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Audit of anti-vascular endothelial growth factor medication use in Ekiti, Southwestern Nigeria

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Abstract
Background: The use of anti-vascular endothelial growth factor (anti-VEGF) agents has increased in recent years. This is because of the increasing detection of vitreo-retinal disorders associated with vascular abnormalities. The indications vary from one location to another. Visual outcome following treatment with these agents also vary with disease severity and promptness of intervention.
Methodology: A prospective observational study was carried out on all patients with retinal disorders who had intravitreal injection between November 2013 and November 2019. Data on demographic characteristics, presenting visual acuity, diagnosis, type of anti-VEGF agent used, post-treatment visual acuity and complications were retrieved and entered into Statistical Package for Social Sciences (SPSS) version 25 and analysed for frequency and proportions.
Results: Seven hundred and thirty two patients with retinal pathologies were seen during the study period. A total of 251 intravitreal anti-VEGF agent injections were administered to 95 patients during the period under review. The mean age of the patients was 64.3 ±12.7 years. The number of injections per eye varied from 2 to 6 with an average of 2.6 per eye. Bevacizumab was the more commonly utilized anti-VEGF medication as it was used for 231(92%) injections. Wet age-related maculopathy was the commonest indication for intravitreal anti-VEGF agent in 61(24.3%) followed by diabetic macula edema in 55(21.9%) and retinal vein occlusion with macular edema in 54(21.5%) injections. Visual improvement was observed in 69 (72.6%) patients.
Conclusion: Anti-VEGF therapy was useful in the management of patients with retinal disorders. The need for multiple injections and the attendant cost still constitutes a major challenge in the use of these medications.

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Keywords: *Intravitreal, Retina, Bevacizumab, Ranibizumab, Retina disorders, Antivascular endothelial growth factor agents.*

Résumé
Contexte: L'utilisation d'agents anti-facteur de croissance endothélial vasculaire (anti-VEGF) a augmenté ces dernières années. Ceci est dû à la détection croissante des troubles vitréo-rétiniens associés auxanomalies. Les indications varient d'un endroit à l'autre. Le résultat visuel après le traitement avec ces agents varie également en fonction de la gravité de la maladie et de la rapidité de l'intervention.
Méthodologie: Une étude observationnelle prospective a été menée sur tous les patients atteints de rétine
troubles ayant subi une injection intravitréenne entre novembre 2013 et novembre 2019. Données sur les caractéristiques démographiques, présentant l'acuité visuelle, le diagnostic, le type de agent anti-VEGF utilisé, l'acuité visuelle post-traitement et les complications ont été récupérées et entré dans le progiciel statistique pour les sciences sociales (SPSS) version 25 et analysé pour fréquence et proportions.
Résultats: Sept cent trente-deux patients atteints de pathologies rétiniennes ont été vus au cours de la période d'étude. Au total, 251 injections d'agent anti-VEGF intravitréen ont été administrées à 95 patients au cours de la période sous revue. L'âge moyen des patients était de 64,3 ± 12,7 ans. Le nombre d'injections par œil variait de 2 à 6 avec une moyenne de 2,6 par œil. Le bévacizumab était le médicament anti-VEGF le plus couramment utilisé car il était utilisé pour 231 injections (92%). La maculopathie humide liée à l'âge était l'indication la plus courante de l'anti-VEGF intravitréen chez 61 (24,3%), suivie de l'œdème diabétique de la macula dans 55 (21,9%) et de l'occlusion veineuse rétinienne avec œdème maculaire dans 54 (21,5%) injections. Une amélioration visuelle a été observée chez 69 patients (72,6%).
Conclusion: La thérapie anti-VEGF a été utile dans la prise en charge des patients atteints de troubles rétiniens. La nécessité de multiples injections et le coût associé constituent toujours un défi majeur dans l'utilisation de ces médicaments.

Mots clés: *Intravitréen, Rétine, Bévacizumab, Ranibizumab, Troubles de la rétine, Agents de facteur de croissance endothélial anti-vasculaire*.

