Baseline CMT (µm), Mean ± SD	Baseline BCVA (Log-MAR), Mean ± SD
Diabetic Macular Edema (DME)	14	405.1 ± 67.3	1.03 ± 0.30
Retinal Vein Occlusion (RVO)	17	526.4 ± 142.1	1.11 ± 0.36
Age Related Macular Degeneration (ARMD)	9	634.2 ± 216.5	1.32 ± 0.42
p-value		0.001*	0.131

***p < 0.05, calculated using Kruskal-Wallis test, indicating a statistically significant difference in Baseline CMT between groups.**

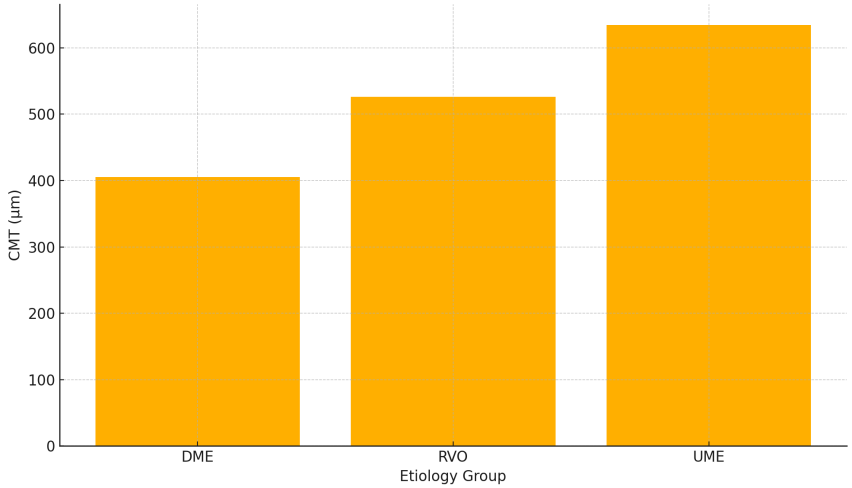

Figure 4: Baseline CMT by etiology

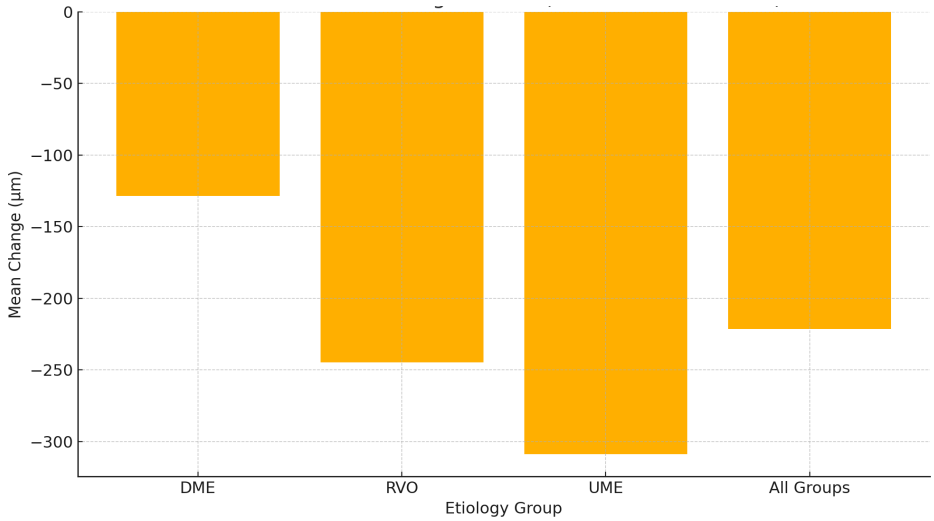

Figure 5: Baseline BCVA by etiology

Table 3: Primary Outcomes - Change in Central Macular Thickness (CMT) from Baseline to Post injection

