Journal of Cardiovascular Disease Research

ISSN: 0975-3583, 0976-2833 VOL09, ISSUE 04, 2018

Efficacy of treatment outcomes of Intravitreal Antivascular Endothelial Growth factor injections and related risk factors in Diabetic macular edema

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Abstract:

Objective: The primary goal of this study was to assess the efficacy of intensive aflibercept therapy in people with diabetic macular oedema (DME). The study additionally aimed to look into the modifiable systemic and ocular variables that affect therapy response in a practical scenario. Methodology: We conducted a retrospective analysis of the medical records of a cohort of patients diagnosed with diabetic macular oedema (DME). The evaluation of diabetic macular oedema (DME) involved the utilisation of central retinal thickness (CRT) and best-corrected visual acuity (BCVA). The study assessed the changes in contrast sensitivity and best-corrected visual acuity (BCVA) in response to each statistically significant factor. Results: The average central retinal thickness (CRT) and best-corrected visual acuity (BCVA) exhibited a significant improvement following the administration of five loading injections. Specifically, the CRT decreased to336.65 ± 61.223 from 486.97 ± 91.23 μm, while the BCVA improved to0.39 ± 0.21 LogMAR, with statistical significance ($p < 0.05$). Over the course of a 12-month follow-up period, it was seen that 16 eyes (53.33%) were able to sustain central retinal thickness (CRT) without requiring any supplementary treatment. Conclusion: In conclusion, administering five monthly loading doses of intravitreal aflibercept injection resulted in notable structural and optical enhancements among individuals diagnosed with diabetic macular oedema (DME).

Keywords: Intravutrealanti-vascular endothelial growth, Diabetic macular Edema, Risk factors

INTRODUCTION:

Diabetic macular edoema (DME) is the primary cause of visual deterioration in persons suffering from diabetic retinopathy [1]. Diabetic macular edoema (DME) is distinguished by the disruption of the blood-retinal barrier and the accompanying elevation in vascular permeability, leading to the abnormal buildup of fluid inside the intraretinal layers of the macula [2]. The pathogenesis of diabetic macular edoema (DME) is significantly influenced by the presence and activity of vascular endothelial growth factor (VEGF). Consequently, intravitreal anti-vascular endothelial growth factor (anti-VEGF) injections have emerged as the predominant therapeutic modality for the management of instances of diabetic macular edoema (DME) involving the central region. This therapeutic method has garnered considerable recognition [3].Aflibercept is the exclusive antiangiogenic drug that successfully hinders all variations of vascular endothelial growth factor (VEGF) and placental growth factor, which is a constituent of the VEGF family. It demonstrates the highest level of affinity for binding and the longest duration of half-life [2]. The most effective treatment regimen for aflibercept has not been definitively established. Nevertheless, there is a prevailing belief that a treatment approach involving a substantial number of initial loading injections, followed by as-needed (pro re nata (PRN)) doses, can improve treatment efficacy and alleviate the treatment burden [4–6].

ISSN: 0975-3583, 0976-2833 VOL09, ISSUE 04, 2018

The study conducted by DRCR.net Protocol T [5] was a crucial randomised controlled trial that provided evidence supporting the superior efficacy of monthly aflibercept injection as a loading regimen in resolving diabetic macular oedema (DME) compared to bevacizumab or ranibizumab. Nevertheless, it should be noted that 31.6% of eyes continued to exhibit persistent diabetic macular oedema (DME) even after receiving the initial six monthly injections of aflibercept, as reported in a previous study [7]. Indeed, predicting the specific outcome of intensive aflibercept treatment poses difficulties in real-world clinical settings due to the exclusion criteria followed in Protocol T, which excluded eyes with systemic diseases other than diabetes (such as significant renal, hypertensive, or cardiovascular disease) or prior treatment for diabetic macular edoema (DME). It is imperative to elucidate the modifiable risk factors that impact the response to this intervention to optimise the therapeutic effectiveness of intensive aflibercept treatment.

