

Role of Diabetic Retinopathy Stage in the Outcome of Anti-VEGF Therapy in Macular Edema

Lional Raj¹, Heber Anandan², J L Dhanisha³, J Mohamed Ali⁴, John Abraham⁵

¹Regional Medical Director, Department of Ophthalmology, Dr. Agarwal's Eye Hospital, Tirunelveli, Tamil Nadu, India, ²Senior Clinical Scientist, Department of Clinical Research, Dr. Agarwal's Eye Hospital, Tirunelveli, Tamil Nadu, India, ³Clinical Research Associate, Department of Clinical Research, Dr. Agarwal's Eye Hospital, Tirunelveli, Tamil Nadu, India, ⁴Associate Professor, Department of Clinical Optometry, Dr. Agarwal's Eye Hospital, Tirunelveli, Tamil Nadu, India, ⁵Senior Consultant, Department of Ophthalmology, Dr. Agarwal's Eye Hospital, Tirunelveli, Tamil Nadu, India

Abstract

Introduction: Diabetic retinopathy is a complication of diabetes and the leading cause of vision impairment. It has been found that vascular endothelial growth factor (VEGF) inhibiting factors will control diabetic macular changes.

Aim: Our study aims to find the effect of the stages of diabetic retinopathy in the outcome of anti-VEGF therapy in macular edema.

Materials and Methods: A retrospective observation study was done in patients with diabetic retinopathy were included. Subjects with ocular diseases other than diabetic retinopathy were excluded from the study. The data on the patient refractive power, ophthalmoscopic findings on the stage of the diabetic retinopathy, the macular thickness as measured by the optical coherence tomography (OCT), and the fundus fluorescein angiography (FFA) findings were noted from the medical records.

Results: A total of 40 patients were included in this study. Twenty-five are male and 15 were female with a mean age of 56 ranging from 43 to 69 years. Forty subjects, 16 subjects belong to the moderate non-proliferative diabetic retinopathy (NPDR) stage. Three subjects had mild NPDR, 13 subjects had severe NPDR, and 8 subjects had proliferative diabetic retinopathy (PDR). The retinal findings included microaneurysm (MA), hemorrhages (HE), neovascularization at the disc (NVD), neovascularization elsewhere (NVE), vitreous hemorrhage (VH), tractional retinal detachment (TRD), and clinically significant macular edema (CSME). The number of cases with high macular thickness has become less post-therapy indicating the decrease in macular thickness with therapy.

Conclusion: There is an improvement in the vision and macular edema with anti-VEGF treatment. It has also been found that the higher the macular edema more efficient the anti-VEGF therapy is.

Key words: Anti-VEGF therapy, Diabetic macular edema, Diabetic retinopathy

INTRODUCTION

Diabetic retinopathy (DR) is a complication of diabetes and the leading cause of vision impairment and blindness among working-age adults. It occurs when diabetes damages the tiny blood vessels in the retina, which is the light-sensitive tissue at the back of the eye. Diabetic retinopathy may lead to diabetic macular edema. The likelihood of

developing diabetic retinopathy is related to the duration of the disease. Type 2 diabetes has an insidious onset and can go unnoticed for years. As a result, patients may already have DR at the time of diagnosis. Type 1 diabetics, on the other hand, are diagnosed early in the course of their disease, and they typically do not develop retinopathy until years after the diagnosis is made. The risk of developing retinopathy increases after puberty. Twenty years after the diagnosis of diabetes, 80% of type 2 diabetics and nearly all type 1 diabetics show some signs of retinopathy. While these numbers are eye opening, diabetics can decrease their risk of retinopathy and slow the progression of the disease after it has begun with tight glucose control.^[1]

Glucose control also has the added benefit of decreasing the risk for other end-organ complications of diabetes,

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Corresponding Author: Heber Anandan, Senior Clinical Scientist, Department of Clinical Research, Dr. Agarwal's Eye Hospital, Tirunelveli, Tamil Nadu, India.

so diabetic patients must be educated on the topic. Time since diagnosis and extent of hyperglycemia is the most significant risk factor for the DR, but other risk factors for development and progression include hypertension, dyslipidemia, smoking, nephropathy, and pregnancy. Diabetic retinopathy involves damage to the retina, the light-sensitive tissue at the back of the eye.^[2]

