



## Original Research Article

# Diabetic macular edema shows a positive response to Aflibercept after previous unresponsive intravitreal Anti-VEGF and steroid therapy

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## ABSTRACT

**Purpose:** To evaluate the efficacy of intravitreal aflibercept in diabetic macular edema unresponsive to prior intravitreal anti VEGF and steroid therapy.

**Materials and Methods:** 10 eyes were prospectively investigated. Each eye was treated with intravitreal aflibercept in case of central macular edema unresponsive to prior anti VEGF therapy and intravitreal steroid. Patient were evaluated preoperatively with BCVA, OCT and fundus evaluation and IOP and followed up at 15 days, 6 weeks.

**Results:** Mean BCVA at presentation was 0.85 log MAR, and that improved to at 15 days and 45 days of intravitreal aflibercept, 0.65 log MAR and 0.52 log MAR. Mean central macular edema at presentation was 662.5  $\mu\text{m}$  (380-905 $\mu\text{m}$ ), after 15 days was 403 $\mu\text{m}$  (185-705 $\mu\text{m}$ ) and after 45 days was 261.25 $\mu\text{m}$  (120-507  $\mu\text{m}$ ).

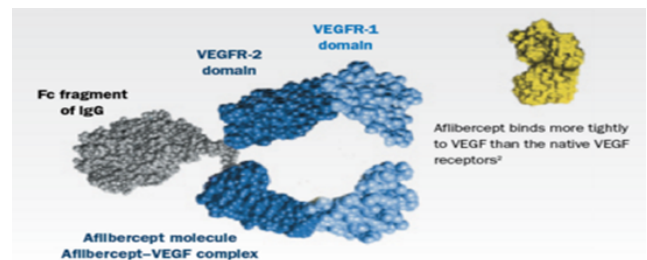
**Conclusion:** Intravitreal aflibercept can be an option to treat unresponsive diabetic central macular edema.

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## 1. Introduction

Diabetic macular edema (DME) is the common cause of visual impairment in patients with diabetic mellitus.<sup>1</sup> The common microvascular complication of diabetes is retinopathy; micro aneurysm, blood retinal barrier dysfunction, and capillary drop out are important contributors of DME.<sup>2</sup> Vascular endothelial growth factor (VEGF) is an important mediator of abnormal vascular permeability in DME.<sup>3,4</sup>

Currently anti VEGF (intravitreal aflibercept, ranibizumab, and off label use of bevacizumab) and corticosteroids<sup>5-9</sup> are used for treatment for DME. Aflibercept is a recombinant fusion protein consisting of portion of human VEGFR-1 and VEGFR-2 extracellular domains fused to the Fc portion of human IgG1- iso osmotic solution for intravitreal administration.



Aflibercept has a high affinity for all isoforms of VEGF-A as well as PlGF.<sup>10</sup> VEGF is typically present in dimeric form, with receptor binding sites located at each pole of the dimer. The molecular structure of aflibercept was designed for tight binding to both end of multiple VEGF subtypes.<sup>11</sup> The results is exponentially greater affinity for VEGF-A. One study showed that the binding affinity of aflibercept was 140 times that of ranibizumab.<sup>12</sup> In addition Eylea has the unique property of being able to bind to VEGF-B as well as PlGF.<sup>10</sup> Aflibercept have longer half-life compared with

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ranibizumab.<sup>13</sup>

In our study we included DME unresponsive to prior anti VEGF therapy and intravitreal steroid for treatment with single injection of intravitreal aflibercept to report the post injection effect.

## 2. Materials and Methods

Our study is prospective, consecutive, non-randomized case series. 10 eyes of 8 patients with DME unresponsive to prior anti VEGF therapy and intravitreal steroids were included. We excluded newly diagnosed central macular edema and Non central macular edema.

Informed consent was procured prior to recruitment in a consecutive manner. Each patient underwent detail eye examination include best corrected visual acuity (BCVA), anterior segment examination, intraocular pressure (IOP) and fundus examination. OCT (Spectral domain – primus Zeiss) scan was done each visit. Each patient received one intravitreal aflibercept injection. Central foveal thickness (CFT) was measured at presentation, at 15 days and 45 days after intravitreal aflibercept injection. Follow up done for 6 months, repeat intravitreal injection done for recurrent macular edema.

## 3. Results

A total of 10 eyes of 8 patients (6 unilateral, 2 bilateral) were reviewed. There were 7 males (87.5%) patient and 1 female (12.5%).

Mean BCVA at presentation was 0.85 log MAR, and that improved to after 15 days and 45 days of intravitreal aflibercept was 0.65 log MAR and 0.52 log MAR.

