Original Article

Indications and Treatment Outcomes of Intravitreal Bevacizumab and Ranibizumab for Retinal Diseases in Benin City, Nigeria

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Abstract

Background: The emergence of intravitreal antivascular endothelial growth factors (antiVEGF) has revolutionalised the treatment and prognosis of many retinal diseases. **Aim:** To determine the indications and treatment outcomes for use of intravitreal antiVEGF agents in retinal diseases among patients in a tertiary hospital in Benin City, Nigeria. **Materials and Methods:** The case folders of patients, who had intravitreal injections of antiVEGF from January 2012 to December 2014, were analysed. Data retrieved included age, sex, indication, type of intravitreal antiVEGF used, number of injections, visual acuity, treatment outcomes, complications and follow-up duration. **Results:** There were 27 patients, consisting of 12 males and 14 females, with a mean age of 61.8 ± 7.8 (range 46–76) years. Intravitreal antiVEGF were administered in both eyes of 14 (51.9%) patients. Bevacizumab and ranibizumab were utilised in 36 (87.8%) and 3 (7.3%) eyes, respectively. Two (4.9%) eyes had both bevacizumab and ranibizumab during treatment switching from ranibizumab to bevacizumab. A total of 72 injections were administered during the study period with a mean number of 2.4 ± 1.5 (range 1–8) injections administered per eye. The most common indication was diabetic macular oedema in 17 (40.5%) eyes. After treatment, vision improved in 21 (51.2%) eyes and was unchanged in 10 (24.4%) eyes. Eyes, which initially improved, worsened in 10 (24.4%) patients following cessation of treatment. The most common complication encountered was subconjunctival haemorrhage in 15 (36.6%) eyes. The mean duration of follow-up was 12.4 ± 6.8 (range 4–26) months. **Conclusion:** Intravitreal antiVEGF are effective in the management of a vast array of retinal conditions. However, the burden of care including costs and the need for multiple injections are still drawbacks that require an alternative treatment strategy.

Keywords: Aflibercept, bevacizumab, intravitreal antiVEGF, ranibizumab

Introduction

Retinal diseases are seen in routine ophthalmic practice in Nigeria.[1-10] These were previously, largely untreatable with poor prognosis and little intervention gotten from medical science. Vascular endothelial growth factors (VEGF) play a pivotal role in the occurrence of retinal neovascularisation/proliferative retinopathies, choroidal neovascularisation and retinal vascular permeability. These retinal conditions include neovascular age related macular degeneration (ARMD), proliferative diabetic retinopathy (PDR), proliferative sickle cell retinopathy (SCR), diabetic macular edema, retinal vein occlusion (RVO) with macula oedema and retinopathy of prematurity.[11-15] The use of antivascular endothelial growth factors (antiVEGF) has revolutionalised the treatment of these diseases with reports of efficacy, reversal of visual loss and even regaining of lost vision.[11] The commonly used intravitreal antiVEGF include ranibizumab, bevacizumab, pegaptanib sodium and aflibercept. Ranibizumab is a humanised monoclonal antibody fragment with an approximate molecular weight of 48 kDa. It strongly binds to VEGF-A receptors and inhibits vasculogenesis. It has been licensed for use by the United States Food and Drug Administration.[11] Bevacizumab is a monoclonal antibody with molecular weight of 149 kDa. It inhibits VEGF by binding with isomers of VEGF receptors A and B, thus reducing the drive for angiogenesis and vascular

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permeability. It is used in many ocular conditions via various routes such as intravitreal, subconjunctival, intracameral and intracorneal routes. The ocular use of bevacizumab is off-label but has become popular being more cost effective compared to other antiVEGF agents.[11] Aflibercept is a fusion protein which binds VEGF-A, VEGF-B and placental growth factors 1 and 2 with high affinity. It suppresses choroidal neovascularisation and has a longer duration of action compared with other antiVEGF drugs.[11] Pegaptanib sodium is a pegylated antiVEGF aptamer that binds to VEGF 165 receptor. It inhibits angiogenesis, reduces vascular permeability and licensed for use in neovascular macular degeneration. However, its use is on the decline.[11]

The study was conducted to determine the indications and treatment outcomes in the use of intravitreal antiVEGF in a group of patients presenting to a tertiary hospital in Southern Nigeria.

