Original Article

Visual Outcome of Anti-vascular Endothelial Growth Factor Injections at the University College Hospital, Ibadan

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Abstract

Aim: The aim of the study was to evaluate the 1-year outcome of intravitreal anti-vascular endothelial growth factor (anti-VEGF) therapy in an eye unit in sub-Saharan Africa. **Methodology:** This retrospective study included 182 eyes of 172 patients managed in the vitreoretinal unit between 2016 and 2019 who were treated with intravitreal anti-VEGF bevacizumab (1.25 mg/0.05 ml) with at least 1 year of follow-up. The outcome measures were change in best-corrected visual acuity (BCVA) over 1 year of follow-up, the number of injections taken, and complications. **Results:** The mean age was 61.1 ± 16.3 years (male-to-female ratio of 1:1.1) and about 62.1% above >60 years. A total of 330 injections were given during the period audited. The mean number of injections was 1.8 ± 0.93. Ninety-four (51.7%) eyes had only one injection, while 33 (18.1%), 50 (27.5%), and 5 (2.7%) had 2, 3, and 4 injections, respectively. About 78.5% had moderate-to-severe visual impairment at baseline and 44.5%, 16.4%, 12.6%, and 7.1% at 1, 3, 6, and 12 months post injections, respectively. The mean BCVA improved for all eyes from 1.67 ± 0.91 logarithm of minimum angle of resolution (logMAR) at baseline to 1.50 ± 1.27 logMAR at 1 year. The logMAR letters gained was 23 at 1 month and 8.25 at 1 year; the eyes that had three injections gained 10 letters, while those that had one injection gained three letters. Eyes with age-related macular degeneration and idiopathic polypoidal choroidopathy gained 7.5 and 9 letters, respectively, at 1 year after at least three injections. There was a statistically significant association between an increasing number of injections and improved visual outcome ($P = 0.043$). One patient each developed endophthalmitis (0.6%) and inferior retinal detachment (0.6%) post injection. **Conclusion:** Visual acuity gain was recorded in patients who had intravitreal anti-VEGF injections in 1 year. It is recommended that patients should have more than one injection.

Keywords: Anti-vascular endothelial growth factor, bevacizumab (Avastin), intravitreal injections, ranibizumab (Lucentis), retina, visual outcome

Résumé

Objectif: Le but de l'étude était d'évaluer le résultat à 1 an d'un traitement intravitréen anti-facteur de croissance endothélial vasculaire (anti VEGF) dans une unité ophtalmologique en Afrique subsaharienne. **Méthodologie:** Cette étude rétrospective a inclus 182 yeux de 172 patients pris en charge dans l'unité vitréorétinienne entre 2016 et 2019 qui ont été traités par bevacizumab anti-VEGF intravitréen (1,25 mg/0,05 ml) avec au moins 1 an de suivi. Les mesures des résultats étaient le changement de la meilleure acuité visuelle corrigée (MAVC) sur 1 an de suivi, le nombre d'injections effectuées et les complications. **Résultats:** L'âge moyen était de 61,1 ± 16,3 ans (ratio homme/femme de 1:1,1) et d'environ 62,1 % au-dessus de > 60 ans. Au total, 330 injections ont été effectuées au cours de la période auditée. Le nombre moyen d'injections était de 1,8 ± 0,93. Quatre-vingt quatorze yeux (51,7 %) n'ont eu qu'une seule injection, tandis que 33 (18,1 %), 50 (27,5 %) et 5 (2,7 %) ont eu 2, 3 et 4 injections, respectivement. Environ 78,5% avaient une déficience visuelle modérée à sévère au départ et 44,5%, 16,4%, 12,6% et 7,1% à 1, 3, 6 et 12 mois après les injections, respectivement. La MAVC moyenne s'est améliorée pour tous les yeux, passant de 1,67 ± 0,91 logarithme de l'angle minimal de résolution (logMAR) au départ à 1,50 ± 1,27 logMAR à 1 an. Les lettres logMAR acquises étaient de 23 à 1 mois et de 8,25 à 1 an ; les yeux qui ont eu trois injections ont gagné 10 lettres, tandis que ceux qui ont eu une injection ont gagné

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trois lettres. Les yeux atteints de dégénérescence maculaire liée à l'âge et de choroïdopathie polypoïdale idiopathique ont gagné 7,5 et 9 lettres, respectivement, à 1 an après au moins trois injections. Il y avait une association statistiquement significative entre un nombre croissant d'injections et une amélioration des résultats visuels (P = 0,043). Un patient a développé une endophtalmie (0,6 %) et un décollement de la rétine inférieure (0,6 %) après l'injection. **Conclusion:** Un gain d'acuité visuelle a été enregistré chez les patients ayant eu des injections intravitréennes d'anti VEGF en 1 an. Il est recommandé que les patients aient plus d'une injection.

