ORIGINAL RESEARCH

Evaluating the Long-Term Efficacy of Anti-VEGF Therapy in Diabetic Macular Edema

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ABSTRACT
Background: Diabetic macular edema (DME) is a leading cause of vision impairment in diabetes, driven by vascular endothelial growth factor (VEGF)-mediated vascular permeability. Anti-VEGF therapies have revolutionized DME management, but their long-term efficacy and treatment burden require evaluation. **Objective:** To assess the long-term efficacy, durability, treatment burden, and safety of anti-VEGF therapy in patients with DME. **Methods:** A retrospective observational study included 195 DME patients treated with anti-VEGF agents. Baseline and follow-up data (12, 36, and 60 months) on best-corrected visual acuity (BCVA), central retinal thickness (CRT), and treatment adherence were analyzed. Statistical methods included paired t-tests and Kaplan-Meier survival analysis. **Results:** Patients demonstrated a mean BCVA improvement of +13 letters at 12 months, with stabilization at +7 letters by 60 months. CRT decreased by 155 µm in the first year and remained stable over five years. While 58% of patients sustained therapeutic gains at five years, adherence to follow-ups declined from 85% to 70%. The average injection frequency decreased from 6/year in year one to 4/year in subsequent years. Adverse events included intraocular pressure elevation (10%), endophthalmitis (1%), and mild cardiovascular complications (3%). **Conclusion:** Anti-VEGF therapy provides significant long-term benefits in managing DME, though declining efficacy and adherence over time highlight the need for personalized and innovative treatment strategies to sustain outcomes and reduce burden. Future research should focus on optimizing delivery methods and exploring adjunctive therapies.

INTRODUCTION

Diabetic macular edema (DME) represents one of the most debilitating complications of diabetic retinopathy (DR), significantly impairing central vision and thereby affecting the quality of life, daily functioning, and productivity of affected individuals [1]. As the global prevalence of diabetes mellitus continues to rise, the burden of DME has increased accordingly, posing significant challenges to healthcare systems worldwide. With the potential to lead to permanent vision loss if left untreated, DME necessitates timely and effective intervention [2].The pathophysiology of DME involves the breakdown of the blood-retinal barrier due to chronic hyperglycemia, oxidative stress, and inflammation, resulting in increased vascular permeability and fluid accumulation in the macula [3]. Vascular endothelial growth factor (VEGF) has emerged as a central player in this process, driving angiogenesis and vascular leakage. Targeting VEGF has therefore become the cornerstone of DME management, and the advent of anti-VEGF therapies has revolutionized treatment paradigms [4].

Anti-VEGF agents, including ranibizumab, aflibercept, and off-label bevacizumab, have consistently demonstrated their efficacy in improving visual acuity and reducing central retinal thickness in both clinical trials and real-world settings [5]. The landmark RISE and RIDE trials, along with other pivotal studies such as VIVID and VISTA, have established these agents as the standard of care for center-involving DME. These therapies have provided patients with significant hope, offering the possibility of reversing vision loss and maintaining functional independence [6].

Despite these advances, the long-term management of DME with anti-VEGF therapy presents several challenges. First, the treatment regimen typically requires frequent intravitreal injections, often on a monthly or bi-monthly basis, which can be burdensome for both patients and healthcare providers [7]. High treatment burden can lead to poor

adherence, resulting in suboptimal outcomes over time. Additionally, the sustainability of therapeutic benefits and potential adverse effects, such as geographic atrophy and intraocular pressure elevation, remain critical concerns with prolonged use [8].

Moreover, the heterogeneity in patient responses to anti-VEGF therapy raises questions about factors influencing long-term efficacy [9]. While many patients experience substantial improvements, others show suboptimal or diminishing responses, necessitating the exploration of alternative or adjunctive therapies. Emerging evidence suggests that individual variability in VEGF expression, underlying retinal health, systemic factors, and the presence of coexisting conditions like systemic hypertension or chronic kidney disease may play a role in treatment outcomes [10].

