Indications of Intravitreal Injection of Bevacizumab in a sample of Iraqi patients

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ABSTRACT

Background: Anti-vascular endothelial growth factors commonly used intravitreally for treatment of variable retinal disease worldwide, which help to regulate the upregulation of vascular endothelial growth factors due to ischemia or/and other retinal insult.

Objective: To review all cases of intravitreal bevacizumab given in the retinal unit of the Eye Specialty Private Hospital in Iraq from December 2015 to June 2016, pointing out the common indications.

Methods: A retrospective study including all cases of intravitreal injections of bevacizumab recorded at the Eye Specialty Private Hospital from December 2015 to June 2016 were retrieved. Age, sex, laterality, diagnosis and the indication for injection were recorded in the data sheet prepared for the study.. The indications for intravitreal injection of bevacizumab are classified into four groups: Group 1: Intravitreal injection for diabetic complications. Group 2: Intravitreal injection for retinal vein occlusion. Group 3: Intravitreal injection for choroidal neovascul-arization Group 4: Intravitreal injection for other retinal disease.

Results: A total of 306 patients underwent intravitreal injection of bevacizumab were enrolled in the study period. The most common indication was group 1 (intravitreal injection for diabetic complications [213 patients (69.6%)] followed by group 3 (choroidal neovascularization) [45 patients (14.7%)] and then group 2 (intravitreal injection for retinal vein occlusion) [42 patients (13.7%)] and lastly group 4 (intravitreal injection for other retinal disease) represent [6 patients (1.96%)].

Conclusion The most common indication for intravitreal bevacizumab was diabetic retino-pathy that need more care for early diagnosis and treatment of diabetic retinopathy and good screening programs to avoid complications.

Keywords: intravitreal, bevacizumab, retinal ischemia.

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INTRODUCTION

Vascular Endothelial Growth Factor (VEGF) is a homodimericglyco-protein which exists in four major isoforms (VEGF-121, -165, -189, -206). The different isoforms are characterized by their molecular weight, ability to bind to heparin and acidity. VEGF is a key regulator of physiological angiogenesis during embryogenesis and also has been implicated in pathological angiogenesis such as tumor growth or intraocular neovascular diseases [(1)]. The binding of VEGF to its receptors on retinal vascular endothelial cells initiates several intracellular signaling pathways resulting in proliferation, differentiation and migration of endothelial cells, in addition to that, VEGF acts as a potent vascular permeability factor resulting in increased fluid leakage in the blood vessel walls [(2)]. VEGF is a pluripotent growth factor that functions as an endothelial cell-specific mitogen and vasopermeability factor and through these mechanisms the VEGF plays a critical role in promoting angiogenesis and vascular leakage [(3)], therefore, the active role of VEGF by disrupting the intercellular tight junctions between the retinal endothelial cells lead to increases in the extracellular accumulation of fluid from the intravascular compartment, as well as, VEGF shows a role in mediating active intraocular neovascularization [(4)].

Bevacizumab

Bevacizumab is a full-length recombinant humanized monoclonal antibody with a molecular weight of 149 kDa [(5)]. It binds to and inhibits all isoforms of vascular endothelial growth factor A (VEGF-A). Bevacizumab is licensed for the intravenous administration for the treatment of malignant solid tumors and is available for off-label use in the treatment of Age-Related macular Degeneration

(AMD)-related Choroidal Neovascularization (CNV) [6].

Off-label, meaning it is not FDA approved for ocular use. It is most commonly used to treat CNV (in AMD and other diseases), diabetic macular edema (DME), and macular edema due to retinal vein occlusions [7].

Antivascular Endothelial Growth Factor in Diabetic Retinopathy

Diabetic retinopathy (DR) is considered the most frequent vascular disorder being detectable in about 40% of diabetic patients 40 years and older [8]. Population-based epidemiological studies have estimated that after 20 years, DR is being virtually universal and that after 30 years a proliferative DR is present in the 70% of patients with diabetes mellitus type 1 [9].

Elevations of VEGF levels in ocular fluids from human patients with tissue hypoxia and active neovascularization secondary to DR have been well documented [10]. There are a temporal correlation between VEGF elevations and active proliferative retinopathy evidencing the role of VEGF as a key mediator of intraocular neovascularization secondary to DR [11].

