Original Article

Effect of Intravitreal Aflibercept on Wet Age-Related Macular Degeneration and Evaluation of Risk Factors on Patient's Response

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ABSTRACT

Purpose: To evaluate the effect of intravitreal Aflibercept injection on wet age-related macular degeneration (AMD) both functionally and anatomically after loading doses. The secondary aim is to evaluate the effect of risk factors including (gender, age, smoking, hypertension, and diabetes mellitus) on the patient's response.

Study Design: Interventional case series.

Place and Duration of Study: Al-Haitham Eyes Teaching Hospital in Baghdad, Iraq, from November 2021 to September 2022.

Methods: Fifty eyes of 47 patients with treatment naïve wet AMD were selected through convenient sampling. Data were collected for age, gender, smoking, and chronic disease. Clinical examination, best corrected visual acuity (BCVA),optical coherence tomography angiography, and spectral domain optical coherence tomography SD-OCT were performed at baseline and then at 16 weeks, after three one-monthly injections of Aflibercept 2 mg/0.05 ml intravitreally.

Results: Mean age was 68.23 ± 8.5 years. Mean difference in BCVA was 0.37 ± 0.03 (P= 0.000) and mean difference in central macular thickness was 105.72 ± 45.05 (P value < .0000) at 16 weeks.CNV was associated with intra-retinal fluid in 52% of cases, subretinal fluid in 72%, pigment epithelial detachment in 20%, intraretinal hemorrhage in 6% and subretinal hemorrhage in 4%. Studying associations between the responses of Aflibercept with the general features of the patients as age, gender, chronic diseases and smoking status, revealed no statistically significant difference.

Conclusion: This study demonstrates that aflibercept is effective for the treatment of patients with wet AMD both functionally and anatomically after the loading doses. The presence of intraretinal fluid at presentation had a negative effect on the vision.

Key Words: Aflibercept, VEGF, anti-VEGF, wet age-related macular degeneration (AMD), prospective study.

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INTRODUCTION

Age-related macular degeneration (AMD) is a degenerative illness that primarily affects macula. AMD mostly affects people over 50 years of age and has two types: dry and wet AMD.[1] The dry type of AMD slowly progresses over many years and can cause a mild to severe loss of vision, while the wet form develops quickly and will lead to blindness if left untreated.[2] Wet AMD is caused by the formation of

neo-vessels and leakage of these vessels which disrupts photoreceptor cell structure and degrades visual acuity. This choroidal neovascularization (CNV) is responsible for 90% of all occurrences of AMD-related blindness.[3]

Vascular Endothelial Growth Factor (VEGF) is an essential neovascularization mediator, it also enhances vessel permeability and is approximately 50,000 times more effective than histamine in causing vascular leakage.VEGF-A165 and VEGF-A121 are the most numerous isoforms of VEGF present in patients with wet AMD.[4]

AMD is known to impact about 10% of persons over the age of 65 years and more than 25% of people over the age of 75 years. AMD is a complex disease, with environmental and genetic factors influencing disease severity and progression. The environmental factors, which represent 40% of AMD risk, include age, cigarette smoking, hypertension, and consuming high-fat diet. Moreover, individuals with a first-degree family member with AMD are almost twice as likely to develop the disease as compared to individuals with no affected first-degree relative.[5]

Active neovascular AMD was characterized by the presence of CNV and its location, as well as subretinal or intraretinal fluid, tissue in these spaces, pigment epithelium detachment or ruptures, macular hemorrhages, and all can be evaluated by clinical examination and SD-OCT.[2] Recently, anti-VEGF therapy drugs have been proven efficient to inhibit CNV. The three most widely used anti VEGF are bevacizumab, ranibizumab and aflibercept. We planned this study to see the effect of Aflibercept in exudative AMD in terms of structure and function in our setup at Iraq.