Introduction

The incidence of Vitreo-retinal disorders has increased within the last two decades [1,2]. This has been opined to be the result of the increasing prevalence of non-communicable disorders, [3] rising uptake of cataract surgical services [1] and increasing adult population among other reasons. Vascular endothelial growth factors (VEGF) play a central role in the development of several vitreo-retinal pathologies characterized by neovascularization and increased vascular permeability [4]. This has led to the increase in the use of anti-VEGF agents in recent years and has revolutionized the treatment of vitreo-retinal diseases [5] especially the proliferative retinopathies like diabetic retinopathy [6], retinal vascular occlusive disorders [7], sickle cell retinopathy [8], retinopathy of prematurity [9], neovascular glaucoma (NVG) [10], choroidal neovascularization [11] from varying causes and wet age related macular degeneration [12]. Their principal mechanism of action is by inducing regression of the abnormal vessels through inhibition of vascular endothelial growth factors with resultant reduction of vascular leakages and edema of the retina. The currently available anti-VEGF agents in Nigeria include Bevacizumab (Avastin®) , Ranibizumab (Lucentis®) and Aflibercept (Eyelea®). Some of the major challenges to the use of anti-VEGF medications in developing nations like Nigeria include cost [13-15] and need for multiple injections [14,15]. Bevacizumab is the only treatment available at a reduced cost to the patients. This is because of the possibility of drawing multiple doses from each vial of Bevacizumab contrary to Lucentis which comes as a single dose preparation. Some documented ocular complications of anti-VEGF medications include endophthalmitis, retinal tear, rhegmatogenous retinal detachment and uveitis. Potential systemic adverse effects of intravitreal anti-VEGF medications include thrombo-embolic events, myocardial infarction, stroke, hypertension, gastrointestinal perforations and kidney disease [16,17]. We carried out an audit of the use of anti-VEGF medications in our centre in order to know the common indications in our environment, response to treatment and complications encountered in the use.

Methodology

The Vitreo-retina clinic of the Ekiti State University Teaching Hospital Ado –Ekiti provides services to patients in Ekiti and its neighbouring states of Ondo, Kogi and Osun. This service was commenced in year 2013. All patients who received any of the anti-VEGF preparations up till November 2019 were prospectively enrolled into this study. All intravitreal injections were performed in the operating theatre under strict aseptic conditions. Records of demographic characteristics, indications, type of intravitreal injection used, visual acuity at presentation, best corrected visual acuity after doses of anti-VEGF as well as number of Snellen's visual acuity lines gained and complications were kept and entered into SPSS (statistical package for social sciences) version 25. Ethical approval was obtained from the ethics and research committee of our institution and study was conducted under the tenets of the Helsinki declaration. Data were analysed. Continuous variables were analysed for mean and standard deviations while categorical variables were analysed for frequency and proportions. Variables were compared and statistical significance inferred at P value <0.05.

Results

Twelve thousand nine hundred and eleven new patients were seen in the eye clinic during the period of study. Seven hundred and thirty two (5.7%) had retinal pathologies out of which 105(14.3%) required anti-VEGF treatment. A total of 95 patients constituting 13% of patients with retinal pathologies received 251 intravitreal anti-VEGF injections during the period of the study. The anti-VEGF medications used comprised 231 (92%) Bevacizumab and 20 (8%) Ranibizumab injections. Patients comprising 37 (38.9%) males and 58 (61.1%) females had the injections. The mean age of the patients was 64.3 ± 12.7 years. Age range was between 5 and 89 years. There were only 6 patients below the age of 51years (Table 1).

Table 1: Age and sex distribution of patients who received anti-VEGF therapy

Age group	Male n (%)	Female n (%)	Total n(%)
0-10	1 (1.1)	0	1(1.1)
11-20	1 (1.1)	0	1(1.1)
21-30	0	0	0
31-40	0	2 (2.1)	2(2.1)
41-50	2(2.1)	0	2(2.1)
51-60	10(10.5)	18 (18.9)	28(29.4)
61-70	10(10.5)	23 (24.2)	33(34.7)
>70	13 (13.7)	15 (15.8)	28(29.5)
Total	37 (38.9)	58 (61.1)	95(100)

The duration of symptoms before presentation ranged from 2 days to 3 years with a median of 4 months. The commonest indication for intravitreal anti-VEGF was wet Age Related Maculopathy (ARM) - 61(24.3%) injections followed by Diabetic Macular Edema (DME) - 55(21.9%), Retina Vascular Occlusion with macular edema (RVO) - 54(21.5%), and Idiopathic Polypoidal Choroidal Vasculopathy (IPCV) - 27(10.8%). Other indications were Neovascular Glaucoma (NVG) - 17(6.8%), Proliferative Diabetic Retinopathy (PDR) - 16(6.4%), Choroidal Neovascular Membrane (CNVM) - 6(2.4%), Parafoveal Telangiectasia (PFT) -5(1.9%), FEVR- 3(1.2%), Coats disease -3(1.2%), Vitreous hemorrhage -2 (0.8%) and Cystoid macula edema (CME) -2 (0.8%) . The highest number of injected doses per eye was six. An average of 2.6 injections was given per eye of patients. Seven patients received injection into both eyes at different times. The presenting visual acuity in the affected eye was less than 6/60 in 11(11.6%) of the patients. (Table 2)

Table 2: Presenting visual acuity in the affected eyes of patients

< 6/60	11(11.6%)
<6/18- 6/60	33(34.7%)
6/4-6/18	51(53.7%)

There was reduction of the pain, regression of rubeosis iridis and ciliary injection in all the patients with NVG. There was also resolution of retinal exudates in the patients with Coats disease. None of these however had any visual acuity improvement. Four cases of PDR and 3 cases of IPCV also had no improvement in vision.