Diabetic macular edema (DMO) which may occur at all stages of diabetic retinopathy (DR) is a severe vision-threatening complication. In most cases, laser treatment does not improve visual acuity. Therefore, research in ophthalmology focuses on the improvement of the prognosis of DMO patients with a drug-based DMO therapy. Vascular endothelial growth factor (VEGF) is considered the most important therapeutic target because this growth factor also is the most potent permeability factor affecting the inner retinal barrier formed by endothelial cells (ECs). Compared to its angiogenic stimulation of proliferation and migration of ECs, the effects of VEGF on permeability have not been studied in all details. *In vitro* investigations on the behavior of primary or immortalized retinal endothelial cells confirmed the key role of VEGF in the regulation of the permeability of the inner retinal barrier. Despite the presence of a variety of other factors found to be elevated in DR, a VEGF disrupted barrier can be completely restored with the VEGF inhibiting ranibizumab and bevacizumab when applied at clinically achievable concentrations. The antibody bevacizumab, but not the antibody fragment ranibizumab, accumulates in both retinal EC and pigment epithelial cells during prolonged treatment. It is not clear that anti-VEGF is the effect in all stages of diabetic retinopathy.^[3] Hence, we would like to find the effect of the stage of diabetic retinopathy in the outcome of anti-VEGF in macular edema.

Aim

Our study aims to find the effect of the stage of diabetic retinopathy in the outcome of anti-VEGF in macular edema.

MATERIALS AND METHODS

This retrospective study was conducted in the tertiary ophthalmic hospital at Tirunelveli. The inclusion criteria for selecting the patient records were defined as patients diagnosed with diabetic retinopathy with the macular thickness measured using OCT and FFA done with the detailed documentation of comprehensive eye examination with pre- and post-anti-VEGF treatment. The age group of the subjects ranged from 43 to 69. Both Type I and Type II diabetic patients were included in the study. All stages of diabetic retinopathy were included in the study.

We excluded the patients who have any other ocular disease other than diabetic retinopathy.

Patients who had undergone vitrectomy, intravitreal application of glucocorticoids, laser photocoagulation, and VEGF inhibitors in combination with laser were also excluded from the study. Intraocular surgery within 3 months of initiation of anti-VEGF therapy was excluded from the study. The presence of significant media opacity that would limit vision recovery (e.g, significant cataract, VH, and corneal scar), presence of coexisting macular disease (e.g, age-related macular degeneration and vascular occlusive disease), vitreomacular traction as determined by spectral domain OCT, macular ischemia if noted by the treating physician based on fluorescein angiography, previous vitreoretinal surgery (e.g, vitrectomy), and less than 1-year follow-up from initial injection was excluded from the study.^[4]

Data extraction was carried out by a single researcher. Visual acuity was extracted from the records for both pre- and post-VEGF therapy. The visual acuity values were the best-corrected visual acuities based on the logarithm of minimal angle of resolution (log MAR).

We extracted the data on the subject's refractive power, ophthalmoscopic findings on the stage of diabetic retinopathy, the macular thickness as measured by the OCT, and the FFA findings.

RESULTS

A total of 40 subjects were included in this study. Twenty-five are male and 15 were female with a mean age of 56 ranging from 43 to 69 years.

In this study, out of 40 subjects with diabetic retinopathy with macular edema was more in the age group 51–60 years (42.50%) and less in the age group ≤ 40 (2.50%) years. The distribution of the number of subjects in the different age groups is listed in Table 1.

Of 40 patients, 2 had Type I diabetes and 38 had Type II diabetes. Overall, the mean metabolic parameters remained relatively stable during the study period. The subjects were at different stages of diabetic retinopathy. The distribution of different stages of DR is plotted in Figure 1.

In this study, out of 40 subjects, 16 subjects belong to the moderate NPDR stage. The background retinal findings included MA, HE, NVD, NVE, VH, TRD, and CSME. The distribution of these findings is plotted in Figure 2.

In this study, out of 40 subjects, clinically significant macular edema is present in all of these patients. Out of

40 subjects, NVD and NVE were present in the same number. In both conditions, it is present in 8 (20%) subjects. MA, HE, and TRD were also present (80%, 77.5%, and 30%, respectively) [Figure 3].