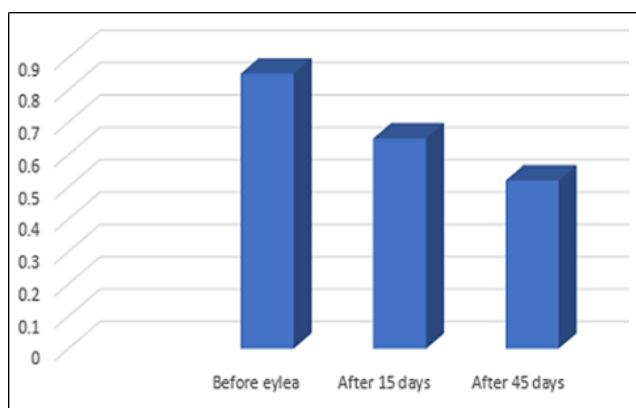


Fig. 1:

Mean Central macular edema at presentation was 662.5 µm (380-905µm), after 15 days was 403µm (185-705 µm) and after 45 days was 261.25µm (120-507µm).

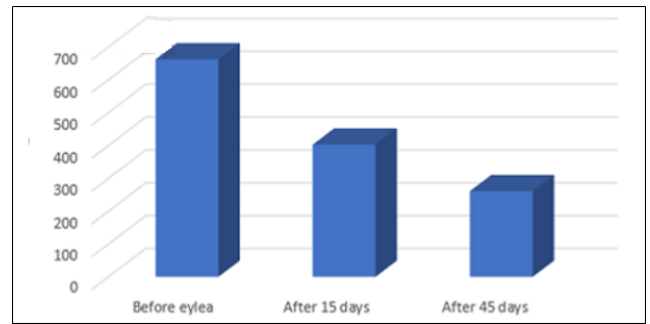


Fig. 2:

## 4. Case 1

A 38 years old male had non resolving ME in both eyes after 3 doses of intravitreal bevacizumab injections given at 6 weekly intervals. He received Aflibercept injection in both eyes. His vision in Right eye (RE) was 6/36 and left eye(LE) was 6/60 which improved to 6/6 in RE and 6/9 in LE at 45 days of intravitreal aflibercept injection.

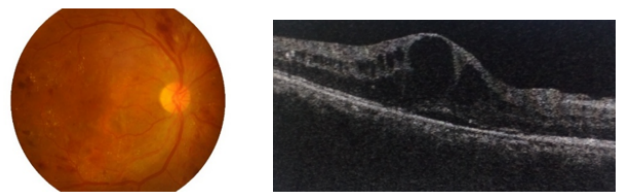


Fig. 3:

RE fundus shows multiple hard exudate with ME and superficial haemorrhages, OCT shows multiple cystoid changes with SRF fluid with good IS/OS junction and few hard exudate far away from fovea.

After 45 days

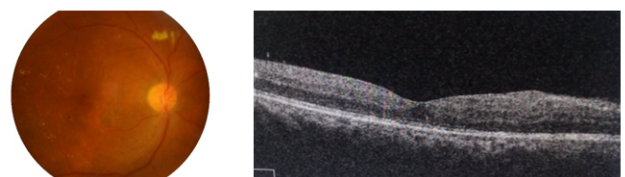


Fig. 4:

RE fundus shows multiple resolving hard exudate with reduced ME and few cotton wool spots, OCT shows normal foveal contour with few hyper reflex dots in foveal region with good IS/OS junction.

LE fundus shows multiple hard exudate with ME and superficial haemorrhage, OCT shows multiple cystoid changes with SRF fluid with good IS/OS junction and few hard exudate far away from fovea.

After 45 days

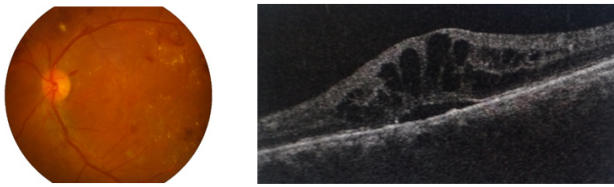


Fig. 5:

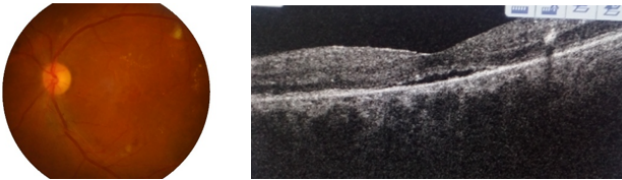


Fig. 6:

LE fundus shows multiple resolving hard exudate with reduced ME and few cotton wool spots, OCT shows mild SRF fluid with good IS/OS junction and few hard exudate far away from fovea with reduced ME.

### 5. Case 2

A male aged 55 years had non resolving ME in RE in spite of having received 3 doses of intravitreal bevacizumab, 5 dose of intravitreal Ranizumab and 1 dose of intravitreal Ozurdex over 2 years period. His vision in RE was 6/36 improved to 6/9 after 45 days of intravitreal Aflibercept injection. RE shows multiple hard exudate with ME, OCT shows central ME with few areas IS/OS junction disruption and few hyper reflex dots and ERM far away from fovea (Figure 7). After Aflibercept injection RE OCT picture shows normal fovea contour with few hyper reflex dots (Figure 7).