Mots-clés: Anti facteur de croissance endothélial vasculaire, bevacizumab (Avastin), injections intravitréennes, ranibizumab (Lucentis), rétine, résultat visuel Dernière modification

Introduction

Vascular endothelial growth factor (VEGF) is stimulated in response to hypoxia in all vascularized intraocular tissue. The pathophysiologic mechanisms of most retinal diseases involve vascular proliferation and leakage in which VEGF is the main signal.[1] Despite the complex pathophysiologic mechanisms of retinal damage in various intraocular vascular diseases, the use of anti-VEGF therapy is an effective therapeutic agent in various clinical trials for choroidal neovascular membrane from age-related macular degeneration (ARMD) (wet AMD), diabetic macular edema (DME), macular edema due to retinal vein occlusion (RVO), myopic choroidal neovascularization, and other retinal diseases.[2]

Anti-VEGF is also commonly used as a standard therapy for various retinal vascular diseases, either as first- or second-line treatment of choice.[2-5] Although the use of bevacizumab (Avastin) is off-label, it has been recommended as a cheaper noninferior option to the other alternatives such as ranibizumab or aflibercept. Similarly, bevacizumab is a preferred choice in low-resource settings like ours where patients in urgent need of anti-VEGF agents have to pay out of pocket.[6]

Various anti-VEGF treatment protocols have been advocated for the management of various retinal vascular diseases, with some dosing regimens supporting multiple injections.[4-7] For instance, the "continuous dosing" regimen proposed by the MARINA study involves the use of monthly injections, while the PRONTO study offered "treatment as required" as guided by the optical coherence tomography (OCT) scan thus making patients require fewer injections unlike the MARINA study but with similar visual outcome.[8,9] Furthermore, the "treat and extend" regime aimed to reduce the treatment burden on patients by extending follow-up and/or treatment as determined by disease stability.[2,10] The use of "initial 3 loading doses" followed by "as-needed treatment" showed excellent visual outcome in the ABC trial.[11] Despite the cost-effectiveness of bevacizumab and proven treatment protocols recommending it to patients, the outcomes of the therapy have varied in the face of pervasive undertreatment in low-resource settings.

In this retrospective study, we seek to evaluate the 12-month visual outcome and relationship with the number of anti-VEGF injections in eyes with retinal vascular diseases to make recommendations for patients' care in our practice and other similar settings to our health system where the scourge of retinal diseases is progressively becoming burdensome.[12,13]

Methodology

In this retrospective study, medical records of patients who were treated with intravitreal bevacizumab at the University College Hospital, Ibadan, Nigeria, from January 2016 to December 2019 were retrieved. This study adhered to the tenets of the Declaration of Helsinki. All patients consented to the off-label use of bevacizumab. All procedures were carried out in the operating theater under aseptic conditions. The eye to be injected was prepared with 10% povidone-iodine to the periocular skin and lids, 5% povidone-iodine drops instilled into the conjunctiva sac, and topical tetracaine was added before the povidone. Caliper measurements from the limbus were done to ensure that injection was given through the pars plana (4 mm for phakics and 3.5 mm for pseudophakics; 1.5 mm for neonates). Intravitreal injections of bevacizumab (Avastin, Roche, Basel, Switzerland- dosage: 1.25 mg/0.05 ml for adults; 0.625 mg for neonates) or ranibizumab (Lucentis, Novartis, Basel, Switzerland-dosage: 0.5 mg/0.05 ml for adults; 0.25mg for neonates) were used. The injections were administered using 27 Gauge needles on insulin syringes. The choice of using either bevacizumab or ranibizumab was based on affordability by the patient. All patients were given topical moxifloxacin qid for 1 week after each injection.