We can see that the number of subjects in the log MAR value 0.00–1.00 (that is the group of best visual acuity increased from 34 to 38) and the number of subjects (that is the group of moderate visual acuity) decreased, indicating that there is an improvement in visual acuity with pre- and post-anti-VEGF therapy [Figure 4]. The intraocular pressure did not have much variation between pre- and post-therapy, as shown in Table 2.

Table 1: Age distribution of subjects

Age in years	No. of subjects	Percentage (%)
≤40	1	02.50
41–50	8	20.00
51–60	17	42.50
61–70	14	35

Table 2: IOP pre- and post-therapy

IOP (mmHg)	No. of subjects	
	Pre-anti-VEGF therapy	Post-anti-VEGF therapy
≤10	2	4
11–20	36	36
21–30	2	0

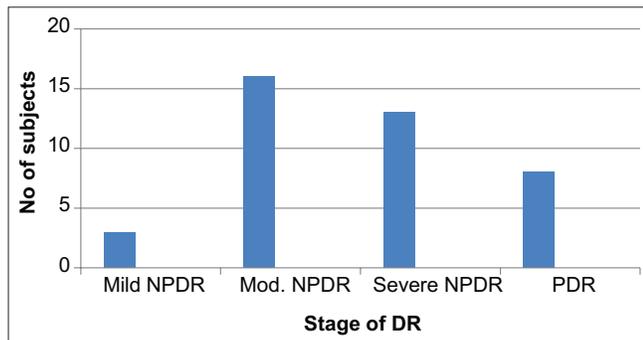


Figure 1: Stages of DR

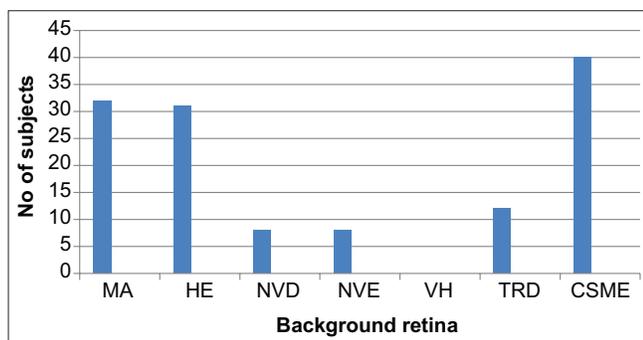


Figure 2: Background retina

As we expect that the macular thickness reduces with the VEGF therapy, we see that the number of cases with high macular thickness has become less post-therapy [Figure 5].

The X-axis was plotted with initial macular thickness and the Y-axis is plotted with the difference in macular thickness between pre- and post-anti-VEGF therapy.

DISCUSSION

Zechmeister-Koss *et al.* analyzed vascular endothelial growth factor inhibitors (anti-VEGF) in the management