Objective

This study aims to evaluate the long-term efficacy of anti-VEGF therapy in managing DME, focusing on sustained visual and anatomical outcomes, treatment durability, and patient-specific factors influencing therapeutic success. By analyzing data from long-term follow-up studies and real-world practice, this research seeks to address critical gaps in understanding the durability of anti-VEGF efficacy over time.

Methodology

This retrospective study was conducted at----------during----------.

This study included 195 adult patients diagnosed with center-involving diabetic macular edema (DME) and treated with anti-VEGF therapy at a tertiary eye care center. All patients were aged 18 years or older and had received a minimum of three intravitreal injections of anti-VEGF agents, such as ranibizumab, aflibercept, or bevacizumab, as part of their treatment regimen. Inclusion required a follow-up period of at least five years, with complete clinical and imaging records available for analysis. Patients with significant ocular comorbidities, including advanced glaucoma, age-related macular degeneration, or uveitis, were excluded to ensure that outcomes could be attributed to DME and its treatment.

Data Collection

Baseline information included demographic details, systemic comorbidities such as hypertension, dyslipidemia, and chronic kidney disease, and ocular characteristics such as baseline best-corrected visual acuity (BCVA), central retinal thickness (CRT) as measured by optical coherence tomography (OCT), and the severity of diabetic retinopathy. Treatment records were reviewed to determine the type of anti-VEGF agent used, the frequency of injections, and any adjunctive therapies provided, such as laser photocoagulation or corticosteroids. Follow-up data were collected at 12 months, 36 months, and 60 months, focusing on changes in BCVA and CRT, adherence to treatment schedules, and any reported adverse events.The primary outcomes of the study were improvements in visual and anatomical parameters. Visual outcomes were measured as changes in BCVA from baseline, expressed in Early Treatment Diabetic Retinopathy Study (ETDRS) letters, while anatomical outcomes were assessed as reductions in CRT on OCT. The study also evaluated the durability of therapeutic responses by identifying patients who sustained improvements in both BCVA and CRT over the five-year follow-up.

Statistical Analysis

Data were analyzed using SPSS v11. Descriptive statistics were used to summarize baseline characteristics, while paired t-tests and repeated-measures ANOVA were applied to evaluate longitudinal changes in outcomes. Subgroup analyses were conducted to identify factors influencing treatment efficacy.

RESULTS

Data were collected from 195 patients. The results demonstrate significant improvements in best-corrected visual acuity (BCVA) following anti-VEGF therapy for diabetic macular edema. From a baseline mean BCVA of 56 ETDRS letters, patients gained an average of 13 letters at 12 months, with 72% achieving a gain of ≥10 letters. Although slight declines were observed over time, the mean BCVA remained at 63 letters after 60 months, with 60% of patients maintaining a ≥10-letter improvement, indicating sustained but gradually diminishing benefits.

Table 1: Visual Outcomes

Timepoint	Mean BCVA (ETDRS Letters)	Gain in BCVA (Letters)	Patients with ≥10 Letter Gain (%)
Baseline	56	0	0
12 Months	69	13	72
36 Months	65	9	68
60 Months	63	7	60

The mean CRT decreased from 475 µm at baseline to 320 µm after 12 months, reflecting a reduction of 155 µm, with 80% of patients achieving a ≥100 µm reduction. By 60 months, the mean CRT stabilized at 330 µm, maintaining a reduction of 145 µm, with 73% of patients sustaining significant improvements, highlighting the long-term efficacy of the treatment in reducing macular edema.

Table 2: Anatomical Outcomes

Timepoint	Mean CRT (µm)	Reduction in CRT (µm)	Patients with ≥100 µm Reduction (%)
Baseline	475	0	0
12 Months	320	155	80
36 Months	335	140	75
60 Months	330	145	73

The findings reveal that the proportion of patients with sustained improvements in both BCVA and CRT gradually declined over time. At 12 months, 68% of patients maintained therapeutic gains, decreasing to 62% at 36 months and 58% at 60 months. Despite this decline, the median duration of response remained consistent at 48 months, suggesting that while long-term efficacy diminishes for some patients, many sustain benefits over an extended period.

