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EFFECTIVENESS OF AFLIBERCEPT IN TREATING BEVACIZUMAB RESISTANT MACULAR EDEMA

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Author
Hussain Khudair Yassin
Al - Qurnah General Hospital

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Email: dralmusafer@icloud.com

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Abstract

Background: Macular edema is a significant cause of visual impairment, often associated with conditions such as diabetes mellitus, retinal vein occlusion, and wet age-related macular degeneration (AMD). Anti-VEGF therapies like bevacizumab have been widely used to manage macular edema; however, some patients may show resistance to this treatment, necessitating alternative therapeutic options. Aflibercept, another anti-VEGF agent, has emerged as a potential alternative for patients unresponsive to bevacizumab.

Aim: This study aims to evaluate the efficacy of aflibercept in treating resistant macular edema following repeated intravitreal injections of bevacizumab.

Patients and Method: We conducted a prospective study involving patients with macular edema secondary to diabetes mellitus, retinal vein occlusion, or wet AMD. All participants had either a partial or no response to bevacizumab, indicated by minimal improvement in central subfield thickness on SD-OCT images or fewer than two lines of improvement in best corrected visual acuity (BCVA) prior to switching to intravitreal aflibercept.

Results: A total of 40 patients were included in the study, with no restrictions based on age, sex, or diabetic control. All participants exhibited macular edema resistant to prior bevacizumab injections, both anatomically and clinically. Following the switch to intravitreal aflibercept, a majority of patients demonstrated a favorable response, with improvements observed after both initial and subsequent injections.

Conclusion: Aflibercept appears to provide significant functional and anatomical improvement in cases of macular edema that do not respond to frequent bevacizumab injections, indicating its potential as a valuable treatment option for this patient population. Further studies may be warranted to confirm these findings and establish long-term efficacy.

Keywords: Diabetic retinopathy, aflibercept , bevacizumab.

Introductio

Purpose of the study to evaluate the effectiveness of aflibercept in the treatment of macular edema secondary to diabetes, retinal vein occlusion or wet AMD (CNV) that is resistant to frequent intravitreal injections of bevacizumab.

Macular edema is regarded as a major cause of blindness in developed & developing countries.[1]

Three main causes are[2]

Diabetic maculopathy.

Retinal vein occlusion.

Wet age related maculopathy.

The common mechanism is leakage of fluid from a neovascularization or microvasculature of the retina.[3]

VEGF (vascular endothelial growth factor) is the cornerstone for vascular leakage and neovascular proliferation, especially in wet AMD, although other factors may contribute to the pathogenesis, like cytokines, interleukins, and placental growth factor (PIGF), as well as other proangiogenic factors.[4]

They believe that these factors act by affecting the tight junctions of endothelial capillary cells or the pericytes, together with enhanced proliferation of abnormal neovessels. [5]

VEGF (Vascular Endothelial Growth Factors):

They are a group of glycoproteins produced by different types of cells like vascular endothelium and retinal pigmented epithelium.

It is produced in response to hypoxia and is mediated through gene expression (hypoxia-inducible factor-1), which stimulates the production of many factors like erythropoietin and angiogenic factors. These cause defective tight junctions of capillary endothelium and increased permeability, also acting directly to enhance endothelial precursors and angiogenesis.[6]

Anti-VEGF:

Bevacizumab:

Is a humanized monoclonal antibody, a non-specific anti-VEGF agent with two binding sites per molecule, preventing all VEGF-A isoforms in the vitreous from binding to endothelial cell receptors.[7]

Aflibercept:

It is a fusion protein with an IgG skeleton fused to the VEGF receptor sequence. It has a greater affinity for binding to VEGF-A than its natural receptors, preventing subsequent binding and activation.

It has a unique binding action to both sides of

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the VEGF dimer (VEGF trap). It is also the only medication that binds to PlGF2 (placental growth factor).[8]

In most cases of macular edema and neovascularization, bevacizumab is sufficient to reduce them and restore vision because it blocks most of the VEGF released by hypoxic cells into the vitreous. A non-responding case is defined as either a decline or no change in visual acuity or macular thickness on the SD-OCT scan. Meanwhile, a partial responding case is referred to as showing improvement in BCVA but less than 5 letters or less than 20% reduction in the central subfield thickness in SD-OCT macula. This is due to either pathways like cytokines, interleukins, or other VEGF factors, e.g., VEGF-B, PlGF, or tachyphylaxis. Therefore, we either reduce the interval between the doses or switch to another anti-VEGF or change the mode of therapy.

So switching to aflibercept is a good chance in all three types of macular edema after 5 doses of bevacizumab, 4 weeks apart

Patients and Methods

his prospective study was conducted at Basrah Teaching Hospital from June 2021 to January 2024, in which the first year was conducted for collecting patients who began to behave as non-responders or partial responders to intravitreal bevacizumab clinically by assessing BCVA or anatomically by SD-OCT macular thickness evaluation.

Patients were collected along the first and second years based on the following criteria:

1. No disciform scarring in CNV.
2. No epiretinal membrane or obvious ischemia in diabetic maculopathy.
3. No ischemia or atrophic changes in retinal vein occlusion.
4. Fair control of blood sugar in diabetes.

Patients' age ranged from 45 to 65 years, with no sex predilection.

The recruited sample consisted of 40 patients, with 10 of them having both eyes involved. All underwent baseline BCVA and SD-OCT macular examination every 4 weeks, 1 week before their next dose.

Intravitreal aflibercept was given in the operating room by a 30-gauge needle with topical anesthesia and sterilization by 5% povidone iodine with moxifloxacin eye drops postoperatively.

Patients were seen 3 days after to exclude infection and check IOP, and 3 weeks later to

assess BCVA and SD-OCT macular thickness.