Visual improvement varying from 1 Snellen's acuity line gain to 7-line gain were obtained in 69 patients. The 7-visual acuity line gain was recorded in one of the patients with RVO. There were 3 (1.2%) cases of endophthalmitis. All occurred within 48hours of intravitreal injections and were promptly diagnosed and appropriately managed. All patients had vitreous tap and injection of intravitreal antibiotics comprising Vancomycin and Ceftazidime One case was a known diabetic who was receiving the 5th dose for diabetic macular edema while the other 2 were receiving their 2nd and 3rd doses for wet ARM. One of the patients had vitrectomy. The other 2 patients developed complicated cataract and neovascular glaucoma. One of the patients who had Ranibizumab injection developed anterior uveitis which was managed with topical steroids and cycloplegic agent.

Discussion

Most of the patients were above 50 years of age. Our patients were mostly middle aged and elderly and this is expected because majority of the conditions treated in this study were diseases of these age groups. The mean age of the patients falls within the range reported in some other studies in Nigeria [13,14]. In Nepal it was reported that patients over 40years of age were mostly affected by vitreoretinal disorders which has become an increasingly important cause of visual impairment and blindness [18]. Bevacizumab was the more commonly used anti-VEGF in our centre. This agrees with findings in the other parts of Nigeria [5,14,19,20] and this has been found to be due to the higher cost of Ranibizumab in our country which is a developing country with lower affordability of this drug among patients.

The most common indication for anti-VEGF therapy in our centre was wet age related maculopathy. This accounted for 24.3% of the total indications. Wet ARM accounted for 17.1% of the indications in Ibadan and another centre in south-south Nigeria [14]. Lower values were reported in Kano (8%) [5] and Port-Harcourt (13.6%) [13] DME accounted for 21.9% of the cases requiring intavitreal injections and was the 2nd leading indication. In Northern Nigeria, diabetic macular edema was the commonest indication for patients receiving intravitreal anti-VEGF medications (42.5%) [5] similar to a centre in Benin city Nigeria (40.5%) [14] and the second most common indication in Port-Harcourt, Nigeria (22.63%) [13]. RVO which was the third leading indication in our study was the leading indication in Ibadan (19.4%) [20] and also a part of South-south Nigeria (32.1%) [13] and the second leading indication in a part of southwest Nigeria (30.6%) [19].

Diabetic maculopathy, retinal vascular occlusion and wet ARM remain the leading indications for intravitreal anti-VEGF medications in our country as revealed from the review of indications from the various geopolitical zones of our nation.

The duration of symptoms before presentation ranged from 2 days to as long as 3years with a median of 4 months. Delayed presentation has been a major challenge in the management of retinal disorders in developing nations like ours [21-24]. The presenting visual acuity varied in the patients at the time of presentation. About half of the patients presented with visual impairment. There was improvement in visual acuity after treatment in about three-quarters of the treated patients with a patient having up to 7-Snellen's acuity line gain (Retinal vein

occlusion) while others varied from 1 to 6 line gain. This drives home the importance of intravitreal anti-VEGF use in the treatment of retinal disorders. Some patients however had improvement in vascular abnormalities but without visual gain. This was the case in some patients with NVG, Coats disease, IPCV and some cases of PDR. This is similar to the experience of some other Nigerian authors [14,25]. It has also been observed that patients who present late and those with advanced level of disease may not record visual improvement after treatment [26]. Some patients had up to 6 injections per eye with an average of 2.6 injections in total. It has been reported that the need for repeat injections is the major challenge with the use of intravitreal anti-VEGF medications as most of the conditions require more than one dose to obtain significant sustained visual improvement.[13, 14, 20] The challenge of this is the cumulative cost to the patients as well as the risk of complications associated with repeated injections.

There were 3 cases of endophthalmitis. Endophthalmitis following intravitreal injections is a potentially devastating complication [27]. They occur mostly as a result of inoculation of microbes either through the needle tract from patients' ocular surfaces, aerosolized contaminants from care givers, contaminated needles, instruments, drug or drug vials. The exact source of infection in our patients could not be ascertained. However more strict measures for asepsis were put in place to avoid a recurrence of similar events.

In conclusion, the use of intravitreal anti-VEGF have contributed to the care of patients with retinal disorders. Some patients actually had significant visual acuity improvement while some others only had improvement in symptoms like pain, redness and perivascular exudates. The need for multiple injections and the attendant cost of these, still constitutes a major challenge in the use of these medications. Strict measures should be put in place to prevent the occurrence of endophthalmitis and when it occurs prompt diagnosis and appropriate treatment should be instituted.

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