

# Aflibercept Versus Ranibizumab as A Second Line Therapy After Bevacizumab For Diabetic Macular Edema

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ORIGINAL RESEARCH

## Aflibercept versus Ranibizumab as a Second Line Therapy After Bevacizumab for Diabetic Macular Edema

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**Purpose:** To compare the visual and anatomic outcomes of aflibercept versus ranibizumab as a second line treatment for persistent diabetic macular edema (DME) after initial bevacizumab injections.

**Methods:** In this retrospective cohort study, patients with center-involved DME of  $\geq 300$   $\mu$ m thickness after bevacizumab intravitreal injections in 2015–2019 were included. Those treated with ranibizumab (R) and aflibercept (A) were grouped as group R and group A, respectively. The change in central macular thickness (CMT) measured by optical coherence tomography (OCT) and the best corrected distance visual acuity (BCVA) before and after three-monthly anti-VEGF injections (anti-VEGF) in group R and group A were compared and reviewed.

**Results:** There were 80 eyes of 75 patients in group R and 80 eyes of 72 patients in group A. The initial bevacizumab injections in group R and group A varied significantly ( $p = 0.01$ ). The median change of the CMT after the three injections was not significantly different in group R (80  $\mu$ m) and group A (81.5  $\mu$ m) ( $p = 0.7$ ). The improvement of BCVA in group R and group A was not significant ( $p = 0.5$ ). Dry macula was noted in 1 vs 14 eyes in group R vs group A.

**Conclusion:** After treating refractory DME with initial bevacizumab injections, 3 injections of either aflibercept or ranibizumab had similar anatomic and functional outcomes. Aflibercept achieved dry macula in more eyes with refractory DME compared to ranibizumab.

**Keywords:** aflibercept, bevacizumab, persistent DME, ranibizumab, VEGF switch, vascular endothelial growth factor



## Introduction

- Diabetic retinopathy (DR) is one of the seven leading causes of global blindness.
- Intra-vitreous (IV) injections of anti-VEGF agents is the current mode of DME management. However refractory DME after IV anti-VEGF is a challenge to the retina specialists.
- Outcome comparison of Aflibercept and Ranibizumab as a second line of treatment for refractory DME after initial Bevacizumab injections have not been studied.



# Purpose

To compare the visual and anatomic outcomes of aflibercept versus ranibizumab as a second line treatment for persistent diabetic macular edema (DME) after initial bevacizumab injections.



## Methods

- Retrospective cohort study
- Patients with refractory DME after initial therapy with Bevacizumab injections were treated with either Ranibizumab injection (0.5 mg/0.05ml) or Aflibercept injection (2 mg/0.05ml) between **March 2015 - July 2019** at a tertiary eye hospital in central Saudi Arabia.
- 80 eyes of 75 patients in Ranibizumab group (R), and 80 eyes of 72 patients in Aflibercept group (A).



## Methods

- Evaluation after initial bevacizumab doses was considered as the baseline for the VA and CMT measurement which was 4 weeks  $\pm 1$  from the last dose of Bevacizumab.
- The primary outcome was the change in CMT from baseline compared to 4 weeks ( $\pm 1$  week) measurement after completion of the three Aflibercept or Ranibizumab injections improvement.
- The secondary outcome was improvement of 2 lines in BCVA at last follow up compared to that at baseline.

### **Inclusion criteria:**

- Patients were having center-involved DME
- Central subfield thickness (CST) more than 300 microns on spectral-domain optical coherence tomography (SD-OCT)
- Initial Bevacizumab injections of three to six doses
- A shift to either Ranibizumab injection or Aflibercept injection