Considerable study has been undertaken to investigate the influence of systemic factors on the onset and progression of diabetic retinopathy. [8–12]. However, there is a lack of scholarly investigation about the influence of systemic and ocular components on the effectiveness of intensive aflibercept monotherapy in managing diabetic macular oedema (DME). Numerous investigations have been undertaken to examine the impact of alternative anti-vascular endothelial growth factors (anti-VEGFs), including bevacizumab and ranibizumab, on diabetic macular oedema (DME) [13-24]. However, there is a shortage of research addressing the effects of aflibercept on this condition. The primary goal of this study was to assess the efficacy of intensive aflibercept therapy in people with diabetic macular oedema (DME). The study additionally aimed to look into the modifiable systemic and ocular variables that affect therapy response in a practical scenario.

METHODOLOGY:

The study was done at the Medical Centre, a tertiary referral centre. We conducted a retrospective analysis of the medical records of a cohort of patients diagnosed with diabetic macular oedema (DME). Specifically, we focused on those individuals who underwent their initial treatment with intense intravitreal aflibercept injections, consisting of five monthly loading doses followed by a pro re nata (PRN) approach. Since April 2020, Indian Health Insurance has initiated coverage for aflibercept, namely for the initial five consecutive injections, followed by bimonthly injections for a maximum of 14 treatments, to address diabetic macular oedema (DME). As to the guidelines outlined by the Indian Health Insurance, individuals with a baseline central retinal thickness of μm were recommended to undergo the prescribed treatment. Eyes were deemed ineligible for inclusion in the study if they had not had comprehensive systemic and ophthalmologic assessments or if they had a medical history of ocular disorders that could potentially lead to macular oedema, such as retinal vein occlusion, age-related macular degeneration, or intraocular inflammation. All patients included in the study provided informed agreement for intravitreal injection. However, the Institutional Review Board (IRB) of Uttarakhand Medical Centre waived the requirement for informed consent specifically for the study, given its retrospective design.

The researchers examined the patient's past medical history and baseline blood test results, which included measurements of glycated haemoglobin (HbA1c), a complete blood count (CBC)before the commencement of the intervention.The evaluation of diabetic macular oedema (DME) involved the utilisation of central retinal thickness (CRT). The measurement of central retinal thickness (CRT) was conducted utilising a spectral domain optical coherence tomography (SD-OCT) methodology. This step involved the systematic scanning of the macula in a horizontal raster pattern, with the fovea serving as the focal point of focus. The scan encompassed a field of vision spanning 20 degrees by 20 degrees. The measurements of CRT were computed automatically by the software embedded in the device. The evaluation of the OCT images was performed by two examiners, who conducted their assessments autonomously. During the study, OCT images evaluation was performed by two examiners and excluded all the displayed inadequate quality or artefacts.

ISSN: 0975-3583, 0976-2833 VOL09, ISSUE 04, 2018

The patients were assigned to receive five consecutive monthly intravitreal aflibercept injections (Eylea; Bayer Inc., 2 mg/0.05 mL each) throughout the initial therapy phase. These injections were administered at baseline and months 1, 2, 3, and 4. The patients were subjected to monthly monitoring after the initial therapy phase. The administration of therapy on an as-needed basis (PRN) was limited to cases where the central retinal thickness (CRT) measured 300 μm or above and had increased by more than 50 μm in comparison to the previous measurement [13].

The assessment of the treatment response in terms of morphology and function involved the utilisation of central retinal thickness (CRT) measurements and evaluations of best-corrected visual acuity (BCVA) during monthly visits. The primary indicator of therapy efficacy in the intensive aflibercept treatment study was evaluated based on two variables: the mean alterations in central retinal thickness (CRT) and best-corrected visual acuity (BCVA), along with the proportion of patients classified as good responders (CRT < 300 μm) and suboptimal responders (CRT > 300 μm) following the administration of five monthly loading injections (at month 5) [7, 28]. In addition, we evaluated the percentage of eyes that retained their central retinal thickness (CRT) without requiring additional treatment during the pro re nata (PRN) regimen, aiming to examine the long-term efficacy of aflibercept loading injections. Comparative analysis was performed on the ocular and systemic parameters at the initial stage to investigate the factors that impact treatment response. This analysis aimed to differentiate between those who achieved good treatment outcomes and those who had unsatisfactory responses. The study assessed the changes in contrast sensitivity and best-corrected visual acuity (BCVA) in response to each statistically significant factor.