METHODS

An interventional case series was conducted at Al–Haitham Eyes Teaching Hospital in Baghdad, Iraq from November 2021 to September 2022. Power analysis and sample size system PASS program was utilized to calculate sample size for research (with alpha error 50%, power at 80%). All patients newly diagnosed with wet AMD, through clinical evidence, optical coherence tomography angiography (OCTA), optical coherence tomography (OCT) and older than 50 years of age were included. Patients who were diagnosed with polypoidal choroidal vasculopathy or retinal angiomatous proliferation, diabetic retinopathy, retinal vein occlusion or CNV caused by diseases other than AMD, dry AMD, advanced AMD with macular scars, patients with post-injection complications that might affect vision (e.g. post-injection endophthalmitis, cataract, vitreous hemorrhage or retinal detachment) were excluded.

Written informed consent was taken by the patients to be enrolled into the treatment regimen. Pre-treatment baseline examination was done. Data were collected for age, gender, smoking, history of hypertension and Diabetes Mellitus. It was followed by assessment of best corrected visual acuity (BCVA) using Snellen chart which was converted to Log Mar chart for statistical analysis. Slit lamp ocular examination of the anterior and posterior segments was carried out with pupil dilation using Tropicamide eye drop 1% and 90 or 78 diopters condensing lens. Optical coherence tomography angiography (by Huvitz OCTA) was performed and spectral domain optical coherence tomography (SD-OCT Heidelberg) was used to calculate Central macular thickness (CMT), presence or absence of Intraretinal fluid (IRF), Subretinal fluid (SRF), Intra retinal hemorrhage (IRH), Subretinal hemorrhage (SRH) and Pigmented epithelium detachment (PED). All patients received three intravitreal Aflibercept injections at four weeks interval and at 16 weeks after the first injection. All the examinations were repeated to compare results with baseline.

Microsoft Excel 2019 and the Statistical Package for the Social Sciences (SPSS, Version 25) were used for data entry and analysis. Continuous variables were displayed as mean (Standard Deviation). The Chi-square test was used to compare categorical data. A paired t-test was used to compare averages of BCVA and CMT to baseline and post-loading doses. $P \leq 0.05$ was considered significant.

RESULTS

The study included 47 patients (50 eyes) with active wet AMD. Mean age of the sample population was 68.23 ± 8.5 years. All eyes completed three, one monthly injections of Aflibercept 2mg/0.05ml intravitreally. There were 44.6% (n = 21) females. There were 36.3% right eyes and 57.4% were left eyes. In 6.3% of the patients, both eyes were affected. (n = 3). Regarding chronic diseases; 28 (59.5%) were known cases of hypertension, 9 (19%) patients were diabetic and 14 (30%) were smokers who were all males.

Table 1: *Association between BCVA and age, chronic diseases and smoking status.*

Factors	BCVA				P value*
	Improved and Maintained(28)		Worsened (19)		
	Number	%	Number	%	
Age (in Years)					
≤ 65	8	50	8	50	0.337*
>65	20	64.5	11	35.5	
Gender					
Males	14	53.8	12	46.2	0.373*
Females	14	66.7	7	33.3	
Hypertension					
Yes	18	64.3	10	35.7	0.424*
No	10	52.6	9	47.4	
Diabetes Mellitus					
Yes	6	66.7	3	33.3	0.63*
No	22	57.9	16	42.1	
Smoking					
Yes	6	42.9	8	57.1	0.128*
No	22	66.7	11	33.3	

*The association was statistically not significant; χ^2 test, df=1, P>0.05

Mean difference in BCVA was 0.37 ± 0.03 (improving from 1.25 ± 0.79 at baseline to 0.88 ± 0.76 after injections) which was statistically significant (P = 0.000). Vision was improved in 19 (38%) eyes, remained same in 27 (54%) eyes and worsened in 4 (8%) eyes.

Mean difference in CMT was 105.72 ± 45.05 µm which significantly decreased from 374.5 ± 106.78 µm at baseline to 268.78 ± 61.73 µm after treatment (P value < .0000).

