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Research Article

Intravitreal Injection of Bevacizumab for Myopic Choroidal Neovascularization, Is It Valuable?

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Abstract

Introduction: Subfoveal choroidal neovascularization (CNV) is a devastating complication of pathological myopia leading to immediate and potentially irreversible vision loss. Although several treatments including thermal laser photocoagulation, photodynamic therapy, macular translocation and surgical removal of CNV, have been attempted to this disease, the beneficial effects are questionable because of severe complications, poor long term results or both. The introduction of pharmacological treatment that block the vascular endothelial growth factor (VEGF) has been used as new treatment of CNV.

Aim of the work: The aim of this study is to evaluate the efficacy of long term effect of 1.25/0.05 ml intravitreal injection of bevacizumab for early CNV secondary to pathological myopia regarding visual outcome, foveal thickness, fluorescein leakage.

Material and Method: This prospective interventional, non-randomized case study included 16 eyes of 16 patients with m CNV who presented to Al-Azhar university Hospital. A written informed consent was obtained from all patients. Inclusion criteria, Pathological myopia defined as spherical equivalent more than -10D, patient age > 30 years old, baseline BCVA less than 0.7 log MAR, Active subfoveal or juxtafoveal CNV confirmed with fluorescein angiography and spectral domain OCT, absence of other ocular disease that can affect BCVA, eyes with idiopathic CNV, AMD, or angoid streaks, any other retinal pathologies or receiving PDT were excluded.

Results: The mean pretreatment BCVA ± SD 1.14 ± 0.22 LogMAR units (range 0.7 - 1.7 LogMAR), Their mean visual outcome after first injection ± SD 0.99 ± 0.46 LogMAR (range 0.3 - 1.3 LogMAR), after second injection mean ± SD 0.61 LogMAR 0.27 LogMAR (range from 0.3 - 1.07 log MAR), after third injection mean ± SD 0.56 ± 0.29 LogMAR (range 0.3 - 1.00 Log MAR). There was a statistically significant difference between pretreatment BCVA and that after the first, second and third injections P value=0.027 by using one way Anova test). Their pretreatment foveal thickness mean ± SD 190.10 ± 80.25 um (range 170 – 390 um), their foveal thickness after first injection mean ± SD 180.75 ± 70.24 um (range 150 – 310 um), After second injection mean ± SD 165.10 ± 45.35 um (range 120 – 270 um), After third injection mean ± SD 120.27 ± 33.61um (range 100 – 170 um). There was statistically significant difference between pretreatment foveal thickness and that after the first, second and third injections p value = 0.043.

Conclusion: This study shows the efficacy of bevacizumab in reduction, contraction and resolving of mCNV with significant improvement in mCNV especially after the first injection and especially in young patients < 50 years old, and so can be used as primary treatment of mCNV with close follow up to the patient as regarding BCVA, foveal thickness and florescence leakage as the patient may require other injections.

Keywords: *Myopic Choroidal Neovascularization; Foveal Thickness; Fluorescein Angiography; Optical Coherence Tomography; Bevacizumab*

Introduction

Subfoveal choroidal neovascularization (CNV) is a devastating complication of pathological myopia leading to immediate and potentially irreversible vision loss [1].

Although several treatments including thermal laser photocoagulation [2], photodynamic therapy [3], macular translocation and surgical removal of CNV [4] have been attempted to this disease, the beneficial effects are questionable because of severe complications, poor long term results or both [5].

The introduction of pharmacological treatment that block the vascular endothelial growth factor (VEGF) has been used as new treatment of CNV [6].

An initial case report by Rosenfeld., *et al*. [7] suggested that 1 mg/0.05ml intravitreal bevacizumab (Avastin, Genentech, San Francisco, California, USA) was safe and effective in treatment of subfoveal CNV secondary to age related macular degeneration (AMD) at 1 month. Avery., *et al*. [8] published data on additional patients with subfoveal CNV secondary to AMD treated with intravitreal 1.25 mg/0.05 ml.

