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A Review of the Use of Anti-vascular Endothelial Growth Factor Drugs at the Eye Foundation Centre for the Prevention of Blindness, Nigeria

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Authors' contributions

This work was carried out in collaboration between all authors. Authors TJB and AH designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors Olufemi Oderinlo and Okonkwo Ogugua managed the analyses of the study. Authors TA, MU and AA managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Aims: To describe the sociodemographic details and indications for the use of anti-vascular endothelial growth factor (anti-VEGF) injections at the Eye Foundation Centres in Nigeria.
Study Design: Retrospective, observational analysis.
Place and Duration of Study: Eye Foundation Hospitals in Lagos, Ijebu-Imushin and Abuja, Nigeria between January 2011 and December 2014.
Methods: Records of all anti-VEGF injections given were assessed. All consecutive cases were taken in proportion seen in the 4 centres. Age, sex, occupation, diagnoses and types of injection were recorded in the data sheet prepared for the study.
Results: This study included 1072 eyes of 540 patients. Mean age was 60.37(12.74) standard deviation years. The age range is from 10 – 92 years. 326(60.4%) males and females 214(39.6%) were seen. Patients that presented were mostly currently employed 40.8%, previously in paid job

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25.8% and businessmen and women 24.5%. Total injections were 2443, given during the study period. Anti-VEGF agents used were Bevacizumab (2278; 93.2%) and Ranibizumab (165; 6.8%). Indications for injection were: proliferative diabetic retinopathy (PDR) 27.4%, retinal vein occlusion (RVO) 17.6% and vitreous haemorrhage (VH) due to proliferative diabetic retinopathy and sickle cell retinopathy 10.6%. There was an association between sex and disease ($p < 0.001$) and age and disease ($p < 0.001$).

Conclusion: The use of anti-VEGF injections are on the increase especially bevacizumab. The most common indications are proliferative diabetic retinopathy, retinal vein occlusion and VH. The treatment was done more for males, middle class and the rich.

Keywords: Antivascular endothelial growth factor; bevacizumab; Ranibizumab; Eye Foundation Centres; non-communicable eye diseases.

ABBREVIATIONS

ARMD : Wet Age-related Macular Degeneration
CME : Cystoid Macular Edema
DME : Diabetic Macular Edema
IPCV : Idiopathic Polypoidal Chorioroidal Vasculopathy
NPDR : Nonproliferative Diabetic Retinopathy
NVG : Neovascular Glaucoma
PDR : Proliferative Diabetic Retinopathy
RVO : Retinal Vein Occlusion
VH : Vitreous Haemorrhage

1. INTRODUCTION

The World Health Assembly in May 2013 adopted a new global programme document entitled "Universal Eye Health: a global action plan 2014-2019" [1]. It states the major priorities for the global prevention of blindness efforts for the next five years. Cataract and refractive errors still remain the major causes of visual impairment [2]. However, several other eye conditions have emerged as a significant threat to people's vision- those which are non-communicable and which are more prevalent with ageing. They are diabetic retinopathy, glaucoma and age-related macular degeneration [3,4].

In the last 2 decades, these non-communicable eye diseases (NCEDs) have become much more significant. The proportion of people blind from infectious eye diseases has decreased from 20% to 2% in the past 30 years; the proportion due to other eye conditions (like NCEDs) has therefore increased. People are living longer and their diet and lifestyles are changing leading to an increase in NCEDs [3,4].

These NCEDs are mostly disorders of the blood vessels of the retina including retinopathy of prematurity are responsible for some of the most common causes of blindness in the world [5].

All of these conditions are caused partly by overproduction of a protein called vascular endothelial growth factor (VEGF). It is important in the growth and development of blood vessels [5,6,7]. It is a 40 kDa dimetric glycoprotein.

VEGF production is increased by hypoxia in different cells of the retina like the vascular endothelium, retinal pigment epithelium and Muller cells which will stimulate the growth of additional blood vessels (neovascularisation) to produce more oxygen. This is harmful in the eye. There can be retina damage because of increased permeability of existing blood vessels (vascular permeability) causing them to leak. Neovascularisation may cause bleed or leak fluid and proteins [5,6,7].