Table 2: *Association between BCVA and active choroidal neovascularization (CNV) lesions.*

Factors	BCVA				P value*
	Improved and Maintained(31)		Worsened(19)		
	No.	%	No.	%	
SRF					
Yes	21	58.3	15	41.7	0.392
No	10	71.4	4	28.6	
SRH					
Yes	0	0	2	100	0.065
No	31	64.6	17	35.4	
IRF					
Yes	20	76.9	6	23.1	0.024*
No	11	45.8	13	54.2	
IRH					
Yes	2	66.7	1	33.4	0.864
No	29	61.7	18	38.3	
PED					
Yes	5	50	5	50	0.382
No	26	65	14	35	

*The association was statistically significant; χ^2 test, df=1, P≤0.05

CNV was associated with IRF in 26 eyes (52%of cases), SRF in 36 eyes (72% of cases) and PED in 10 eyes (20% of cases), while IRH and SRH were found in 3 (6%) eyes and 2 (4%) eyes respectively. Some eyes had multiple signs.

Studying associations between the responses of Aflibercept with the general features of the patients as age, gender, chronic diseases and smoking status, revealed no statistically significant difference (Table 1).

Studying the associations between the response of BCVA of patients with retinal signs at presentations show there is only statistically significant association with IRF (χ^2 test, df = 1, P ≤ 0.05) as shown in (Table 2).

DISCUSSION

Our study found that intravitreal Aflibercept is useful in cases of wet AMD to prevent progression of central vision loss. It enhances visual acuity after the loading doses. Based on the current findings, the mean difference in BCVA before and after treatment was 0.37 ± 0.03at 16 weeks (P = 0.000). Our findings on the improvement in BCVA were comparable to and in agreement with improvement in visual acuity seen in clinical trials including eyes with treatment-naive neovascular AMD that received Aflibercept.[6,7] Therefore, improvement or maintained visual acuity in 92% was comparable to MARINA and ANCHOR studies, which showed that 94.6% and 96.4% of patients were saved from vision loss, respectively.[8,9]

It may be thought of as having an 'initiation phase' in which there is a fast gain in visual acuity in response to the first three treatments, followed by a stability phase in which visual acuity remains stable.

Regression of disease activity by considering CMT was assessed in our study as a further indicator of success of therapy. Mean CMT was significantly decreased from 374.5 ± 106.78 µm at baseline to 268.78 ± 61.73 µm (P value < .0000) at 16 weeks which was statistically significant. Similar results were seen in VIEW 1 and VIEW2 studies, which evaluated the safety and efficacy of Aflibercept therapy and showed that a majority of eyes had positive anatomical and functional outcome.[7] Similar results were seen in the study by Miyamoto et al.[10] Greatest decrease in macular thickness was achieved within the first three months.

It was observed in our study that the most common signs associated with neovascularization were presence of SRF in 72%, IRF in 52%, PED in20%, IRH and subretinal hemorrhage in 6% and 4% respectively. In another study, IRF was seen in 51%-53% of eyes, SRF in 66% – 75% of eyes and PED in 74% – 85% of cases.[11] While another trial revealed that 72% of patients had IRF, 85% had SRF, and 51% had PED.[12] We had similar results except that PED was lower which might be caused by the difference in ethnicity because most of the other studies were done in Caucasian population.

In our investigation, we found no correlation between age and visual outcome (P value 0.337), indicating that the association was statistically insignificant. These findings agreed with the majority of the studies which did not demonstrate an association between age and the effect of anti-VEGF on the response of neovascular AMD. However, two studies showed that younger patients responded better to anti-VEGF medication.[14,15] This association was most probably caused by many patients older than 70 years in these studies who might have more severe photoreceptor impairment.

There was no relation of gender with response to anti-VEGF therapy and the outcome was similar to previous studies.[16]

In our study, the percentage of smokers was 30% (14 of 47 patients), and we did not detect a relationship between smoking and visual outcome (p value 0.128). This was in agreement with Graw M et al, who observed no link between smoking and the functional and morphological outcomes of anti-VEGF after 12 months.[17] Others studies show that cigarette smoking raises the probability of getting AMD, with heavy smokers having an increasingly higher risk.[18] Furthermore, it has been found that smoking, even in the past is positively related with the development of neovascular AMD.[18]Our study did not show such relation which might be because most of the smoking patients in our study were not heavy smokers (less than 10 cigarettes per day). The methods by which cigarette smoking harms retina are not well understood although several hypotheses have been proposed.