Nguyen., *et al*. [9] reported two patients with subfoveal CNV secondary to pathological myopia treated with intravenous bevacizumab (5 mg/kg).

Vascular endothelial growth factor (VEGF) is believed to be a key factor in development and progression of CNV [10,11] and anti-VEGF are expected to overcome the disadvantages of conventional treatment.

Bevacizumab originally developed for treatment of metastatic carcinoma of colon and rectum [12,13], is a recommended humanized monoclonal antibody against all VEGF isoforms [14].

The aim of this study is to evaluate the efficacy of long term effect of 1.25/0.05 ml intravitreal injection of bevacizumab for early CNV secondary to pathological myopia regarding visual outcome, foveal thickness, fluorescein leakage.

Patients and Methods

This prospective interventional, non-randomized case study included 16 eyes of 16 patients with m CNV who presented to Al-Azhar university Hospital. A written informed consent was obtained from all patients. Inclusion criteria, Pathological myopia defined as spherical equivalent more than -10D, patient age > 30 years old, baseline BCVA less than 0.7 log MAR, Active subfoveal or juxtafoveal CNV confirmed with fluorescein angiography and spectral domain OCT, absence of other ocular disease that can affect BCVA, eyes with idiopathic CNV, AMD, or angoid streaks, any other retinal pathologies or receiving PDT were excluded.

All the patients' clinical data were collected including age, sex, affected eye, spherical equivalent of refraction, preoperative duration of visual impairment. Patients were followed weekly for 1 month and then monthly for 9 months for routine examination including BCVA with Landolt's chart, fundus examination through dilated pupils, spectral domain optical coherence tomography.

Measurement of foveal thickness and CNV size using spectral domain OCT (Nidek) with cross, map and line mode settings 6mm, decrease 10% of baseline is recorded to be improvement, increase 10% of baseline is recorded to be worsening. The activity of mCNV was evaluated by late phase of FA (12 minutes) carried out before treatment and 3 months after treatment.

Fluorescein angiography was done by Topcon image net camera, CNV size is presented at disc area, reduction > 10% from baseline was defined as reduction to baseline and increase > 10% was recorded to be increase to baseline.

The leakage of CNV was recorded in late phase 10 - 12 minutes compared with early phase 1 - 2 minutes. The leakage compared before and after treatment and recorded after 3 months as resolved, reduced unchanged.

The patients received 3 consecutive 1.25 mg/0.05 ml intravitreal injection of bevacizumab monthly for 3 months one month interval depending on the activity of mCNV.

Technique of injection: before injection Benoxinate 0.2% was applied topically as drop and at the site of injection, betadine 5% was irrigated on conjunctival surface, and lid speculum was placed. using a 30 gauge needle 1.25 mg/0.05 ml of bevacizumab was injected into the vitreous cavity at a distance from the limbus 3.5 mm in pseudophakic eyes and 4 mm in phakic eyes, no paracentesis was required to lower IOP, pressure was applied at site of injection to avoid reflux of the drug. Topical antibiotic was used for 5 days, follow up occurred at routine intervals to detect fluorescein leakage or fluid collection as imaged by OCT.

Statistical Analysis

Data were Statistically described in terms of mean ± standard deviation and range when appropriate. All statistical calculations were done using Statistical package for the social science (SPSS) (SPSS INC., Chicago, IL, USA). A p value < 0.05 was considered Statistically significant.

Results

This study included 16 eyes of 16 patients 9 female (56.2%) and 7 male (43.8%) their mean age ± SD 43.38 ± 10.3 years (range 31 - 65 years), 9 eye right (56.2%), 7 eyes left (43.8%), Their mean refractin (spherical equivalent) ± SD -15.21 ± 3.09D (range -10 to -22 D), The position myopic CNV was juxtafoveal in 6 eyes (37.5%), subfoveal in 10 eyes (62.5%), (table 1).