Because VEGF can damage the eye, drugs have been developed to block its activities [5,6]. Bevacizumab was the first VEGF-A inhibitor that was approved by the food and drug administration (FDA) in the united states (US) in 2004. Pegaptanib and Ranibizumab were approved in 2004 and 2006 respectively as the first VEGF-A inhibitors in ophthalmology. The 2 most widely used drugs are Lucentis (Ranibizumab) and Avastin (bevacizumab). Ranibizumab and Bevacizumab are registered for use in Nigeria by the National Agency for Food and Drug Administration and Control (NAFDAC). Indications for which Ranibizumab was approved are: Neovascular age related macular degeneration (nAMD), visual impairment due to diabetic macular edema (DME) and for visual impairment due to macular edema secondary to Branch retina vein occlusion (BRVO) and central retinal vein occlusion (CRVO) [8]. Bevacizumab was approved for colonic and other types of cancers but it is used as an off-label indication for proliferative Neovascular eye diseases like exudative age-related macular degeneration and proliferative

diabetic retinopathy. The use of anti-VEGF drugs can be combined in some cases with laser photocoagulation and intravitreal steroids in the treatment of ocular neovascular disorders. The purpose of this study is to describe the sociodemographic details and indications for the use of anti-VEGF at the Eye Foundation Centres in Nigeria.

2. MATERIALS AND METHODS

2.1 Study Population

Records of all anti-VEGF injections given from January 2011 to December 2014 were retrieved from the theatre register of Lagos (Ikeja and Victoria Island), Abuja and Ijebu centres of Eye Foundation Hospitals in Nigeria. All consecutive cases were taken in proportion seen in the 4 centres. Age, sex, occupation, diagnoses and types of injection were recorded in the data sheet prepared for the study.

2.2 Method of Injection

Intravitreal injections are always given by an ophthalmologist: retinal specialist, consultant ophthalmologist and ophthalmic residents.

The injection is given in the theatre under sterile condition. After an informed consent and topical anaesthetic (Tetracaine hydrochloride 0.5% or Amethocaine 0.5%) has been applied, 1.25 mg of bevacizumab (Avastin ®, Genentech, South San Francisco, CA, USA) is given intravitreally in the superolateral quadrant or inferotemporal quadrant, 3mm, 3.5mm or 4mm from the limbus in pseudophakic, aphakic and phakic eyes respectively. Same applies for 0.5mg of 0.05ml of Ranibizumab. Anterior chamber paracentesis is done after the injection is given to reduce the intraocular pressure. Topical povidone-iodine 5% was instilled before and after the injection. The patient will then be given an antibiotic (g.ciprofloxacin 6 hourly for at least 2 weeks) and anti-inflammatory (g.diclofenac eye drops 8 hourly for at least 2 weeks). To be seen the next day, one week and one month after for examination under the slit lamp and monitoring of the intraocular pressure. Injections are given every 4-6 weeks.

The patients are always told to watch out for any drop in their vision or significant pain and report to the hospital immediately. IOP before injections is less than or equal to 20mmHg. After injection, if the IOP is high (>22mmHg), the patient is placed on pressure-lowering eye drops and or tablet. Or they see the glaucoma specialist if necessary. Patients are followed up for at least 12 months.

2.3 Statistical Analysis

Results were analysed using Stata version 14.1 (Texas, USA). It was reported as frequency distributions, percentages, and means ± standard deviation (SD). Chi square is the statistical test which was used for the comparison. P-values of <0.05 were considered statistically significant.

3. RESULTS

3.1 Sociodemographic Details

This study included 1072 eyes of 540 patients. The P value for the association between sex and disease is <0.001, age and disease is <0.001. Mean age was 60.37(12.74) standard deviation years (range 10 – 92 years), the subjects included males 326(60.4%) and females 214(39.6%), male: female ratio 1.5:1. Patients that presented were mostly currently employed 40.8%, previously in paid job 25.8% and businessmen and women 24.5% (Table 1) making a total of 91.1%.

Table 1. Sociodemographics of patients

Demographic details	No (%)
Gender	
Male	326(60.4)
Female	214(39.6)
Age Category (in years)	
<=30	14(2.6)
31-40	16(3.0)
41-50	75(13.9)
51-60	169(31.3)
61-70	158(29.3)
71-80	89(16.5)
81-90	17(3.2)
91-100	2(0.4)
Age in years	
Mean(SD)	60.37(12.74)
Min-Max	10 – 92
Occupation	
Employed	220(40.8)
Unemployed	6(1.1)
Housewife	17(3.1)
Previously in paid job	139(25.8)
Businessman/Women	132(24.5)
Student	16(3.0)
Others	9(1.7)

3.2 Anti-VEGF Injections

Total injections were 2443, given during the study period. Anti-VEGF agents used were Bevacizumab (2278; 93.2%) and Ranibizumab (165; 6.8%) as shown in Table 2 and Fig. 1.

3.3 Indications for Injections

Fig. 2 shows indications for injection: proliferative diabetic retinopathy (PDR) 27.4%, retinal vein occlusion (RVO) 17.6% and vitreous haemorrhage (VH) 10.6%. Others are diabetic macular edema (DME), cystoid macular edema, Neovascular glaucoma (NVG), nonproliferative diabetic retinopathy (NPDR), wet age-related macular degeneration (ARMD) and idiopathic polypoidal choroidal vasculopathy (IPCV).