Furthermore, all patients were scheduled to have treatment on an as-needed basis after the initial monthly three loading dosage. Eligible patients were those who had at least one injection and attended follow-up evaluation within the first 4 weeks after injection. Patients were reviewed 1st-day postinjection for signs of undue inflammation and raised intraocular pressure. Patients were then reviewed monthly. Visual acuity assessment and dilated fundus examination were done at every visit. This was done by trained and dedicated ophthalmic clinic assistants using the illuminated Snellen visual acuity chart at 6 m. Best-corrected visual acuity (BCVA) was taken as test result one with patient's spectacle correction or as with pin-hole estimation. All results were reviewed by the ophthalmologist at the point of examination and inconsistent results were repeated. OCT scan was requested when visual acuity deteriorated.

Data extracted from case notes include clinical characteristics of the patients such as age, sex, eye (s) injected, systemic comorbidities, number of injections, and BCVA. The outcome measures were the change in BCVA over 1 year of follow-up, the number of injections taken, and any associated complications.

Data were analyzed using the Statistical Package for the Social Sciences (SPSS), version 24 (SPSS Inc., Chicago, Illinois, USA) and reported as frequency distributions, percentages, and means ± standard deviation. Snellen visual acuities were converted to logarithm of minimum angle of resolution (logMAR) for statistical analysis. BCVAs from the baseline, 1, 3, 6, and at 12 months were compared. Categorical variables were compared using Chi-square, and continuous variables were compared using the paired sample *t*-test. $P < 0.05$ was considered statistically significant.

Results

A total of 206 patients' medical records were requested, but only 172 (83.5%) were retrieved successfully, the rest probably lost within the medical records. One hundred and eighty-two eyes of 172 patients (10 had bilateral injections) who had injections were analyzed with a follow-up of 12 months. One hundred and fifty-five eyes completed 12-month follow-up. The mean age was 61.1 ± 16.3 years (89 males, male-to-female ratio of 1:1.1), with about 62.1% being 60 years and above [Table 1]. The most common indication was retinal venous occlusion, 64 (35.2%), followed by wet ARMD, 42 (23%).

Table 1: Demographic and clinical characteristics of patients who had intravitreal anti-vascular endothelial growth factor injections in Ibadan

	Frequency (*n*=182), *n* (%)
Age (mean) (years)	61.1±16.3
≥60	113 (62.1)
17-39	6 (3.3)
40-59	57 (31.3)
6-16	2 (1.1)
Infant-5	4 (2.2)
Sex	
Male	89 (48.9)
Female	93 (51.1)
Eye	
Right eye	94 (51.6)
Left eye	88 (48.4)
Baseline Snellen visual acuity (logMAR equivalent) (*n*=179)	
6/6	5 (2.7)
6/9 (0.2)	4 (2.2)
6/12 (0.3)	7 (3.8)
6/18 (0.5)	16 (8.8)
6/24 (0.6)	8 (4.4)
6/36 (0.8)	17 (9.3)
6/60 (1.0)	16 (8.8)
CF (2.3)	77 (42.3)
HM (2.5)	25 (13.7)
LP (3.0)	2 (1.1)
NLP (4.0)	2 (1.1)

logMAR=Logarithm of minimum angle of resolution, CF=Counting fingers, HM=Hand movement, LP=Light perception, NLP=No light perception

About 78.5% of the eyes had moderate-to-severe visual impairment at baseline and 44.5%, 16.4%, 12.6%, and 7.1% at 1, 3, 6, and 12 months post injections, respectively [Figure 1]. A total of 330 injections were given with the mean number of injections of 1.8 ± 0.93. Ninety-four eyes (51.7%) eyes had only one injection, while 88 (48.3%) had at least two injections [Table 2]. Fifty-five (30.2%) eyes had three injections as initially counseled. The majority, 180 (98.9%), had bevacizumab injection, while only 2 (1.1%) had ranibizumab injection. One patient each developed endophthalmitis (0.6%) and inferior retinal detachment (0.6%) post injection.

The mean BCVA improved for all eyes from 1.67 ± 0.91 logMAR at baseline to 1.21 ± 1.01 logMAR, 1.41 ± 1.09

Table 2: Distribution of intravitreal anti-vascular endothelial growth factor injections, indications, and complications patients who had intravitreal anti-vascular endothelial growth factor injections in Ibadan

	Frequency (*n*=182), *n* (%)
Number of injections (mean)	1.8±0.93
1	94 (51.7)
2	33 (18.1)
3	50 (27.5)
4	5 (2.7)
Type of injection	
Bevacizumab (Avastin)	180 (98.9)
Ranibizumab (Lucentis)	2 (1.1)
Indications	
Wet age-related macular degeneration/CNVM	42 (23.0)
CRVO	34 (18.7)
PDR/DME	27 (14.8)**
IPCV	18 (9.9)
HRVO	16 (8.9)
BRVO	14 (7.7)
CME	9 (4.9)
SCR	6 (3.3)
RAM	4 (2.2)
ROP	3 (1.7)*
NVG	2 (1.0)
Others	7 (3.9)***
Complications	
Endophthalmitis	1 (0.6)
Retinal detachment****	1 (0.6)

