Research Article
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Three-month outcome of ZIV-AFLIBERCEPT for diabetic macular edema

Abstract

Purpose: Is to show the 3-month efficacy and safety of treatment diabetic macular edema treated with intravitreal ziv-aflibercept as studies have shown that Ziv-aflibercept does not cause retinal pigment epithelial toxicity and to study it cost effectiveness.

Methods: Ten eyes in eight patients diagnosed with central diabetic macular edema were enrolled for three consecutive intravitreal injection of ziv-aflibercept 1.25 mg every 4 weeks, a complete exam including BCVA and CRT at baseline and 12 weeks with evaluation of ocular and systemic complications.

Results: Improvement of best corrected visual acuity was clinically significant from baseline LogMAR 0.77 and 0.35 at 12 weeks and statistically significant (P<0.05) along with reduction of central retinal thickness from 562,4 µm and 317.7 µm at 12 weeks follow up (P<0.05) with no signs of ocular nor systemic complications.

Conclusion: Ziv aflibercept is a safe and effective in diabetic macular edema treatment for 12 weeks follow up with cost effectiveness especially in countries where aflibercept is not available.

Keywords: dme, anti vegf, vegf trap, diabetes, diabetic retinopathy, zaltrap, ziv aflibercept

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Abbreviations: DME, diabetic macular edema; VEGF, vascular endothelial growth factor; FDA, food and drug administration

Introduction

Diabetic macular edema (DME) is a primary cause of early onset of visual acuity reduction in patients diagnosed with diabetes mellitus and in term it will lead to a reduction in vision related quality of life in a working age group.[1] One of the main pathological factors of DME is up regulation of VEGF (Vascular endothelial growth factor) which in turn will lead to increased vascular permeability[2] and fluid accumulation in the macula. DME can be treated with focal/grid laser photocoagulation, intravitreal Anti-VEGF pharmacotherapy, or steroids. Anti-VEGF has become the first line therapy in central involved macular edema, many studies have shown the safety and efficacy of anti-VEGF treatment, there are two FDA approved agents for DME treatment which are ranibizumab (Lucentis, Genentech, South San Francisco, CA) 0.3 mg and aflibercept (Eylea, Regeneron, Tarrytown, NY) 2.0 mg where bevacizumab (Avastin, Genentech) 1.25 mg is used off label, both bevacizumab and ranibizumab has the similar mechanism of action by preventing VEGF-A isoforms from binding to VEGF receptors in endothelial cells where aflibercept is a recombinant fusion protein which works as a trap to VEGF itself and inhibits VEGF iso forms of VEGF-A, VEGF-B and PIGF.

The Diabetic Retinopathy Clinical Research Network has studied head to head the efficacy of three agents and concluded that aflibercept is more effective in cases of worse baseline visual acuity and no deference in efficacy of all agents in cases of mild loss of visual acuity.[3] Both ranibizumab and aflibercept are expensive drugs and cause a cost burden to the patient and healthcare system and therefore many ophthalmologists prefer to treat with bevacizumab as a first line. Ziv-aflibercept (Zaltrap, Sanofi-Aventis US, LLC, Bridgewater, New Jersey, USA and Regeneron Pharmaceuticals, Inc, Tarrytown, New York, USA) has the identical recombinant fusion protein of Eylea with a different buffer that results in a higher osmolar solution (1000 mOsm/kg) and has previously gained Food and Drug Administration (FDA) approval for metastatic colorectal cancer with cheaper affordable price for 550 USD per vial and make up to 40 doses where single dose of Eylea is 1900$ and Lucentis is 1200$.

Because of the high osmolarity there is a risk of retinal damage and detachment but Malik et al.,[4] has studied RPE toxicity all four agents *in vitro* and concluded that, neither aflibercept nor ranibizumab produced evidence of mitochondrial toxicity or cell death but, Ziv-aflibercept and bevacizumab showed mild mitochondrial toxicity at clinically relevant doses whereas Mansour et al.[5] Suggested a final osmolarity of 312 mOsm/kg after a single injection of Ziv aflibercept 1.25 mg in 0.05 mL in a 4-mL vitreous and concluded that Ziv-aflibercept improves visual acuity without ocular toxicity.[6]

Methods

Study design

This is a single center and open label single arm interventional study that adhered to the declaration of Helsinki the study was registered at clinical trials.gov (NCT02772497), the research received approval

by Al Arabi Hospital review board (FEB/2016), signed consent was obtained by patients after explaining the possible complications.

Participants

i. The inclusion criteria are the following:

ii. Patients with central diabetic macular edema

iii. Best corrected visual acuity is 20/25 or less

iv. Central macular thickness more than 250 microns

v. Patients who are able to come for all follow-up

The exclusion criteria:

1) Significant renal disease, defined as a history of chronic renal failure requiring dialysis or kidney transplant.

2) Myocardial infarction, other acute cardiac event requiring hospitalization, stroke, transient ischemic attack, or treatment for acute congestive heart failure within 4 months prior to randomization

3) For women of child-bearing potential: pregnant or lactating or intending to become pregnant within the next 3 years.