		No. (%)
Age	Mean ± SD	43.38 ± 10.33years
	Range	31 – 65years
Sex	Female	9 (56.2%)
	Male	7 (43.8%)
Rt / Lt	Rt	9 (56.2%)
	Lt	7 (43.8%)
Refraction in diopters	Mean ± SD	-15.21 ± 3.09D
	Range	-10 - -22D
Position of CNV	Juxtafoveal	6 (37.5%)
	Subfoveal	10 (62.5%)

Table 1: *Patient's characteristics (age, sex, Rt/Lt, refraction in diopters, position of CNV).*

Follow up period after intravitreal injection 9 months, all patients had received three consecutive intravitreal bevacizumab injections with interval time 30 days between injections.

The mean pretreatment BCVA ± SD 1.14 ± 0.22 LogMAR units (range 0.7 - 1.7 LogMAR), Their mean visual outcome after first injection ± SD 0.99 ± 0.46 LogMAR (range 0.3 - 1.3 LogMAR), after second injection mean ± SD 0.61 LogMAR 0.27 LogMAR (range from 0.3 - 1.07 log MAR), after third injection mean ± SD 0.56 ± 0.29 LogMAR (range 0.3 - 1.00 Log MAR).

There was a statistically significant difference between pretreatment BCVA and that after the first, second and third injections P value=0.027 by using one way Anova test) (Table 2) (Figure 1).

	Visual acuity (Log MAR units)		One way ANOVA test	
	Mean ± SD	Range	F	P value
Pretreatment vision	1.14 ± 0.22	0.7 - 1.7	4.121	0.027
After first injection	0.99 ± 0.46	0.3- 1.07		
After second injection	0.61 ± 0.27	0.3- 1.07		
After third injection	0.56 ± 0.29	0.3- 1.00		

Table 2: *Comparison between the pretreatment vision and that after the first, second and third injections.*

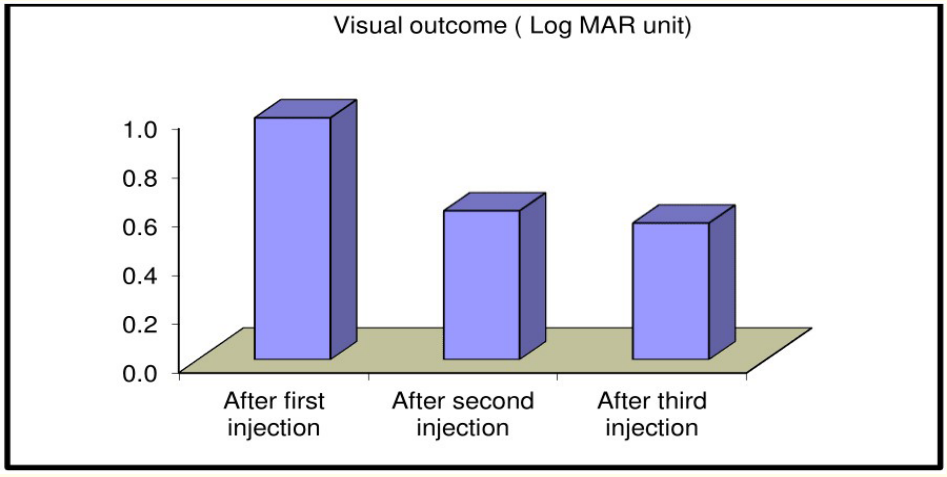


Figure 1: *Comparison between the pretreatment vision and that after the first, second and third injections.*

Their pretreatment foveal thickness mean ± SD 190.10 ± 80.25 um (range 170 – 390 um), their foveal thickness after first injection mean ± SD 180.75 ± 70.24 um (range 150 – 310 um), After second injection mean ± SD 165.10 ± 45.35 um (range 120 – 270 um), After third injection mean ± SD 120.27 ± 33.61 um (range 100 – 170 um).

There was statistically significant difference between pretreatment foveal thickness and that after the first, second and third injections p value = 0.043 (Table 3).