Materials and Methods

A retrospective hospital-based study of patients who had intravitreal injection of antiVEGF for various conditions between January 2012 and December 2014 was conducted. The medical folders of all patients who had intravitreal injection of antiVEGF were retrieved from the register and a retrospective review was performed. Demographic and clinical data retrieved included age, sex, indications for intravitreal antiVEGF injection, eye involved, type of intravitreal antiVEGF administered, number of injections, visual acuity (VA), treatment outcomes, complications and duration of follow-up. Patients were treated with either 0.05 ml of ranibizumab (0.23 mg in 0.23 ml vial) or 1.25 mg/0.05 ml bevacizumab. The protocol involved obtaining written informed consent from patients or their delegated representative, a close relative prior to the procedure. Patients, who entertained fears, were shown a video clip of the procedure to allay their anxiety and educate them on what the procedure entailed. Patients were usually informed that multiple injections would likely be required before complete resolution of the varied conditions. Prior to the procedure, the VA, intraocular pressure and blood pressure were performed to ensure normal values. Intravitreal injections were performed as an outpatient procedure in the operating theatre under strict asepsis. The area for injection was cleaned with 5% povidone–iodine and draped. Topical anaesthesia (tetracaine 1%) was instilled, and the injection site, located in the inferotemporal quadrant, was marked by measuring with a calipers at 3.50 mm and 4.00 mm from the limbus in pseudophakic and phakic eyes, respectively. Intravitreal antiVEGF was injected with a 29G or 30G needle. A sterile cotton bud was applied to the injection site immediately following withdrawal of the needle. A rough idea of the intraocular pressure was determined by applying very gentle pressure with a sterile cotton bud on the central cornea. If ascertained to be raised, a paracentesis was performed. Gross VA was assessed immediately after the procedure by checking for light perception or ability to see hand movement. An eye pad was then placed over the eyes briefly and discarded before patient went home. Possible symptoms/complications were explained to the patients, and patients were advised to present immediately any abnormality occurs such as noticing a decline in VA or presence of ocular aches or pains. In patients who required injections in both eyes, an interval of 1 week was given before the second eye injection was performed to ascertain the state of the previously injected eye for signs suggestive of complications such as endophthalmitis. Patients were reviewed the next day after an injection following, for which, a follow-up visit was scheduled usually at 4 weeks. Applicable guidelines regarding use of human subjects were followed in this study. Data obtained were analysed with GraphPad Instat Software, Inc. version V2.05a program, San Diego, California.

Results

A total of 27 patients had intravitreal antiVEGF during the study period. This patient group consisted of 12 males and 14 females. There were a total of 41 eyes made of 21 right eyes and 20 left eyes. Intravitreal injections were administered in both eyes of 14 (34.1%) patients. The mean age of the patients was 61.8 ± 7.8 (range 46–76 years). Bevacizumab was used in 36 (87.8%) eyes while ranibizumab was used in 3 (7.3%) eyes. Two (4.9%) eyes had both bevacizumab and ranibizumab during the course of treatment with a switch from ranibizumab to bevacizumab. The mean number of injections administered in an eye was 2.4 ± 1.5 (range 1–8). There was reluctance to continue with intravitreal injections in 20 (74.1%) patients after the first three injections primarily on financial reasons. A total number of 72 injections were administered during the study period.

The most common indication for intravitreal antiVEGF was diabetic macula oedema in 17 (40.5%) eyes. The indications for intravitreal antiVEGF are presented in Table 1. The VA after intravitreal antiVEGF is presented in Table 2. Improvement in VA following treatment with antiVEGF was sustained in 21 (51.2%) as at the last follow-up visit. The number of eyes with vision >6/18 increased from 10 (24.4%) to 19 (46.3%) eyes.