Etiology Group	n	Baseline CMT (µm) Mean ± SD	Post injection CMT (µm) Mean ± SD	Mean Change (µm)	p-value
Diabetic Macular Edema (DME)	14	405.1 ± 67.3	276.4 ± 67.1	-128.7	<0.001*
Retinal Vein Occlusion (RVO)	17	526.4 ± 142.1	281.5 ± 41.8	-244.9	<0.001*
Age Related Macular Degeneration (ARMD)	9	634.2 ± 216.5	325.2 ± 125.3	-309.0	0.008*
All Groups	40	507.9 ± 162.8	286.5 ± 78.6	-221.4	<0.001*

***p < 0.05, calculated using Wilcoxon signed-rank test for within-group change from Baseline**

Table 4: Primary Outcomes - Change in Best Corrected Visual Acuity (BCVA) from Baseline to Post injection

Etiology Group	n	Baseline BCVA (LogMAR) Mean ± SD	Post injection BCVA (LogMAR) Mean ± SD	Mean Change (LogMAR)	p-value
Diabetic Macular Edema (DME)	14	1.03 ± 0.30	0.75 ± 0.22	-0.28	<0.001*
Retinal Vein Occlusion (RVO)	17	1.11 ± 0.36	0.77 ± 0.26	-0.34	<0.001*
Age Related Macular Degeneration (ARMD)	9	1.32 ± 0.42	0.86 ± 0.31	-0.46	0.008*
All Groups	40	1.13 ± 0.36	0.78 ± 0.25	-0.35	<0.001*

***p < 0.05, calculated using Wilcoxon signed-rank test for within-group change from Baseline**

Table 5: Subgroup Analysis of Eyes with Severe Macular Edema (Baseline CMT >500 µm)

Parameter	n	Baseline Mean ± SD	Post injection Mean ± SD	Mean Change	p-value
Central Macular Thickness (µm)	18	682.2 ± 152.4	327.8 ± 95.6	-354.4	<0.001*
BCVA (LogMAR)	18	1.31 ± 0.34	0.85 ± 0.28	-0.46	<0.001*

***p < 0.05, calculated using Wilcoxon signed-rank test.**

Table 6: Correlation between Change in CMT and Change in BCVA at Post injection (Spearman's Rho)

Etiology Group	n	Correlation Coefficient (ρ)	p-value
Diabetic Macular Edema (DME)	14	0.614	0.019*
Retinal Vein Occlusion (RVO)	17	0.721	0.001*
Age Related Macular Degeneration (ARMD)	9	0.783	0.012*
All Groups	40	0.689	<0.001*

***p < 0.05, indicating a statistically significant positive correlation between the reduction in CMT and the improvement in BCVA (LogMAR).**

Results

The table 1 illustrates that out of the total study participants, the mean age was 58.4 years, and the study population consisted of 65% males and 35% females (Figure 3). It also shows that 55% of the eyes included were right eyes, while 45% were left eyes. Regarding the underlying etiology of macular edema, 42.5% of the cases were due to retinal vein occlusion, 35% were diabetic macular edema, and 22.5% were Age Related Macular Degeneration (ARMD).

The table 2 illustrates that out of the total study participants distributed across the three etiological groups, diabetic macular edema had a mean Baseline central macular thickness (Figure 4) of 405.1 µm, retinal vein occlusion showed a higher value of 526.4 µm, and Age-Related Macular Degeneration (ARMD) demonstrated the highest thickness of 634.2 µm. The table also shows that Baseline visual acuity (Figure 5) was 1.03 LogMAR in diabetic macular edema, 1.11 LogMAR in retinal vein occlusion, and 1.32 LogMAR in Age Related Macular Degeneration (ARMD), indicating a progressive decline across the groups.

The table 3 illustrates that out of the total study participants evaluated for change in central macular thickness, all three etiological groups demonstrated a reduction from Baseline to Post injection, with diabetic macular edema showing a mean decrease of 128.7 µm, retinal vein occlusion showing a larger reduction of 244.9 µm, and Age Related Macular Degeneration (ARMD) showing the greatest reduction of 309.0 µm, while the overall study population showed a mean reduction of 221.4 µm.