	Foveal thickness (um)		One way ANOVA test	
	Mean ± SD	Range	F	P value
Pretreatment foveal thickness	190.10 ± 80.2	170 - 390	3.521	0.043
After first injection	180.75 ± 70.24	150 - 310		
After second injection	165.10 ± 45.35	120 - 270		
After third injection	120.27 ± 33.61	100 - 170		

Table 3: *Comparison between the pretreatment foveal thickness and that after firsr, second and third injections.*

There was highly statistically significant correlation between the visual outcome and foveal thickness after the first, second and third injections p value < 0.001 (Table 4).

	Visual outcome (log mar)		Foveal thickness (um)		Independent t-test	
	Mean ± SD	Range	Mean ± SD	Range	t	P-value
After first injection	0.99 ± 0.46	0.10 - 1.30	180.75 ± 70.24	150 - 310	10.248	< 0.001
After second injection	0.61 ± 0.27	0.30 - 1.07	165.10 ± 45.35	120 - 270	12.104	< 0.001
After third injection	0.56 ± 0.29	0.30 - 1.00	120.27 ± 33.61	100 – 170	12.646	< 0.001

Table 4: *Comparison between visual outcome and foveal thickness after first, second and third injection.*

The Size of CNV had been decreased significantly after first intravitreal injection and reduced latter minimally, all patients are markedly improved as regarding the visual outcome and foveal thickness.

Fluorescein leakage had been resolved in 9 eyes (56.25%), reduced in 6 eyes (37.5%), unchanged in 1 eye (6.25%).

There was a statistically significant correlation between the age and final foveal thickness, Young ages respond rapidly with obvious reduction in the foveal thickness after first injection and become more steady during the follow up period (p value < 0.001) (Table 5) (Figure 2).

	Age	
	r	P-value
Final Foveal	0.984	< 0.001

Table 5*: Correlation between final foveal thickness and patient age.*

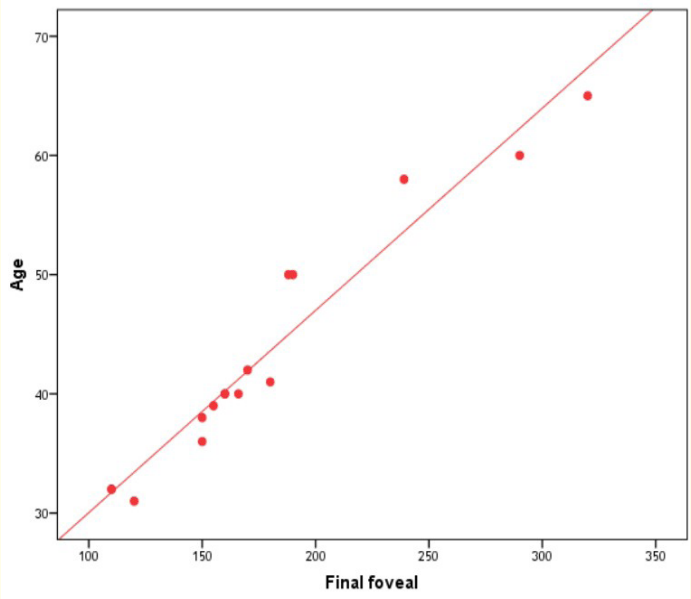
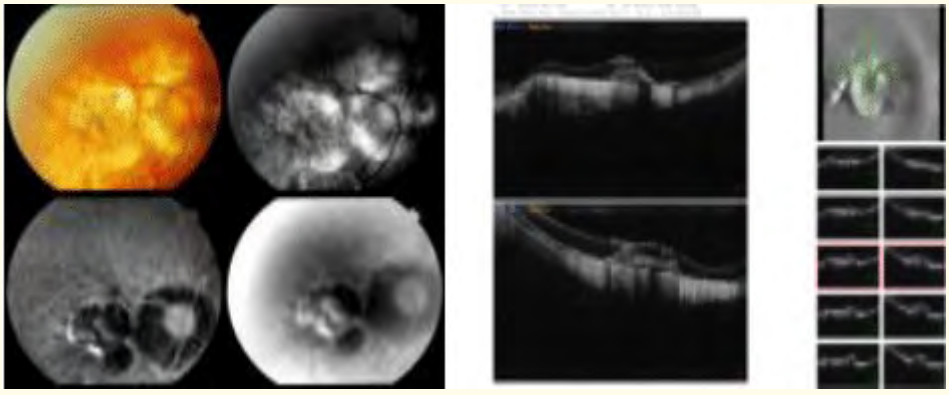