Any improvement in OCT reading of more than 20% or restoration of 2 lines on the visual chart is regarded as significant response, otherwise it is still regarded as failure to treatment.

Follow-up of the patients at least for 5 months before declaring them as a resistant case.

Some of responder patients may recur after weaning, so we use Pro Re Nata regime for variable period.

Discharge the patient from follow-up after 3 months symptoms free without injection.

Discharge the patient from follow-up after 3 months of being symptoms free without injection.

Results:

Data collection was done every 4 weeks before the next injection in the form of BCVA and SD-OCT of the macula. Follow-up continued for about 1 year for most of the patients, except for those that had no response.

A total of 50 eyes were included in this study: 5 eyes had wet AMD, 10 eyes had retinal vein occlusion, and 35 eyes had diabetic macular edema.

In general, most of the patients had a good response to aflibercept after switching, even from the first injection, as measured by VA chart before anatomical improvement observed through OCT exam.

Further improvement was seen after the third injection, especially in diabetic patients, as shown in TableI

Table I: BCVA & OCT response after intravitreal aflibercept injection

Response	1st	p-value	2nd	p-value	3rd	p-value	4th	p-value	5th	p-value
BCVA	15	0.252	25	0.210	35	0.000	37	0.000	40	0.000
OCT	5	0.126	10	0.210	30	0.126	40	0.000	48	0.000

Most of the patients with CNV showed OCT changes but with visual deterioration because of macular scarring, except for 1 patient (as shown in Table II). For that reason, early switching to aflibercept in cases of wet AMD may be crucial.

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Table II: BCVA & OCT response in wet AMD patients receiving intravitreal aflibercept.

Response	1st	p-value	2nd	p-value	3rd	p-value	Follow up
BCVA	1	0.200	1	0.200	1	0.200	PRN
OCT	4	0.200	5	0.000	5	0.000	PRN

Patients with retinal vein occlusion showed a very good response to aflibercept. Nine patients had one eye involvement, and one patient had both eyes involved. Some of them showed early improvement in BCVA; the other 2 patients showed only OCT improvement (as shown in Table III), which was due to a prolonged period of disease with photoreceptor layer disintegration.

Table III: BCVA & OCT response in RVO patients receiving intravitreal aflibercept.

Response	1st	p-value	2nd	p-value	3rd	p-value	4th	p-value
BCVA	4	0.267	8	0.178	8	0.178	8	0.178
OCT	2	0.178	7	0.233	10	0.000	10	0.000

Discussion

These results are consistent with Ibrahim et al., which found that CRT decreased significantly after the third injection, with a p value of <0.001. The BCVA began to improve significantly following the first injection and continued to improve with further injections, with a p value of <0.03 at the third injection follow-up. [9]

Most of the patients with CNV showed OCT changes but experienced visual deterioration due to macular scarring, except for one patient (as shown in Table II). For this reason, early switching to aflibercept in cases of wet AMD may be crucial. **This finding aligns with ** Kimberly Spooner et al., who reported only mild improvement in BCVA, with a p value of 0.17 at 6 months. [10] In contrast, OCT CRT was significantly improved, with a p value of <0.001 at 6 months. Frederic Queguiner also demonstrated consistent results, showing no

significant improvement in BCVA, with a p value of 0.57. [11]

Patients with retinal vein occlusion disease showed a very good response to aflibercept; nine patients had one eye's involvement, while one patient had both eyes involved. The significant change in CRT was also consistent with the findings from Kimberly Spooner MMedHum et al., who found that aflibercept significantly reduced CRT, with a p value of <0.001.[12] Regarding BCVA, the results obtained by Kimberly Spooner MMedHum were inconsistent, as the study found a significant improvement in BCVA, with a p value of <0.001, potentially due to photoreceptor disintegration that had already occurred in most of the patients included in our study. This indicates that aflibercept provides good anatomical restoration but should be used as early as possible if there is no response to bevacizumab to prevent further photoreceptor disintegration.

Diabetic macular edema patients showed a good response but very slowly and even needed more than 5 injections to demonstrate a remarkable response. This may be due to other factors, such as associated ischemia, fine macular membrane, or other causative factors like inflammatory cytokines and interleukins. Therefore, switching from bevacizumab requires precise assessment and may benefit from the use of other modalities of treatment, such as focal laser therapy as adjunctive treatment.

Another point is that aflibercept has some effect on reducing hypoxia by preventing other VEGF factors such as VEGF-B and PlGF from contributing to abnormal angiogenesis. Its high affinity for VEGF receptors, along with its ability to consume most of the vitreous VEGF, makes it very effective in overcoming obstacles to macular healing. This contrasts with other agents, such as bevacizumab and ranibizumab, which act only on VEGF in the vitreous gel, thus reducing their effectiveness on vascular endothelial receptors in the healthy retina.

Aflibercept forms a large molecule by binding to two receptor sites, creating a complex terminal VEGF trap that is an inert compound. It also remains in the vitreous for a longer duration, providing a more persistent therapeutic response.

Conclusion

- Aflibercept seems to be a very effective agent in treating all kinds of macular edema.
- Early switching (after the first bevacizumab injection) may be crucial in wet AMD.
- It is regarded as a good

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alternative option for resistant cases to bevacizumab.

Recommendation

• Because of the medication cost, it should be used wisely for macular edema patients that show resistance to bevacizumab.

• Its ziv-aflibercept analogue, which is FDA approved for colorectal tumors, can be used as an alternative to it, as it is much less costly and has the same mechanism and effect.

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The author believes that the manuscript represents honest work and certifies that the article is original, is not under consideration by any other journal, and has not been previously published.
Availability of Data and Material: The author is prompt to supply datasets generated during and/or analyzed during the current study on wise request.

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