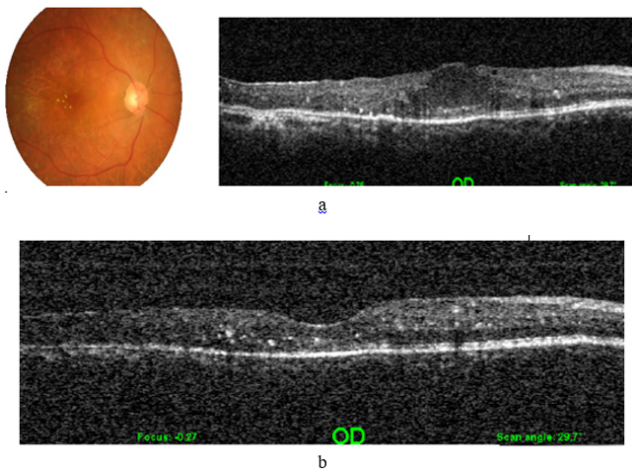


Fig. 7:

### 6. Case 3

A male 78 years old had non resolving ME in RE in spite of received 6 dose of intravitreal bevacizumab, 1 dose of ozurdex and focal laser over 18 months period. His vision in RE was 6/60 and improved to 6/24 after aflibercept injection. RE fundus shows few hard exudate with macular edema, OCT shows central cystoid macular edema with few hyper reflex dots (Figure 3a). After aflibercept injection RE OCT picture shows cystoid ME with mild disruption of IS/OS junction (Figure 8).

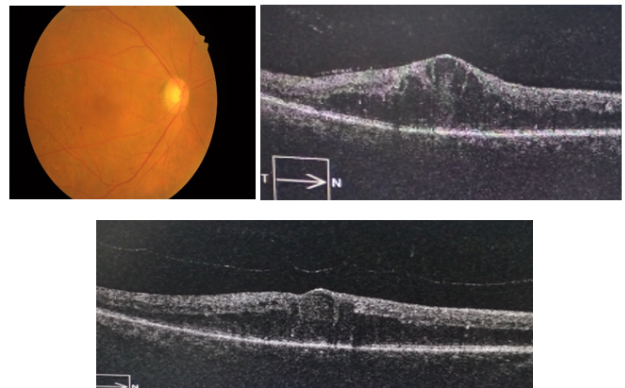


Fig. 8:

In our study shows out of 10 eyes, complete resolution of macular edema seen in 7 eyes (70%), significant resolution of macular edema seen in 1 case (10%) and mild resolution of macular edema in 2 case (20%).

### 7. Discussion

DME is the common cause of visual impairment in patients of retinopathy with diabetic mellitus. VEGF is an important mediator of abnormal vascular permeability in DME.<sup>3,4,14</sup> Aflibercept is the newer drug and it appears to have theoretical advantage of : (a) had greater affinity to VEGF-A<sup>10</sup> (b) it binds to growth factor PGF 1 and VEGF-B<sup>10</sup> and (c) the vitreous half-life is 7.3 days.<sup>13</sup>

Our definition of unresponsive is arbitrary but consistent with other studies; persistent or increasing sub or intraretinal fluid after 3 or more consecutive monthly injections.<sup>15,16</sup>

In our study we noticed significant reduction of macular edema with improvement in vision in majority of the patient after switch to intravitreal aflibercept injection. Patient who have long standing disease have more chance to develop receptor resistance to the anti VEGF and steroid drug. The reasons for a response to a newer drug after being refractory or unresponsive to a intravitreal injection may be many. Tachyphylaxis may be one. There is also a possibility of certain set of patients being responsive to one drug over the other. Receptors for VEGFs may vary from patient to patient. In our case series we noticed significant reduction of macular edema in 80% of eyes whereas 20% eyes had

only mild resolution. Mean BCVA improved from 0.85 log MAR to 0.52 log MAR at 6 weeks. Mean Central macular edema was reduced from 662.5  $\mu\text{m}$  to 261.25  $\mu\text{m}$  at 6 weeks. The reason for mild reduction in 20% of patients may be many and needs a larger study looking for the concentration of VEGF levels in the vitreous cavity and invitro studies of response to a particular molecule.

Filipe Mira et al<sup>17</sup> is retrospective review of DME unresponsive to previous anti VEGF switched to aflibercept with 3 months follow up showed Central macular edema reduced from 501.47  $\mu\text{m}$   $\pm$  150.51  $\mu\text{m}$  to 367.97  $\mu\text{m}$   $\pm$  124.61  $\mu\text{m}$  at 3 months and log MAR BCVA improved from 0.76  $\pm$  0.36 to 0.65  $\pm$  0.33 at 3 months comparably to our case series.

## 8. Conclusion

Management of unresponsive DME is challenging for retina specialist. We require treatment armamentarium to manage unresponsive DME apart from improving the systemic health. Aflibercept can be an option we can try for these patients. Aflibercept had a significant anatomical and functional improvement in DME patients in our study.

Timing of switching the therapeutic agents, choosing an ideal molecule and biomarkers to suggest the same is the need from future studies.

## 9. Source of Funding

None.

## 10. Conflict of Interest

None.

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