The table 4 illustrates that out of the total study participants assessed for improvement in visual acuity, diabetic macular edema showed a mean LogMAR reduction of 0.28, retinal vein occlusion demonstrated a reduction of 0.34, and Age Related Macular Degeneration (ARMD) showed the greatest improvement with a reduction of 0.46, while the combined group exhibited an overall improvement of 0.35. The table 5 illustrates that out of the eyes with severe macular edema exceeding 500 µm at Baseline, the subgroup demonstrated a substantial mean reduction of 354.4 µm in central macular thickness and an improvement of 0.46 in visual acuity at Post injection.

The table 6 illustrates that out of the total study participants included for correlation analysis, all three etiological groups showed a significant positive association between reduction in macular thickness and improvement in visual acuity, with correlation coefficients of 0.614 in diabetic macular edema, 0.721 in retinal vein occlusion, and 0.783 in Age Related Macular Degeneration (ARMD), while the overall correlation for the full sample was 0.689.

Discussion

This study demonstrates that combining posterior subtenon interferon alpha-2b with intravitreal bevacizumab results in significant anatomical and functional improvement in macular edema regardless of etiology. The overall reduction in CMT of 221.4 µm and improvement in BCVA of 0.35 LogMAR are consistent with previously reported findings indicating that interferon has a synergistic effect when added to anti-VEGF therapy. Our results support the earlier observations of Karimi et al., who reported enhanced reduction of macular thickness and improved vision in DME patients treated with topical interferon plus intravitreal bevacizumab compared to bevacizumab alone[1].

Similarly, Afarid et al. demonstrated favourable anatomical outcomes with adjunct topical interferon [3], and Farzan et al. confirmed its beneficial effect on edema reduction [9]. Our findings extend these observations by showing that posterior subtenon delivery, with better posterior segment penetration, may achieve comparable or superior results.

The anatomical improvements observed in this study align closely with the work of Modarres et al., who reported that posterior subtenon interferon resulted in meaningful structural improvement in refractory DME [4]. The ARMD subgroup in our study showed the greatest CMT reduction (309 µm), which is consistent with Cellini et al.'s case describing marked resolution of edema following subtenon interferon [2]. These findings collectively suggest that interferon's anti-inflammatory and anti-angiogenic effects may provide additional therapeutic benefit beyond VEGF suppression.

The functional improvements recorded here mirror the anatomical gains. The mean visual improvement of 0.35 LogMAR across the cohort matches closely with visual gains reported in large bevacizumab trials such as those by Wells et al. and Rosenfeld et al.[11,12]. Our correlation analysis ($\rho = 0.689$) demonstrates a strong association between restoring macular thickness and visual improvement, consistent with existing literature on OCT-based prognostication [12,23].

Posterior subtenon delivery offers an important safety advantage. Unlike corticosteroids, interferon does not induce elevated intraocular pressure or posterior subcapsular cataract, issues frequently reported in studies evaluating posterior subtenon triamcinolone, including those by Sharma et al. and Falavarjani et al.[8,21]. The absence of steroid-related complications further supports the suitability of interferon as a steroid-sparing adjunct in chronic or refractory macular edema. Overall, the results suggest that this dual-mechanism approach—VEGF blockade combined with

cytokine modulation—offers superior outcomes compared to anti-VEGF monotherapy, especially in severe edema where inflammatory pathways may be more predominant. Although our study is limited by its observational design and short-term follow-up, the consistency of improvements across etiologies and their agreement with previously published work support the potential value of this treatment strategy.

Conclusion

Posterior subtenon interferon alpha-2b combined with intravitreal bevacizumab significantly improves central macular thickness and visual acuity in macular edema. The approach is effective across etiologies and particularly beneficial in severe edema. Its steroid-sparing profile enhances safety. Further randomized trials are required to validate long-term efficacy.

Data Access: The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions: Dr. Pallavi conceived and conducted the study and drafted the manuscript. Dr. Asima and Sadiya contributed to data collection and study implementation. Dr. Sajad supervised the research and critically revised the manuscript. All authors approved the final version.

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