3.4 Comparison of Diagnosis in the Different Age Groups

The peak age group for all categories of diagnosis are 51-60 and 61-70 (51-70). The highest indication for diagnosis at 51-70 years of age is PDR 108 followed by RVO 50 and VH 29.

Table 2. Anti-VEGF injections in the eye foundation hospital group 2011-2014

Anti-VEGF	Ikeja	Abuja	Victoria island	Ijebu-Imushin	Total	%
Bevacizumab	1697	392	98	91	2278	93.2
Ranibizumab	109	49	5	2	165	6.8

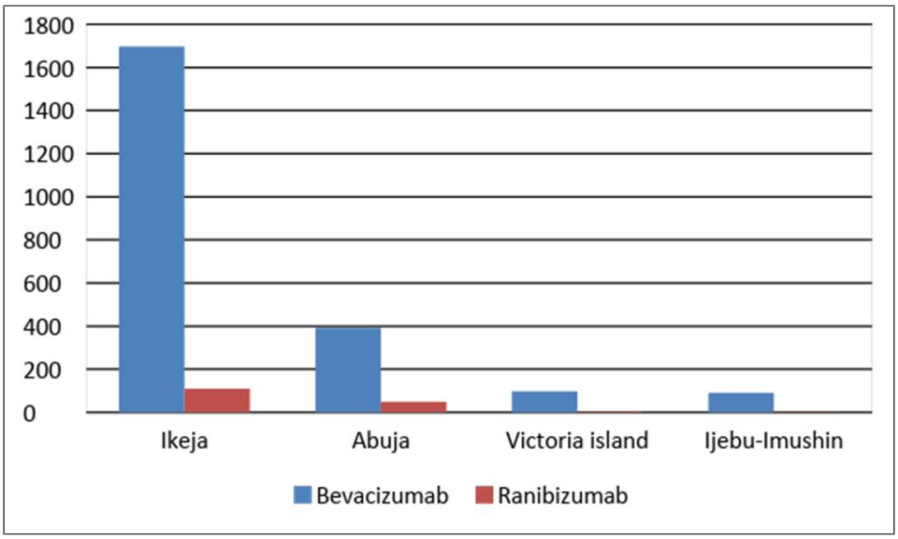

Fig. 1. Bar chart of antivegf injections

Table 3. Comparison of diagnosis in the different age groups

Diagnosis	Age category (in years)								Total
	<=30	31-40	41-50	51-60	61-70	71-80	81-90	91-100	n (%)
ARMD	0	0	1	2	7	8	3	1	22(4.1)
CME	1	2	4	10	16	8	0	0	41(7.6)
DME	0	0	11	12	19	5	0	0	47(8.7)
IPCV	0	0	4	4	5	3	3	0	19(3.5)
NPDR	1	1	2	14	7	1	0	0	26(4.8)
NVG	0	0	6	12	8	4	4	0	34(6.3)
PDR	2	1	21	67	41	15	1	0	148(27.4)
RVO	0	4	7	19	31	27	6	1	95(17.6)
VH	7	5	9	15	14	7	0	0	57(10.6)
Others	3	3	10	14	10	11	0	0	51(9.3)
Total	14	16	75	169	158	89	17	2	540(100)

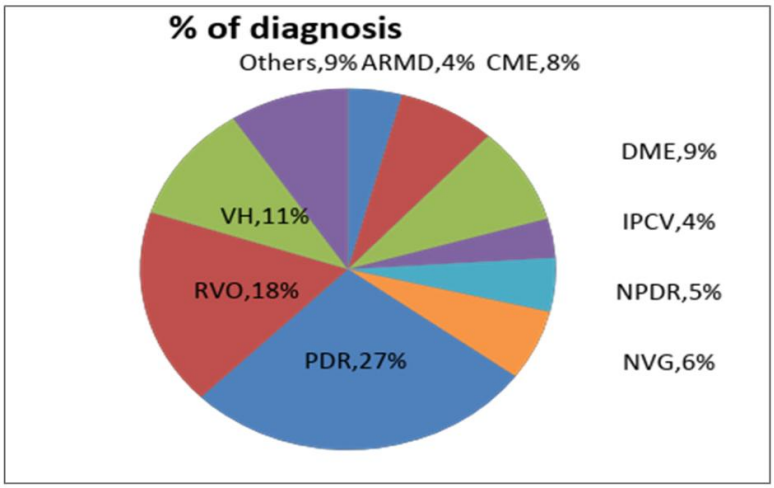

Fig. 2. Indications for injection based on primary diagnosis (number of patients)

4. DISCUSSION

This study shows the result of collation of data from 4 centres in the Eye Foundation Hospital group in the southwestern and northern central part of Nigeria. Even though it is retrospective, it is a multicentre study and this is the first of its kind in antivegf study in Nigeria. Other studies are of smaller samples and from one centre.