In current study, systemic arterial hypertension was not significantly associated with post-treatment visual acuity response. Similar results were obtained by Zhao et al[19] and van Asten et al.[15] They found no connection between the presence of arterial hypertension and visual outcomes with intravitreal treatment in neovascular AMD patients. The absence of arterial hypertension, on the other hand, in study by Piermarocchi et al, was associated with much better visual improvements and a higher percentage of functional responders (69.57%) but, CMT reductions were same between patients with and without arterial hypertension.[20] It is believed that the presence of arterial hypertension prior to the administration of anti-VEGF medication decreases the probability of BCVA improvement. It is possible that these patients had worse BCVA before the development of macular neovascularization that would explain the poor functional improvement observed despite the relatively good anatomical response to anti-VEGF. As demonstrated by the previous research, arterial hypertension reduced choroidal flow and the nourishment of the retinal pigment Epithelium (RPE) and photoreceptors.[21]

We found no indication of a significant correlation between the functional and morphological outcomes of Aflibercept treatment and diabetes mellitus which was in agreement with Graw M et al.[17] They observed no link between the outcomes of anti VEFG and diabetes. In contrast, another study, done by van Asten et al, indicated an increased risk for non-responders in diabetic patients.[15]

In our study there was no relationship between the presence of SRF with decreased or increase visual acuity when compared to the absence of SRF after treatment (P value 0.392). Similarly, there was no association in the other studies.[7,22] In contrast, another study achieved better initial visual findings and

maintained them throughout the duration of the first, second and fifth years in the presence of SRF.[23] The relation between SRF and visual acuity is less clear. A systematic review on the role of fluid compartments showed that treatment strategies that allow the presence of stable SRF (but not IRF) may lead to better visual results in neovascular AMD.[24]

In our study, patients with IRF had significantly worse visual acuity than patients without IRF (P value = 0.024). Similarly, the presence of IRF has been linked to poorer vision both at beginning and during therapy in major clinical studies.[11,23,25] As a result, from previous studies it was suggested that patients with IRF at baseline should have aggressive treatment.

In our study, only 20% eyes showed PED. This proportion is lesser than that in other reports.[11,13] A post-hoc analysis in a study found that patients with PED at baseline who acquired IRF through follow-up had the lowest visual acuity gain of any anatomic parameter combination.[25] Based on these findings, therapy targeted at removing or lowering the size of a PED is presently not recommended. However, continued monitoring and management of any symptoms of retinal exudation, particularly IRF, is suggested, considering worse prognosis when IRF is combined with PED.

IRH and SRH were found in very few patients and the association with visual acuity was statistically not significant.

This study is an essential step towards developing a straightforward prediction strategy to assist in identifying AMD patients who are at a higher risk of not responding to Aflibercept treatment. However, small sample size and single center study are the limitations.

CONCLUSION

Aflibercept is effective treatment for wet AMD both functionally and anatomically. Presence of intraretinal fluid at presentation had negative effect on the response to treatment while all other factors showed insignificant effect on response to loading dose of Aflibercept in patient with wet AMD.

Ethical Clearance: Ethical Approval was obtained from the Scientific Research Ethics Committees at Department of Pharmacology/College of Medicine, University of Baghdad and Ibn-Al-Haitham Eyes Teaching Hospital for Ophthalmology/Ministry of Health, Iraq.

Conflict of Interest: Authors declared no conflict of interest.

Ethical Approval

The study was approved by the Institutional review board/Ethical review board **(305/2-2022).**

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Author's Designation and Contribution

Rasha Abdulelah Mustafa Alkazraji; MSc Student: *Concepts, Literature search, Manuscript preparation, Manuscript editing, Manuscript review.*

Samara M Ali; Assistant Professor: *Concepts, Statistical Analysis.*

Zaid Rajab Hussein; Vitreoretinal Consultant: *Concepts, Design, Literature Search, Statistical Analysis, Manuscript Preparation, Manuscript Editing, Manuscript Review.*