### **Exclusion criteria:**

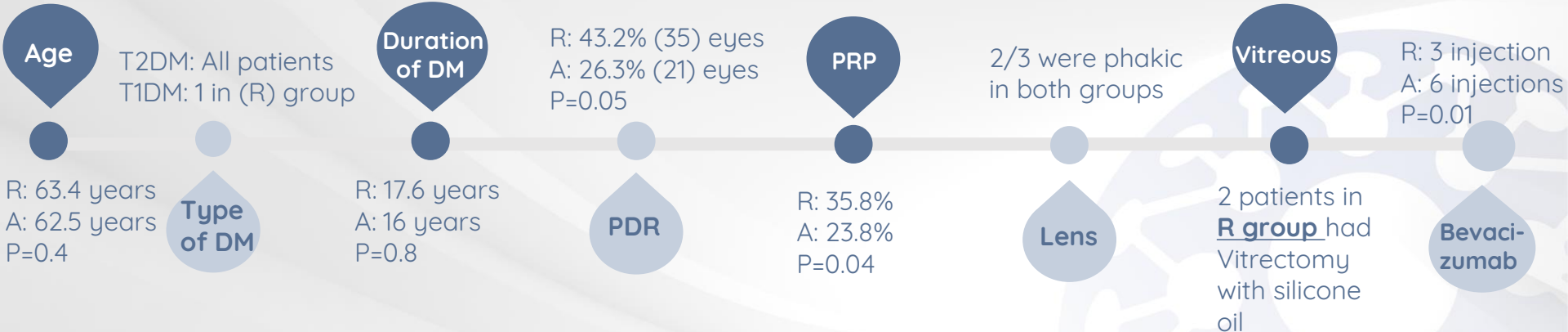
- Pregnant women
- Uveitis
- Tractional type of DME



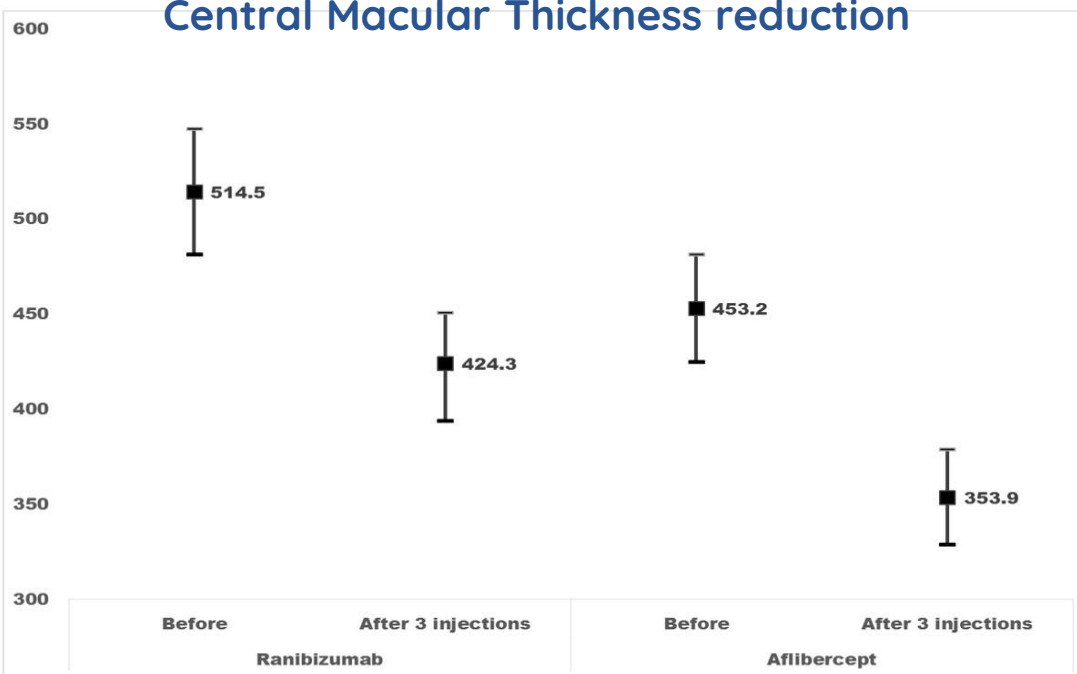
# RESULTS







### Central Macular Thickness reduction



CMT at baseline (after initial Bevacizumab injections) was significantly higher in Ranibizumab group comparing to Aflibercept group,  $514.5 \pm 148.6 \mu$  versus  $453 \pm 157 \mu$  respectively, (**P = 0.006**).