4.1 Sociodemographic Details

This study involves males 326(60.4%) and females 214(39.6%) (M: F ratio 1.5:1). There is a strong association between sex and disease ($p < 0.001$). This is comparable to a previously published paper by Okoye et al in a sister centre of the Eye Foundation Hospital Group [9]. Other studies in Nigeria and abroad have female preponderance [9,10] and [11]. This is in contrast to World health Organisation (WHO) publications [12] that women tend to seek medical attention than men. This may be due to the fact that men are more empowered financially than women. Men presented for the treatment more than women. However, in the occupational groups, 91.1% are employees, employers or retired. The association between occupation and disease is statistically significant ($p < 0.001$). In Nigeria, antivegf injections are expensive. Many cannot afford the treatment except for bevacizumab by the middle class and the rich [9,10,13,14]. There is a statistical association between age and disease ($p< 0.001$). Mean age was 60.37(12.74) standard deviation years. The age range was from 10 – 92 years: This is about the same in Port Harcourt, Nigeria (10), Thailand (13) and Benin, Nigeria (14). The mean age is higher in America where Ravi Parkh et al reported it to be 73.2 (12.5) [11].

4.2 Antivegf Injections

2443 injections were given during the study period with Bevacizumab (2278; 93.2%) and Ranibizumab (165; 6.8%) as shown in Table 2 and Fig. 1. Bevacizumab is much less costly. This is why it is mostly preferred. This is about the case all over the world [9,10,11,15,13,14].

4.3 Indications for Injections

The commonest indication is proliferative diabetic retinopathy (PDR) 27.4%, followed by retinal vein occlusion (RVO) 17.6% and vitreous haemorrhage (VH) secondary to proliferative diabetic retinopathy and sickle cell retinopathy 10.6%. This is in contrast to studies done in Nigeria by Fiebai et al. [10] and Oluleye et al. [14] where retinal vein occlusion (RVO) is the commonest indication. Diabetic retina disease is the second commonest in United of America by Parikh et al. [11] and Thailand by Kanavisarut et al. [15].

Diabetes has been on the increase in Nigeria, Africa and indeed the world. This is due to massive migration to towns and cities with attendant change in lifestyle leading to poor nutrition and little physical activity [16,17]. Diabetic retinopathy is fast maturing in to a significant cause of blindness in Nigeria [16,17,18].

Retinal vein occlusion comprising of central retinal vein, branch retinal vein and hemiretinal vein occlusions is the second most common cause for indication for antivegf injection in this study. This is similar to findings from Kano, Nigeria by Shuaib et al [19] and in Benin, Nigeria by Uhumwangho [13]. Systemic hypertension has been implicated as a strong risk factor for RVO and it is very common among adults in Nigeria [14,20,21].

Vitreous haemorrhage (10.6%) due to proliferative diabetic retinopathy and sickle cell retinopathy is the third commonest indication. This is comparable to the study from Kano Nigeria by Shuaib et al. [19] where at 9.8%. The major cause of VH in Nigeria is trauma [22]. In Nepal in a study by Sharma et al it is proliferative diabetic retinopathy (PDR) in adult and trauma in children [23]. In the western world the major cause is PDR [24].

4.4 Comparison of Diagnosis in the Different Age Groups

The peak age group in this study is 51-70 years (60.37 (12.74). This is similar to the series by Fiebai et al. [10] with peak age range of 50-69 years (59.56 +- 11.66). This is different from the studies from United States which peaked at +75 (73.2 +- 12.5) (11) and Germany with mean age of 74.6 +- 10.3 [25]. The mean age is about 10 to 15 years lower in Nigeria. This can be attributed to the shorter life span in Nigeria, compared to developed countries like America and Germany that have a longer life span.

5. CONCLUSION

The use of antivegf injections are on the increase especially bevacizumab. The most common indications are proliferative diabetic retinopathy, retinal vein occlusion and vitreous haemorrhage. The treatment was done more for males, middle class and the rich. The assistance of governments and insurance companies is needed to help the poor.

CONSENT

It is not applicable.

ETHICAL APPROVAL

This study was approved by the Olabisi Onabanjo University Teaching Hospital's Health Research Ethics Committee, Sagamu, Nigeria. Certificate approval number: NHREC/08/10/ 2012.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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