4) Macular edema is present that is considered to be related to ocular surgery such as cataract extraction

5) Substantial cataract that, in the opinion of the investigator, is likely to be decreasing visual acuity by 3 lines or more

6) History of major ocular surgery (including vitrectomy, scleral buckle, any intraocular surgery, etc.) within prior 4 months or anticipated within the next 6 months following randomization.

7) Exam evidence of severe external ocular infection, including conjunctivitis, chalazion, or substantial blepharitis

Intervention

Ziv aflibercept comes in a single used vial 100 mg/4ml or 200mg/8ml, we injected 0,05 ml/1.25 mg of Ziv aflibercept using 1 ml syringes with Luer-Lok tip, clear polycarbonate barrel after withdrawal from vial under sterile hood using filter needle after storing it in the refrigerator in 4 degrees celsius. All 10 eyes (8 patients) received intravitreal Ziv aflibercept injections under sterile conditions every 4 weeks for three consecutive injections, injection site was prepared by disinfecting the skin using povidone iodine 7% and the conjunctiva using povidone iodine 4% after installing topical anesthesia, the injection is carried out after placing sterile drape and lid speculum isolating eye lashes in the superior temporal quadrant, injection site was measured with calipers 4 mm from the limbus in phakic patients and 3.5 mm in pseudophakic patients, 30 gauge half inch needle is used to inject 0,05 ml/1.25 mg of Ziv-aflibercept (ZALTRAP) then cotton tip applicator is placed over the injection site to prevent reflux of fluid, topical and systemic antibiotics were used pre and post injection where the standard dose for aflibercept (Eylea) is 2.0 mg.

Follow up/ Outcome measures

All patients had BCVA (best corrected visual acuity) at baseline, 4 weeks, 8 weeks, 12 weeks using snellen chart then converted to LogMAR to monitor efficacy where SD-OCT (OTI:OCT/SLO HEIDELBERG ENGINEERING) was obtained at baseline and week 12 measuring central macular thickening to evaluate structural outcomes. Cataract status was evaluated at baseline and week 12 where intraocular pressure was monitored at base line, 4 weeks, 8 weeks, and 12 weeks. Safety parameters include the presence of ocular and non-ocular side effects such as intraocular inflammation, toxicity or retinal detachment along with systemic events.

Statistical methods

Clinical data obtained were analyzed using SPSS V.20.0 Paired student t Test Calculator for 2 Independent Means was used to analyze the difference between the mean 12 weeks outcome and mean baseline values for visual acuity and CMT.

Results

The study has enrolled 10 eyes in 8 patients 4 men and 4 women with mean age 57,9±9,2 years' Table 1 shows summarized baseline characteristics, all patients received intravitreal ziv-aflibercept every 4 weeks for three consecutive injections. According to (Table 2) there is no significant change in IOP follow up from baseline where best corrected visual acuity was converted from Snellen to LogMAR for statistical analysis, The LogMAR improved from 0.77±0.3 (20/120) at baseline to 0.35±0.2 (20/45) at 12 weeks follow up (P=0.03) Figure 1 shows visual acuity outcome from baseline at 12 weeks follow up; Where CRT was decreased from baseline of 562.4±167.14 µm to 317.7±115.83 µm to 12 weeks follow up (P=0.03), 56.40% is the overall decrease in CRT, (Figure 2) reduction of central retinal thickness from baseline to 12 weeks follow up (Figure 3).

Table 1 Characteristics of patients at presentation

Age,Years (Mean±SD) 57,9±9,2	
Sex, N (%)	
Men	4 (50)
Women	4 (50)
Eyes: N (%)	
Right	7 (87.5)
Left	3 (12.5)
Race: N (%)	
Arab	5 (62.5)
Caucasian	3 (37.5)
Lens: N (%)	
Phakic	7 (87.5)
Pseudophakic	3 (12.5)
Other Systemic conditions, N (%)	
Hypertension	8 (100.0)
Cardiovascular	3 (37.5)

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Table 2 Mean changes of IOP, BCVA in LogMAR units, and CRT from baseline and after three consecutive injections of ziv-aflibercept

	Baseline	Change	P
Intraocular Pressure mmHg	15.8±2.0	-1.1±2.0	0.12
BCVA, LogMAR Units	0.77±0.3 (20/120)	-0.42±0.2 (20/45)	0.03
Central Retinal Thickness µm	562.4±167.14	-244.7±115.83	0.03

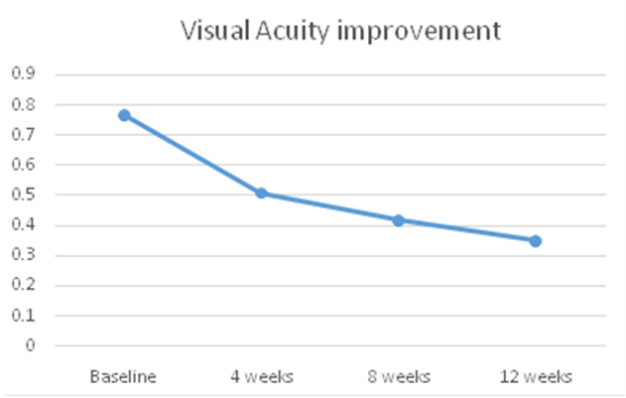

Figure 1 95% Confidence interval- BCVA, LogMar units according to time assessment.