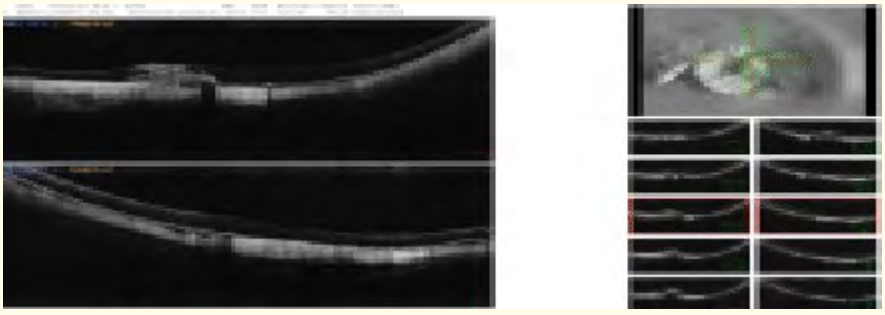
Figure 2.

No injection or drug related complications, including endophthalmitis, cataract, retinal detachment, glaucoma or uveitis were observed with no systemic side effects were observed during the follow up period.

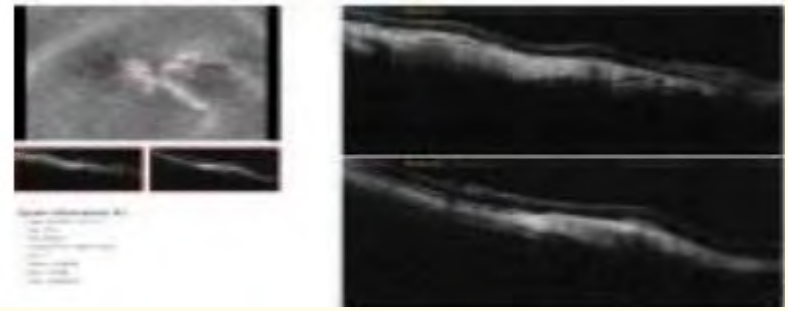


Case (1)

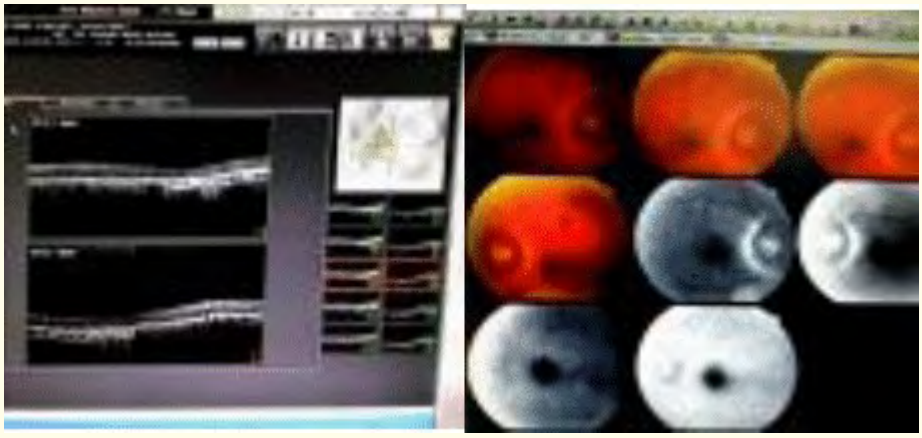
(a) Baseline fluorescein angiography shows actively leaking classic subfoveal cnv (b) OCT shows subfoveal cnv with subretinal fluid.