Antivascular Endothelial Growth Factor for Retinal Vein Occlusions

Retinal vein occlusion (RVO) is the second most common vascular retinal disease, following diabetic retinopathy [12].

RVO leads to reduced or missing outflow of venous blood, followed by retinal vascular leakage and macular edema due to an increased intracapillary pressure. Exudation of blood components causes segmental intraretinal hemorrhages with two occlusion types (ischemic and non-ischemic) can be distinguished [13].Acute RVO is associated with thrombotic changes in the vascular system, leading to intraluminal narrowing and venous congestion with increased venous pressure [14]. This intravascular alteration consecutively causes a breakdown of the blood- retina barrier with extravasation and typical, flame-shaped intraretinal bleedings. The barrier defect results from a primarily unobstructed arterial blood flow and simultaneously reduced venous outflow. In the case of Central Retinal Vein Occlusion (CRVO) or Branch Retinal Vein Occlusion (BRVO) with affection of the central retina, stasis with hypertension also causes the typical extracellular macular edema: local ischemia with an expression of VEGF and related cytokines and the particular anatomic structure of the macular retina play an important role in its genesis.

Anti-VEGF treatment is effective in the treatment of the ischemic complications of RVO, reducing the risk of neovascularization and rubeosisiridis, and lowering intraocular pressure in neovascular glaucoma [15].

Antivascular Endothelial Growth Factors in Age-Related Macular Degeneration

Age-related macular degeneration (AMD) is the leading cause of irreversible vision loss in adults aged over 50 years in developed countries [16].

AMD is a term used to summarize different pathological age-related changes of the macula, namely drusenmaculopathy, geographic atrophy (dry form) and choroidal neovascularization (CNV) (wet or neovascular form). AMD is characterized by a progressive loss of central vision resulting from degenerative and neovascular changes in the macula [17].

CNV membranes obtained from patients with AMD contain VEGF as shown in immunohistochemical studies [18]. Analysis of different retinal cell types in post-mortem eyes with AMD revealed higher VEGF levels in the retinal pigment epithelial (RPE) cell layer and the outer nuclear layer than in healthy control eyes [19]. The ability of RPE cells to secrete VEGF has also been shown in invitro experiments when cells are cultured under hypoxic conditions [20]. Furthermore, significantly increased levels of VEGF have been found in the aqueous humor of human eyes with neovascular AMD as compared to healthy controls [21].

PM is defined as an eye having a minimum refractive error of –6 D with an axial length >26 mm, associated with degenerative changes of the retina, choroid and sclera at the posterior segment [22].

Choroidal neovascularization (CNV) is the most common vision-threatening macular complication in PM, being detectable in 4–11% of the eyes affected [23].

In PM, mechanical tissue strain caused by axial length elongation may lead to the development of choroidal ischemia followed by atrophy of the RPE and overlying retina and subsequent vascular endothelial growth factor (VEGF) release [24]. Intravitreal injections of anti-VEGF molecules, such as bevacizumab and ranibizumab, are able to inhibit all the VEGF isoforms and have shown promise in the treatment of myopic CNV [25].

METHOD

A retrospective descriptive study conducted in Eye Specialty Private Hospital in Iraq between December 2015 to June 2016 in which the files of the patients admitted for intravitreal injection of Bevacizumab retrieved and recorded the demographic factors for each patient, including sex, age and laterality (Right or left or bilateral) and then recorded the diagnosis and the specific indication of the intraviteal injection of Bevacizumab in each patient.

Method of injection: the injection was done in a sterile operative room using topical tetracaine and standard disinfection with 5%povidone iodine and 1.25mg of bevacizumab (Avastin) in 0.05ml was given 4mm behind the limbus and topical antibiotic moxifloxacin four times per day was given post injection for one week for all patients.

The indications for intravitreal injection of bevacizumab are classified into four groups:

1- Group 1: intravitreal injection for diabetic complications.
2- Group 2: intravitreal injection for retinal vein occlusion.
3- Group 3: intravitreal injection for choroidal neovascularization
4- Group 4: intravitreal injection for other retinal disease.

Then each of these four groups is subdivided according to the specific indication of intravitreal bevacizumab.

All these were recorded in a prepared paper and the results were compared in tables and analyzed using proportion and percentages.

RESULTS

The demographic data of these 306 patients show that the males were 159 patients representing 52% while the females were 147 patients representing 48%.