*3 infants with retinopathy of prematurity had no objective assessment of visual acuity of documented, **One patient had severe nonproliferative diabetic retinopathy, ***Vitreous hemorrhage in POAG, presumed toxoplasmosis, choroidal melanoma, intraretinal mass (unspecified), Hemorrhagic macular detachment, specific uveitis, and myopic CNVM, ****Inferior bullous detachment developed post third injection. CNVM=Choroidal neovascular membrane, AMD=Age-related macular degeneration, CRVO=Central retinal vein occlusion, PDR=Proliferative diabetic maculopathy, DME=Diabetic macular edema, IPCV=Idiopathic polypoidal choroidal vasculopathy, HRVO=Hemi-retinal vein occlusion, BRVO=Branch retinal vein occlusion, CME=Cystoid macular edema, SCR=Sickle cell retinopathy, RAM=Retinal arterial macroaneurysm, ROP=Retinopathy of prematurity, NVG=Neovascular glaucoma, POAG: Primary open-angle glaucoma

logMAR, 1.44 ± 1.17 logMAR, and 1.50 ± 1.27 logMAR at 1 month, 3 months, 6 months, and 1 year, respectively. The letters gained progressively declined from 23 at 1 month post-injection to about 8 letters at 12 month follow-up review [Figure 2]. The eyes that had three injections gained 10 letters, while those that had one injection gained three letters. Patients who had at least three injections were significantly (P = 0.043) more likely to have better visual outcomes than those who had <3 injections [Table 3].

Discussion

The mean age of patients involved in this study is similar to that in other centers in Nigeria.[14-17] However, the wide age range was due to the inclusion of babies who received anti-VEGF for retinopathy of prematurity.

Almost all our patients, 180 (98.9%), had the less expensive bevacizumab injection, which is akin to other studies done both locally.[14-17] On the other hand, a report from the oil-rich setting of Port Harcourt in Nigeria reported about 25% usage of ranibizumab.[18] A vial of bevacizumab is shared (repackaged bevacizumab) by 10–20 patients to further reduce the cost in a pooled funding system of the unit to encourage compliance with the treatment regime. Even though our patients had been counseled on the need to have the recommended monthly dose of three injections, only about 27.5% (50) complied to the regimen and 51.7% (94) had only one injection due to financial constraints as they

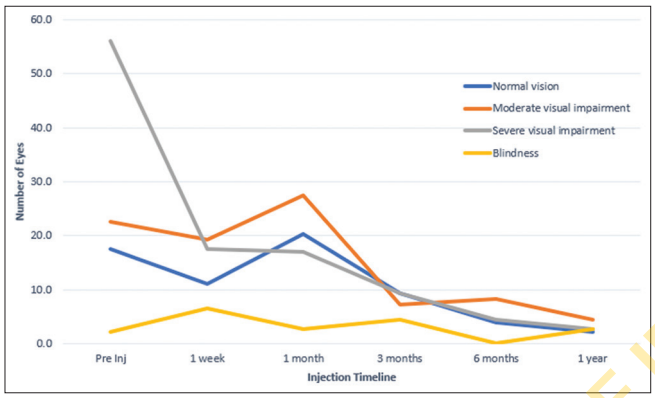

Figure 1: The trend in visual function with follow-up

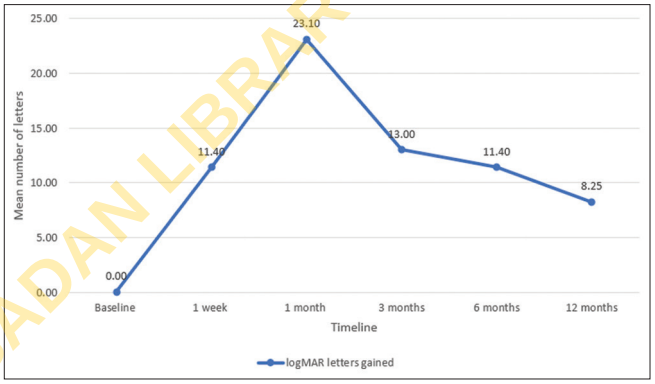

Figure 2: Trend analysis of mean change in mean best-corrected visual acuity represented by letters gained