All the calculations were performed using SPSS software, specifically version 21.0. TKaplan-Meier analysis was used to assess the long-term effectiveness of aflibercept loading injections during the maintenance phase while Mann-Whitney and Wilcoxon signed-rank tests were utilised to evaluate the disparities in systemic and ocular components between groups, categorised according to the variables. Furthermore, two way Annova was used to measure the statistical significance of the alterations in CRT and BCVA compared to their respective initial measurements. Logistic regression analysis was utilised in the study to evaluate the association between poor treatment response and various systemic and ocular factors. A statistical significance was attributed to a significance level below 0.05.

RESULTS:

A comprehensive assessment was conducted on 30 eyes belonging to 23 patients diagnosed with diabetic macular oedema (DME). The baseline characteristics of the subjects are presented in Table 1. A total of 18 eyes (60%) were identified as having non-proliferative diabetic retinopathy (NPDR), whereas 12 eyes (40%) were diagnosed with proliferative diabetic retinopathy (PDR). Out of the total number of eyes observed, 26.66% (eight eyes) had not received any prior treatment, while the remaining eyes had undergone different treatment regimens. Specifically, 13.33% (four eyes) had undergone vitrectomy and pan-retinal photocoagulation (PRP), 16.66% (five eyes) had received bevacizumab injection in addition to PRP, another 16.66% (five eyes) had received bevacizumab injection simply. Finally, 26.66% (eight eyes) had undergone PRP treatment exclusively. Upon the conclusion of the loading injection process, which occurred in the fifth month, there was a notable and statistically significant improvement in the mean central retinal thickness (CRT) and best-corrected visual acuity (BCVA). Based on the findings of the clinical trial in the fifth month, it was observed that eleven eyes (36.66%) exhibited a favourable response, whereas nineteen eyes (63.33%) demonstrated a subpar response.

The average central retinal thickness (CRT) and best-corrected visual acuity (BCVA) exhibited a significant improvement following the administration of five loading injections. Specifically, the CRT decreased to336.65 ± 61.223 from 486.97 ± 91.23 μm, while the BCVA improved to0.39 ± 0.21 LogMAR, with statistical significance ($p < 0.05$). (Table 2) Over the course of a 12-month follow-up period, it was seen that 16 eyes (53.33%) were able to sustain central retinal thickness

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(CRT) without requiring any supplementary treatment. Individuals with a history of diabetes mellitus (DM) affecting the eyes for a duration of at least 15 years, an estimated glomerular filtration rate of mL/min/1.73 m2, serum mg/dL and mmol/L, and the existence of an epiretinal membrane (ERM) were shown to be at a higher probability of exhibiting a suboptimal response to the treatment.