The laterality of the injected eyes in study show that right eye was in 132 patients representing 43.14% while left eye was in 96 patients representing 31.37% while bilateral eye injected was in 78 patients representing 25.49% of patients.

The mean of age of patients was 58.8 years and the youngest patient was 17 years old and the indication was choroidal neovascularization due to choroidal osteoma, while the oldest patient was 81 years old and the indication was wet aged related macular degeneration with choroidal neovascularization. The result shows that the most common indication was group 1 in which the intravitreal injection was indicated for diabetic complications in 213 patients then followed by group 3 which was the choroidal neovascularization in 45 (14.71%) patients then group 2 which was the retinal vein occlusion in 42 (13.73) patients while group 4 which includes other retinal disease in only 6 (1.96%) patients. The specific indication for each group shows the following results: **Group 1** (intravitrealbevacizumab for diabetic complications) show that the main indication was diabetic macular edema in 141 patients then followed by vitreous hemorrhage in 42 patients and then persistent neovascularization of disc (NVD) or elsewhere (NVE) in proliferative diabetic retinopathy in 21 patients and lastly neovascular glaucoma in 9 patients (table 4). **Group 2** (retinal vein occlusion) shows that central retinal vein occlusion (CRVO) was the indication in 25 patients and the branch retinal vein occlusion (BRVO) was the indication in 17 patients. **Group 3** (choroidal neovascularization) show that wet aged related macular degeneration(AMD) was the main cause in 26 patients (57.8%) followed by myopia in 14 patients (31.1%) and others in 5 patients (11.1%). The other causes of CNV were 2 angioedstreak and one from each of choroidalosteoma, punctate inner choroiditis and

tuberculouschoroidatis. **Group 4** was the other indications of intravitreal bevacizumab and show that the main indication was central serous chorioretinopathy (CSCR) in 5 patients and only one patient with a circumscribed choroidal hemangioma.

DISCUSSION

The results show clearly that diabetic retinopathy was the main indication for intravitrealbevacizumab in 69.6% of the cases and this may be due to that diabetic is common in Iraqi's population with prevelance of diabetic in Iraq in 2010 about 10.2% of the population [(26)] to 19.7% in 2012 [(27)] with no screening programs for diabetic complications.

The main specific indications for diabetic patients were diabetic macular oedema in 66.2% while others as proliferative diabetic retinopathy represent 33.8% of total diabetic patients and this may be caused by that the diabetic macular oedema is the most common symptomatic presentation of diabetic patients and usually patients presented when they are symptomatic with deficient in screening programs in Iraq.

In comparison to other studies as Sanaullah Jan [(28)] which shows also that diabetic retinopathy was the main indications in 59.6%, and Ahmed S AL-Hinai [29] show the diabetic was also the main indication in 50.9% while T.S. Oluleye [(30)] show that the diabetic retinopathy was the indication in only 22% which was the third indications after vein occlusion and aged related macular degeneration and the most likely cause for such difference is that T.S, Oluleye study conducted in Nigeria for African and diabetic mellitus is less common in Africans [31].

The second indication was choroidal neovascularisation (with variable causes) in 14.7% (including wet AMD in 8.5%, myopic CNV in 4.6%, and others in 1.6%), also the choroidal neovascularization represent the 2nd cause in T.S. Olueye study [(30)] representing 23% and the second in Al-Hinai study [29] in 24.3% and the 3rd in Sanullah study[28] representing 29% while aged related AMD was the main cause in LiXHu study [32] which may be due to the long life of Chines and the race difference.

The 3rd indications in our study was retinal vein occlusion (including both central and branch retinal vein occlusion), in 13.7% of indications (CRVO was 8.16% while BRVO was 5.55%),also in Sanullah [28] show that retinal vein occlusion was the second cause after diabetic retinopathy and indicated in 28.64% including CRVO in 17.64% and BRVO in 11% while Al-Hinai study[(29)] show that vein occlusion was the third in 11.5% ,but in T.S.Olueye study [30] show that retinal vein occlusion was the main indication in 36% including CRVO in 26% and BRVO in 10% of cases and this might be due to that the hypertension which is the main risk factor for retinal vein occlusion is the most common systemic disease in African [(31)]

COCLUSION

The most common indication for intravitreal bevacizumab was diabetic retinopathy that need more care for early diagnosis and treatment of diabetic retinopathy and good screening programs to avoid complications.

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