There was significant reduction in the CMT after both types of injections compared to baseline (**p value <0.001**)

 Results

### Central Macular Thickness reduction

	Ranibizumab treatment regimen		Aflibercept treatment regimen		Mean difference (95% CI)  P value
	Mean ( $\mu$ )	SDV ( $\mu$ )	Mean ( $\mu$ )	SDV ( $\mu$ )	
<b>Before treatment</b>	514.5	148.6	453.2	127.2	61.3 (18.2 ; 104.3)  P =0.006
<b>After treatment regimen</b>	424.3	129.1	353.9	112.5	70.4 (32.8 ; 108.8) P  <0.001
<b>Matched pair analysis:</b>					
<b>Mean difference</b>		90.6 (62.5 ; 117.8)		99.3 (74.7 ; 123.9)	



## Results

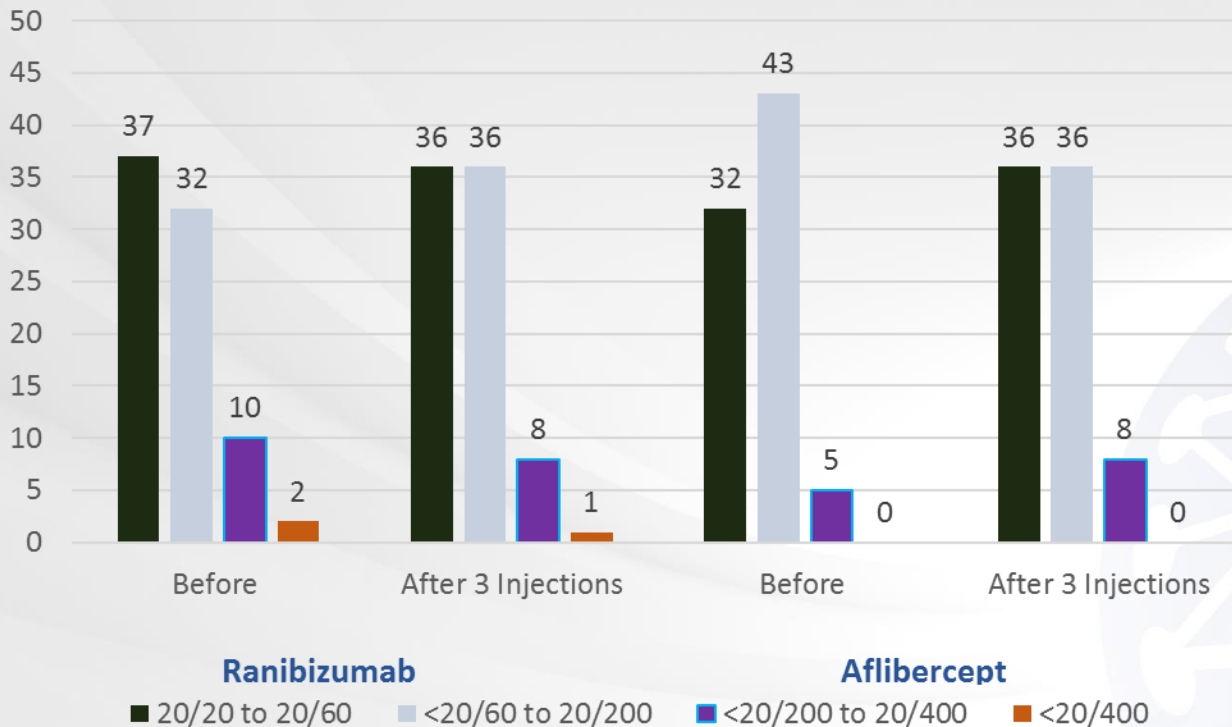
The mean difference in the CMT was not statistically different between Ranibizumab vs Aflibercept injections (90 microns vs 99 microns respectively) (**P = 0.7**).