During the maintenance phase of the PRN regimen, the average central retinal thickness (CRT) exhibited a rise, coinciding with a decline in best-corrected visual acuity (BCVA). However, it should be noted that the observed values did not surpass the baseline measurements, as indicated in Table 2. Out of the total number of eyes seen, 53.33% (16 eyes) were able to sustain the enhanced contrast sensitivity without requiring any further treatment. However, 46.66% (14 eyes) necessitated as-needed treatment during the 12-month follow-up period. The distribution of these eyes requiring PRN treatment was as follows: 1 eye (3.33%) at month 5, 5 eyes (16.67%) at month 6, 7 eyes (23.33%) at month 7, and 1 eye (3.33%) at month 10, as illustrated in Figure 2. Out of the total number of eyes seen, 7 eyes (23.33%) were treated solely with aflibercept, while 7 eyes (23.33%) transitioned to alternative therapies. Specifically, 2 eyes (6.66%) received a combination of Ozurdex and bevacizumab, 1 eye (3.33%) received a combination of Ozurdex and sub-tenon triamcinolone injection, 3 eyes (10.00%) were treated exclusively with Ozurdex, and 1 eye (3.33%) received bevacizumab alone. During the whole period of the cohort research, it was noted that the administration of rigorous aflibercept treatment did not provide any statistically significant ocular or nonocular outcomes. Our findings indicate that eyes with longer duration of diabetes mellitus (DM), lower estimated glomerular filtration rate (eGFR), higher serum creatinine and potassium levels, and the epiretinal membrane (ERM) exhibited a lesser reduction in CRT following therapy with aflibercept. The observed pattern of changes in best-corrected visual acuity (BCVA) closely paralleled that of central retinal thickness (CRT) during the whole duration of the study. However, it is important to note that while there was a general alignment between the two variables, they were not entirely consistent, and BCVA changes exhibited more pronounced variations.

Table 1: Demographic characteristics of participants

Parameters	N (%)
Age	59.89 ± 8.76
Gender	
Male	19 (63.3%)
Female	11 (36.6%)
Duration of Diabetes mellitus	13.23 ± 8.67
Hemoglobin A1c	6.78 ± 1.52
Medication	
Oral hyoglycemic agents	26 (86.66%)
Insulin	4 (13.3%)

Table 2: Ocular parameters of participants

Variable	N (%)	p-value
Severity of diabetic retinopathy		0.644
Non proliferative diabetic retinopathy	18 (60%)	
Proliferative diabetic retinopathy	12 (40%)	
Treatment		0.568
Vitrectomy along with Pan-retinal photocoagulation	4 (13.3%)	

ISSN: 0975-3583, 0976-2833 VOL09, ISSUE 04, 2018

Pan-retinal photocoagulation	8 (26.6%)	
Bevacizumab	5 (16.6%)	
Bevacizumab along with pan-retinal photocoagulation	5 (16.6%)	
No treatment	8 (26.6%)	

Table 3: Treatment score of central retinal thickness and best corrected visual acuity

	Central Retinal Thickness	Best corrected visual acuity	p-value
Baseline	486.97 ± 91.23	0.51 ± 0.29	0.021
First dose	366.37 ± 73.45	0.44 ± 0.23	0.028
Second dose	337.87 ± 56.78	0.36 ± 0.28	0.014
Third dose	328.56 ± 130.24	0.37 ± 0.28	0.014
Fourth dose	333.65 ± 70.23	0.35 ± 0.23	0.011
Fifth dise	336.65 ± 61.223	0.39 ± 0.21	<0.0001

DISCUSSION:

The present investigation provides evidence to support the efficacy of intensive aflibercept treatment in improving both morphological and functional outcomes in patients with diabetic macular oedema (DME). Significantly, ocular conditions characterised by extended duration of diabetic macular oedema (DM), reduced estimated glomerular filtration rate (eGFR), elevated levels of serum creatinine and potassium, as well as the presence of epiretinal membrane (ERM), were found to be correlated with an inadequate response to treatment. To the best of our current understanding, this study represents the initial examination of both systemic and ocular parameters that impact the outcomes of intensive aflibercept treatment in patients with diabetic macular oedema (DME) within a real-world context.