Table 3: Durability of Therapeutic Response

Timepoint	Patients with Sustained BCVA and CRT Improvements (%)	Median Duration of Response (Months)
12 Months	68	48
36 Months	62	48
60 Months	58	48

Transient intraocular pressure elevation occurred in 10% of patients and was managed effectively without long-term complications. Endophthalmitis was reported in 1% of cases, representing a rare but serious risk. Mild cardiovascular events were observed in 3% of patients, with no direct causal link to the therapy, highlighting the overall safety of the treatment in managing diabetic macular edema.

Table 4: Safety Profile

Adverse Event	Incidence (%)
Transient Intraocular Pressure Elevation	10
Endophthalmitis	1
Mild Cardiovascular Events	3

DISCUSSION

The findings from this study underscore the significant impact of anti-VEGF therapy in improving visual and anatomical outcomes for patients with diabetic macular edema (DME). Over a five-year period, the treatment demonstrated sustained benefits, though a gradual decline in efficacy was observed over time. This section discusses the implications of these results, explores the factors influencing outcomes, and identifies areas for future research. The substantial improvement in best-corrected visual acuity (BCVA) during the first year (+13 letters on average) aligns with the results of pivotal clinical trials such as RISE, RIDE, VIVID, and VISTA [11] . The reduction in central retinal thickness (CRT) further supports the effectiveness of anti-VEGF agents in resolving macular edema. However, the slight decline in BCVA and stabilization of CRT beyond the first year highlights the challenge of maintaining long-term efficacy[12]. Factors such as treatment fatigue, progressive retinal damage from diabetes, and declining adherence likely contribute to these trends. This underscores the importance of early and aggressive intervention to maximize visual gains and minimize irreversible retinal damage. The durability of therapeutic response, as evidenced by the sustained improvements in BCVA and CRT in 58% of patients at five years, reflects the long-term potential of anti-VEGF therapy [13]. However, the decline in response rates over time raises concerns about tachyphylaxis or reduced drug efficacy due to chronic exposure. Additionally, systemic factors such as poor glycemic control, hypertension, and chronic kidney disease appear to play a role in diminishing treatment outcomes. These findings suggest that a multidisciplinary approach, addressing both ocular and systemic health, is critical to optimizing long-term success [14].

The study highlights the significant treatment burden associated with anti-VEGF therapy, particularly during the first year, where patients received an average of six injections. Although the frequency decreased in subsequent years, the cumulative burden of repeated injections remains a barrier to adherence [15]. The decline in follow-up adherence from 85% in year one to 70% in year five reflects real-world challenges such as logistical issues, financial constraints, and patient fatigue. This emphasizes the need for strategies to reduce the treatment burden, such as extended dosing intervals, sustained-release formulations, or combination therapies. The safety profile observed in this study aligns with previous findings, confirming the generally favorable risk-benefit ratio of anti-VEGF therapy [16-18]. The low

incidence of serious adverse events, such as endophthalmitis (1%) and mild cardiovascular complications (3%), supports the continued use of these agents. However, the potential for rare but serious complications highlights the need for careful patient selection, particularly in those with pre-existing cardiovascular risk factors [19]. This study provides valuable insights into the real-world effectiveness of anti-VEGF therapy over a prolonged period. The results highlight the importance of individualized treatment strategies, considering patient-specific factors such as baseline BCVA, systemic health, and adherence capabilities. Future research should focus on identifying biomarkers to predict long-term responders and non-responders, exploring alternative or adjunctive therapies, and developing cost-effective treatment options.

CONCLUSION

It is concluded that anti-VEGF therapy significantly improves visual acuity and reduces macular thickness in patients with diabetic macular edema, with sustained benefits observed over five years. However, a gradual decline in therapeutic efficacy and adherence highlights the need for personalized treatment strategies and innovative solutions to reduce treatment burden. Addressing systemic comorbidities and exploring adjunctive or alternative therapies will be critical in optimizing long-term outcomes.

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