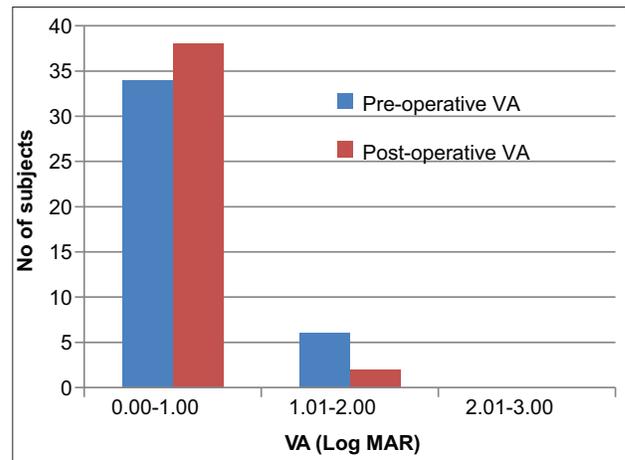


Figure 3: Visual acuity pre- and post-anti-VEGF therapy

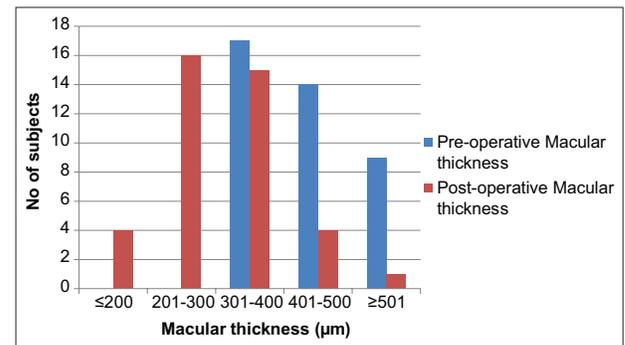


Figure 4: Macular thickness pre- and post-anti-VEGF therapy

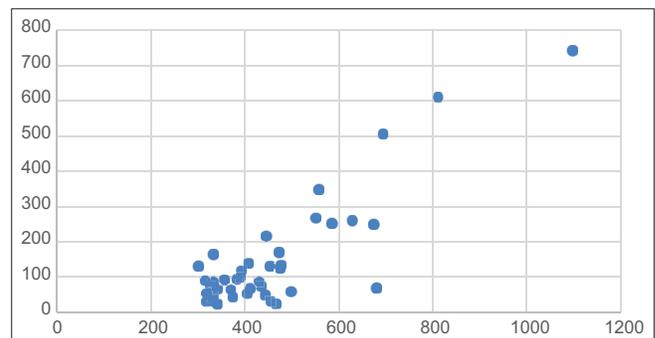


Figure 5: Treatment efficiency versus the amount of macular edema

of diabetic macular edema. Vascular endothelial growth factor inhibitors lead to better clinical outcomes than current treatments in patients with clinically manifest diabetic macular edema which is the leading cause of vision loss in the working-age population in developed countries. In a proportion of patients, VEGF inhibitors result in better visual acuity than in patients treated with laser photocoagulation or sham injection. The number of injections required for long-term improvement as well as the general long-term efficacy is unknown. The evidence is not sufficient to confirm the safety of the products in patients with DMO and does not suggest the superiority of a single product. They concluded that for some patients with DMO, VEGF inhibitors seem to be more effective as a short-term treatment option than alternative therapies. Decisions on financing should take into account the high price difference between the products and ongoing research.^[2]

Jiang *et al.* compared the treatment patterns of anti-vascular endothelial growth factor and laser therapy among patients with diabetic macular edema. A diabetic macular edema is a form of diabetic retinopathy caused by continued leakage from retinal blood vessels. The use of anti-vascular endothelial growth factor injections has gained in popularity in the treatment of DME due to satisfactory efficacy, while laser photocoagulation is still the first-line therapy. Examining anti-VEGF treatment patterns may improve understanding of real-world medication-taking behaviors retrospective cohort analysis was conducted with Texas Medicaid medical and prescription claims for patients who were aged 18–63 years, continuously enrolled 1-year pre- and post-index, diagnosed with DME, and treated with anti-VEGF or laser therapies. Treatment patterns included treatment frequency and switching between anti-VEGF and laser therapies. Logistic regression and multinomial analysis were used to determine factors associated with switching and initiation of anti-VEGF therapy while controlling for demographic and clinical characteristics. Patients who switched from anti-VEGF injections to laser surgery were more likely to be Hispanic males who have fewer prescriptions and less likely to have no visual impairment. Multinomial regression results showed that anti-VEGF users were more likely to remain on the same therapy if they had more prescriptions. They concluded that anti-VEGF use is increasing; laser use is still more prevalent. Over 40% of patients who initiated anti-VEGF injections switched to laser surgery. Additional research should be conducted to determine factors associated with this high rate of switching.^[5]

Studies also proved that the anti-VEGF factors inhibit vascular endothelial growth factors.^[6-12]

This is not only used in the treatment of diabetic macular edema but used in series of conditions such as macular edema secondary to central retinal vein occlusion and branch retinal vein occlusion.^[13,14]

The anti-VEGF treatment has also been proved to be effective for long term.^[12]

We see an improvement in vision and a decrease in macular thickness post-anti-VEGF therapy. Figure 5 shows that the difference in macular thickness between pre- and post-anti-VEGF therapy increases with an increase in the initial macular thickness.

CONCLUSION

The current study shows that there is an improvement in the vision with anti-VEGF treatment. We also found that there is a decrease in macular thickness with treatment. It has been noted that higher macular edema more efficient the anti-VEGF therapy is. Hence, we can conclude that the anti-VEGF therapy is efficient in the treatment of diabetic retinopathy.

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