Table 1: Indications for use of intravitreal antivascular endothelial growth factors

Indications	Number of eyes (%)
Diabetic macula oedema	17 (41.5)
Retinal vein occlusion with macula oedema	10 (24.4)
Neovascular ARMD	7 (17.1)
Proliferative diabetic retinopathy with vitreous haemorrhage	3 (7.3)
Neovascular glaucoma	2 (4.9)
Inflammatory CNVM	1 (2.4)
Myopic CNVM	1 (2.4)
Total	41 (100.0)

ARMD = age related macular degeneration, CNVM = choroidal neovascular membrane.

Table 2: Visual acuity in treated eyes

Visual acuity	Pre-treatment (%)	Post-treatment at last follow-up visit (%)
>6/18	10 (24.4)	19 (46.3)
6/18–6/60	19 (46.3)	14 (34.1)
<6/60	12 (29.3)	8 (19.5)
Total	41 (100.0)	41 (100.0)

Vision was retained in 10 (24.4%) eyes with treatment while vision which initially improved worsened in 10 (24.4%) eyes following cessation of treatment with intravitreal antiVEGF. Cessation in treatment was due to patient's financial constraints. Adjunctive treatment with retinal laser photocoagulation was performed in 9 (22.0%) eyes. The complications encountered were subconjunctival haemorrhage in 15 (36.6%) eyes and transient elevated intraocular pressure in 3 (7.3%) eyes. The mean duration of follow-up was 12.4 ± 6.8 (range 4–26) months.

Discussion

The use of intravitreal antiVEGF has improved the management of many vitreoretinal conditions with stabilisation of vision and even regaining vision lost.[10,15-22] This is reflected in the improvement in VA following treatment which improves the quality of life of patients who would have been significantly negatively impacted. The most common indication for use of intravitreal antiVEGF was diabetic macula oedema in 41.5%. This is in contrast with the study in Ibadan, in which macula oedema from RVO (19.4%), wet ARMD (17.1%) and vitreous haemorrhage from proliferative SCR (16.4%) were the common indications for intravitreal antiVEGF.[15] The rising prevalence of diabetes in our environment can lead to a concomitant increase in the number of diabetic-related complications.[23,24] These include diabetic macular oedema, diabetic retinopathy and risk of retinal vascular occlusions with macula oedema. These conditions are treated with intravitreal antiVEGF. However, the need for multiple injections to maintain vision gained is a major challenge in our environment. This is because the burden of care in terms of costs of injections and clinic visits which usually include an accompanying person. This results in loss of productivity for both the patient and the person who accompanies the patient. Time off work, travel costs and risk of complications such as endophthalmitis and retinal detachment can become a great burden. For instance, the cost of vitrectomy for endophthalmitis or retinal detachment can be quite expensive for many patients who already have challenges with the cost of intravitreal antiVEGF.[1,8,25] There is thus, need for other less invasive strategies to be approved for the management of these chronic conditions. The phase 11a clinical trial study of darapladib, a lipoprotein-associated phospholipase A_2 inhibitor in diabetic macula oedema, looks promising as an oral drug in the management of diabetic macula oedema.[26] If it finally secures approval, it may obviate the need for multiple injections and its attendant risk of complications.

In the eyes that switched antiVEGF, the switch was due to cost of ranibizumab in 1 (2.4%) eye and tachyphylaxis to ranibizumab in 1 (2.4%) eye after five injections of ranibizumab. There was subsequent improvement on the use of bevacizumab. Eyes with elevated intraocular pressure were managed with gutt timolol b.d., a topical intraocular pressure-lowering drug. This occurred after more than three injections in eyes that had raised intraocular pressure. There is a need for good patient selection on the type of antiVEGF to be utilised considering reports of increased risk of serious adverse events such as cardiovascular embolic events with use of bevacizumab.[21] It is recommended that intravitreal antiVEGF such as bevacizumab be included in the list of approved drugs accessible to patients on the National Health Insurance Scheme so that more persons can benefit. On the other hand, ranibizumab could be subsidised by the government to make it readily affordable similar to the subsidised cost of artemisinin-based combinations (ACTs) for the treatment of malaria.[27] This is important with the rising prevalence of diabetes mellitus in the country which could translate to an increase in diabetic-related eye complications such as diabetic macula oedema and PDR.[23,24]

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Conflicts of interest

There are no conflicts of interest.

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