The number of previous bevacizumab injections ( $p = 0.13$ ) and the status of diabetic retinopathy ( $p = 0.3$ ) were not significantly influencing the correlation of CMT reduction to the type of intervention as second line of treatment.



# Results

## Visual Acuity



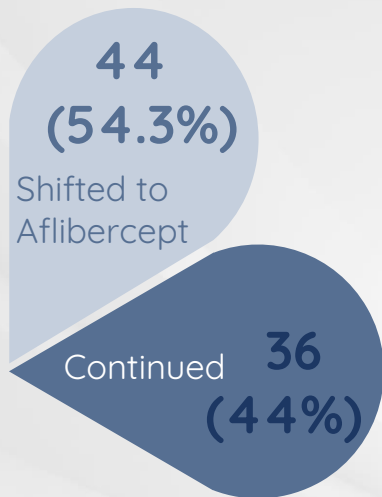
There was no significant difference between both groups after therapy.  
**p value = 0.9**



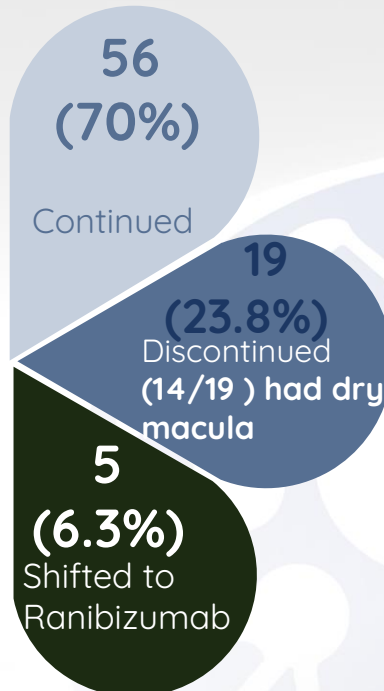
# Results

After 3 injections of the second line therapy

**Ranibizumab**  
80 eyes



**Aflibercept**  
80 eyes





## Results

Continuation of aflibercept after completed second line treatment was significantly more compared to ranibizumab, and the chance for shifting to another anti-VEGF were significantly more after ranibizumab treatment (**p <0.001**).



# DISCUSSION





## Discussion

- Three injections regimen of both anti-VEGF Ranibizumab and Aflibercept in eyes with refractory DME after treatment of intravitreal Bevacizumab had similar effect on the reduction of CMT and no significant difference in the visual gain.
- However, more eyes seem to achieve dry macula after Aflibercept than Ranibizumab treatment regimen.
- Reduction of macular thickness noted in our study did not match with vision improvement following treatment of refractory DME.



## Discussion

- To the best of our knowledge, our study is unique in comparing two commonly used anti-VEGF in refractory DME after 3 to 6 bevacizumab injection regimen.
- Demircan et al. studied the effect of continuing on ranibizumab vs switching to aflibercept injection after initial three injections of ranibizumab. They noted better outcomes of aflibercept treatment regimen than ranibizumab treatment in the reduction in mean CMT.
- Of note is that CMT was lower in aflibercept group to start with; however, this was overcome by evaluating the reduction in the CMT compared to baseline rather than the final CMT in both groups.



## Discussion

The cases allotted in Ranibizumab and Aflibercept group in present study were influenced by the practice pattern in our institute where Bevacizumab used to be given for three injections before physicians can switch to Ranibizumab.

The median number of initial bevacizumab injections was 3 injections in Ranibizumab group compared to 6 injections in Aflibercept group (**P=0.01**).

Despite that in multivariate regression analysis the number of prior Bevacizumab injections did not influence the outcome i.e. reduction in CMT.

## Conclusion

- After completing the second line of 3 consecutive anti-VEGF injections, eyes that continued or switched to aflibercept were more than those continued with ranibizumab .
- Evidence from the present study is still inconclusive for recommending a shift from initial bevacizumab to aflibercept or ranibizumab.
- Studies like prospective cohort or randomized clinical trial would be better to confirm our study outcomes.

**Thank You**