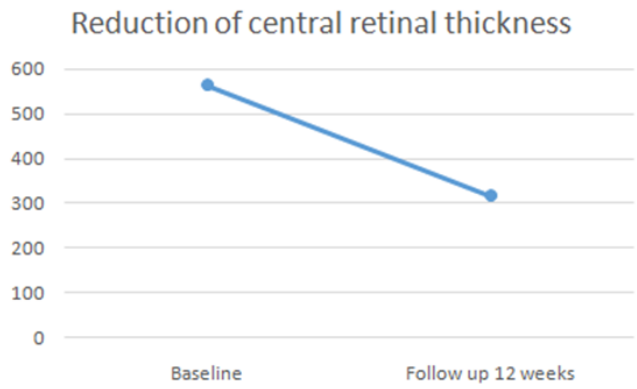

Figure 2 95% Confidence interval-CRT µm according to time assessment.

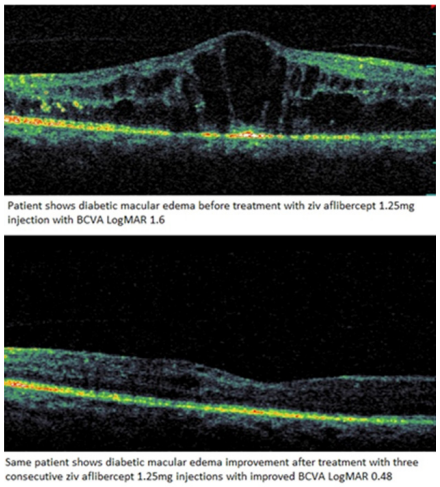

Figure 3 Shows OCT of a patient with DME before and after the treatment with Ziv aflibercept 1.25.

According to Table 1 eight patients were analyzed with the mean age of patients is 57,9±9,2 of whom 4 are Men and 4 are Women.

Changes of mean BCVA (P<0.05) and CRT (P<0.05) after the treatment where reduction of 0.42 in BCVA and 244.7 in CRT are noticed in Table 2, Figures 1&2.

However, one of the eyes that have been enrolled in this study presented with diabetic macular edema and epiretinal membrane has shown neither clinical significant visual improvement nor reduction of central retinal thickness. There was no evidence of intraocular inflammation nor toxicity or cataract progression neither systemic complication due to intravitreal injection of Ziv-Aflibercept.

Discussion

This single arm study has shown that intravitreal injection of Ziv aflibercept for DME as a monotherapy can improve visual acuity and reduce central retinal thickness within 12 weeks with no sign of retinal or ocular toxicity. Multiple studies have shown the efficacy and safety of anti-VEGF for central DME but only Ranibizumab and Aflibercept have gained FDA approval however studies such as Protocol T by DRCR.net[4] have shown that Aflibercept and Ranibizumab have similar effect in good baseline BCVA where Aflibercept is more effective in cases of worse baseline BCVA. The main problems of aflibercept (Eylea) and Ranibizumab (Lucentis) are the availability in poor countries and price as single dose will cost about 1900$ where ziv-aflibercept has the same fusion protein but with different buffer hyper osmolar solution which cost only about 50$ for a single dose, but brought some concerns about it safety.

Studies were conducted addressing the safety issue *in vitro* and *in vivo* and showed that there is non-significant RPE toxicity in vitro by Malik et al.,[4] where Masnour et al.,[5] has shown the safety of intravitreal Ziv aflibercept in six patients and all patients didn't show any signs of retinal nor ocular toxicity or inflammation and suggested that the 0.05 ml Ziv aflibercept is intravitreally injected is diluted in 4 ml of vitreous i.e. it is diluted 80 times that's mean that the final osmolarity of 312 mOsm/kg after a single injection of Ziv aflibercept 1.25 mg.[5] However, Gabriel et al.,[6] has demonstrated that there is neither retinal nor ERG changes after administrating six consecutive injections of Ziv aflibercept with improvement of vision in cases of diabetic macular edema.

The weakness of this study is the following:

1) The short time follow up
2) The small number of eyes that have been tested with Ziv aflibercept
3) The unknown toxicity of the long term delivery of hyper-osmolar solutions

Conclusion

This study has shown the safety and effectiveness of Ziv aflibercept for diabetic macular edema treatment for 12 weeks follow up and Ziv aflibercept is a cost effective option specially in countries where aflibercept (Eylea) is not available or can't be purchased due to it high price tag, as Protocol T shown that Eylea is more effective than Avasin in cases of DME with baseline BCVA less than 20/50 in poor countries ZALRAP may be an option for DME treatment with poor BCVA at baseline. However, a long term studies are required to evaluate the long term safety and effectiveness of Ziv aflibercept and

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to compare Ziv aflibercept with other VEGF blockage agents such as aflibercept, bevacizumab, and Ranibizumab.

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None.

Conflicts of interest

The author declares there are no conflicts of interest.

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