(c) OCT scan after first injection.



(d) OCT scan after second injection.



(e) FA after third injection shows no leakage (f) OCT shows markedly decreased foveal thickness with disappearance of cnv.

Discussion

Several studies have reported the efficacy of intravitreal injection of bevacizumab in treatment of CNV associated with AMD. Laud., *et al*. [15] reported that most patients showed reduced time in angiographic leakage from neovascular CNV and BCVA improved noticeably. The current study shows resolved angiographic leakage from myopic CNV in (56.25%) with reduced leakage in (37.5%) with marked improvement in BCVA and marked improvement in foveal thickness.

Xoshida., *et al*. [16,17], reported that 21% of eyes with mCNV improved to more than one to three lines of BCVA over 3 months during treatment. It was also reported that BCVA improved to more than one to three lines in 25% of eyes with mCNV 3 months after PDT.

Sakaguchi., *et al*. and Ergun., *et al*. [18,19] reported improvement of BCVA of two or three lines in 75% of eyes Milani., *et al*. [20] reported BCVA was significantly better than baseline every month until 2 months (p value < 0.05), Mathieu., *et al*. [21] reported that intravitreal bevacizumab is effective in treatment of mCNV and only small number of injections is required to treat it.

This study showed that BCVA improved to two or more lines which is highly significant at final treatment with stability of BCVA after final injection at the period of 9 months follow up. Youn., *et al* and shaher., *et al*. [22,23] reported that bevacizumab may penetrate the full retinal thickness. This finding is matching with our results that show the efficacy of bevacizumab on subretinal CNV.

Baba., *et al*. [24] reported that 12 eyes with mCNV treated with 1.25 mg/0.05 ml IVB had significant improvement of visual outcome from 0.75 ± 0.25 Log MAR units at baseline to 0.50 ± 0.38 Log MAR units at 24 months after injection, and mean number of injections was 1.6 ± 0.8 times.

Ikuno., *et al*. [25] reported that 11 eyes with m CNV treated by 1 mg/0.05ml IVB showed significant improvement in visual outcome from 0.68 ± 0.29 Log MAR units to 0.56 ± 0.31 Log MAR units at 1 month interval, and improvement was maintained to for 12 months. However, the significance of improvement was not present at 18 and 24 months after the initial treatment, and the mean number of injections was 2.9± 2.4 times.

Voykov., *et al*. [26] reported that 11 eyes treated by 1.25 mg/0.05ml IVB monotherapy showed gradually improvement of visual outcome from 0.7 - 0.5 Log MAR units with2.2 times of injections at 24 months after IVB, however, the improvement was marginal not significant.

1.25 mg/0.05 ml of intravitreal bevacizumab was used in this study. Beer., *et al*. [27] reported up to 2.5 mg/0.05 ml intravitreally can be tolerated and not to be toxic on the rabbits retina. Lotfi., *et al*. [28] reported the efficacy of both bevacizumab and ranibizumab in increasing the visual acuity with maintain the stability of vision for long time.

Generally, intravitreal administration of bevacizumab seems to be an efficient treatment of mCNV with no ocular side effects were observed during the follow up period in this study. The vitreous cavity in myopic eyes is generally longer which can dilute the concentration of intravitreal injection to bevacizumab and turn over may be slower because of the function of thinner retina and retinal pigment epithelium, the pathology of mCNV is not completely understood until now, its development and progression [29], the administration of bevacizumab led to contraction of mCNV is most of our patients [29].

Conclusion

This study shows the efficacy of bevacizumab in reduction, contraction and resolving of mCNV with significant improvement in best corrected visual acuity especially after the first injection and especially in young patients < 50 years old, and so can be used as primary

treatment of mCNV with close follow up to the patient as regarding BCVA, foveal thickness and fluorescein leakage as the patient may require other injections.

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