Table 3: Relationship between clinical characteristics and number of intravitreal anti-vascular endothelial growth factor injections

Variables	<3 injection, *n* (%)	Three or more injections, *n* (%)	χ^2	*P*
Sex				
Female	62 (48.8)	31 (56.4)	1.22	0.54
Male	65 (51.2)	24 (43.6)		
Eye				
Left	62 (48.8)	27 (49.1)	0.001	0.97
Right	65 (51.2)	28 (50.9)		
Age (years)				
<60	54 (42.5)	15 (27.3)	5.55	0.24
>60	73 (57.5)	40 (72.7)		
BCVA 1 month post injection				
Better than 0.8 logMAR (6/6–>6/60)	86.8 (69.4)	38.5 (72.6)	11.87	0.29
0.8 logMAR or worse (<6/60)	38.2 (30.6)	14.5 (27.4)		
BCVA 3 months post injection				
Better than 0.8 logMAR (6/6–>6/60)	63.3 (53.6)	28.9 (55.6)	7.29	0.69
0.8 logMAR or worse (<6/60)	54.7 (46.4)	23.1 (44.4)		
BCVA 6 months post injection				
Better than 0.8 logMAR (6/6–>6/60)	20.8 (17.6)	29.5 (61.5)	7.82	0.05
0.8 logMAR or worse (<6/60)	97.2 (82.4)	18.5 (38.5)		
BCVA 12 months post injection				
Better than 0.8 logMAR (6/6–>6/60)	42 (40)	33.4 (66.7)	7.08	0.04*
0.8 logMAR or worse (<6/60)	63 (60)	16.6 (33.3)		

*Statistically significant level (P<0.05). BCVA=Best-corrected visual acuity, logMAR=Logarithm of minimum angle of resolution

pay out of pocket. The average number of injections in this cohort (1.8 ± 0.9) is akin to a similar study reported in a tertiary hospital in Benin[16] but at variance with the higher mean number of injections reported in major landmark clinical trials that have shaped the preferred practice pattern for intravitreal anti-VEGF injections.[2,8-10,12,19] A strong health system with an effective financial payment and insurance coverage could have been the reason for this disparity. We found that this cohort had improved vision which was better in those that had at least three injections over the 12-month follow-up period. The average number of letters gained was highest at 1-month post injection but was not sustained as it declined to 13 and finally to 8.5 letters (1.7 lines) at 12 month, but this improvement was still a statistically significant outcome. Uhumwangho[16] similarly reported visual improvement in about 50% of studied patients. Lai *et al*.[20] reported 14 letter (2.8 lines) improvement for myopic choroidal neovascular membrane (CNVM) at 24 months. Conversely, Low *et al*.,[7] that reviewed 17 trials, stated that none of them had any clinically significant visual improvement (>5 letters) across the three major retinal vascular diseases scheduled for anti-VEGF injections (wet ARMD, DME, and central/branch RVO irrespective of the type of anti-VEGF agents used (bevacizumab, ranibizumab, and aflibercept).

Pham *et al*.[2] in their systematic review and meta-analysis reported varying levels of visual outcomes depending on the specific disease. Chin-Yee *et al*,[4] found a mean improvement in visual acuity of 5.4 letters for wet age-related macular degeneration (ARMD) following PRN (as needed) regimen of anti-VEGF, and about 10 letters improvement following treat and extend regimen, with an average of 5.6 and 8 injections over 12 months respectively. In our subanalysis, the eyes with ARMD/CNVM gained 7.5 at 1 year after at least three injections (loading doses). The number of letters gained in our review was higher in eyes with at least three injections and the better outcome in Chin-Yee *et al*.'s study could be due to multiple injections of up to eight injections.

Conclusion

Our review has shown that the visual gain was more in those who had at least three injections. It is recommended that patients should have more than one injection and anti-VEGF agents should be made available on the National Health Insurance Scheme and enrolment the scheme should be expanded. These acts will among other things, make anti-VEGF available and accessible to those that need it, thereby aiding to ease the various burdens associated with accessing these drugs.

Limitations

The study being a retrospective study may be limited by accurate data retrieval from case records. Furthermore, the conversion to BCVA from Snellen could have resulted in measurement bias.

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Conflicts of interest

There are no conflicts of interest.

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