The present investigation additionally observed that administering five aflibercept loading injections resulted in notable morphological and optical enhancements. Additionally, it was shown that 53.33% of eyes could sustain corneal reshaping therapy (CRT) without requiring any further intervention throughout the 12-month follow-up period.Nevertheless, in this particular investigation, it was shown that DME continued to persist in over half of the eyes (63.33%) following the administration of five loading injections. A retrospective review of Protocol T [7] revealed that 31.6% of the eyes exhibited persistent diabetic macular oedema (DME) following the initial six monthly aflibercept injections. However, the likelihood of DME persistence was lower when treated with bevacizumab. In current study the initial administration of the injection resulted in the most substantial improvement in both central retinal thickness (CRT) and best-corrected visual acuity (BCVA). However, a steady improvement was observed as the frequency of injections increased during the loading phase. Out of the sample, three eyes, including 10% of the total, exhibited a suboptimal response subsequent to the third injection. Nevertheless, the aforementioned eyes exhibited a favourable response and exhibited a positive reaction subsequent to the administration of the fifth injection. It is imperative to acknowledge that the data pertaining to these individuals who experienced delayed responses has not been published. Furthermore, it is important to highlight that after discontinuation of monthly loading injections, there was an observed rise in central retinal thickness (CRT) which did not fully revert to the level reported during the loading period, even with pro re nata (PRN) treatment.

Numerous research studies have examined the correlation between systemic variables and the response to treatment for diabetic macular oedema (DME) [14-23]. However, the findings of these studies have been inconclusive and primarily

ISSN: 0975-3583, 0976-2833 VOL09, ISSUE 04, 2018

focused on the use of ranibizumab or bevacizumab. The present investigation aimed to ascertain the risk variables associated with a suboptimal response to aflibercept injection. These risk factors included an extended duration of diabetes mellitus, reduced estimated glomerular filtration rate, elevated serum creatinine and potassium levels, and epiretinal membrane.

Remarkably, the findings of our investigation revealed that the longitudinal alterations in CRT and BCVA exhibited a degree of similarity, albeit not entirely consistent. These results imply that visual function cannot be fully explained by anatomical resolution alone. A retrospective analysis of Protocol T [24] demonstrated a modest to moderate connection between retinal thickness and visual acuity during the study. In addition, it should be noted that alterations in retinal thickness explained only a small fraction (12-14%) of the observed variations in visual acuity. According to a prior investigation, macular ischemia in diabetic macular oedema (DME) leads to a disparity between the anatomical and visual enhancements following treatment with ranibizumab [14]. These findings indicate that additional factors may contribute to visual acuity in diabetic macular oedema (DME) beyond the presence of tissue oedema.

Contrary to our research findings, certain studies [17,19] have indicated insufficient evidence to support the association between systemic parameters such as glycemic management, blood chemistry, or renal function and the treatment outcomes of ranibizumab. On the other hand, some individuals assert that inadequate glycemic management, as indicated by elevated levels of HbA1c, is the primary determinant of unfavourable treatment outcomes associated with anti-VEGF therapy. The lack of a definitive resolution for the discrepancy observed in the outcomes of the studies is evident [15,17-21,23]. Nevertheless, it is postulated that the variations above mostly stem from disparities in the demographics of the study cohort, research methodology, types of medications employed, and duration of observation. Hence, it is imperative to exercise prudence while interpreting our research findings. If the analysis were to incorporate individuals with chronically uncontrolled diabetes mellitus (DM), the study's findings would deviate from the present findings. Nevertheless, our data holds significance as it indicates that managing kidney dysfunction or serum electrolyte levels could potentially enhance the efficacy of aflibercept treatment, even in patients with relatively well-regulated glucose control.

Regarding ocular variables, our study findings align with previous research indicating that the presence of abnormalities at the vitreomacular interface, particularly the epiretinal membrane (ERM), has been linked to worse treatment outcomes for diabetic macular oedema (DME) [25,26]. According to a recent in vitro investigation, it has been determined that the resistance of diabetic macular oedema (DME) to anti-vascular endothelial growth factor (anti-VEGF) treatment can be attributed to a reduction in the permeability of antibodies via the epiretinal membrane (ERM) [27].

CONCLUSION:

In conclusion, administering five monthly loading doses of intravitreal aflibercept injection resulted in notable structural and optical enhancements among individuals diagnosed with diabetic macular oedema (DME). Individuals diagnosed with diabetes mellitus for an extended period, exhibit impaired kidney function, or have end-stage renal disease are more likely to experience a less-than-ideal response to treatment.

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