

Profile of Patients Treated with Intravitreal Anti-Vascular Endothelial Growth Factor Injections in Bhutan

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Purpose: Ocular vascular diseases are common causes of visual impairment and blindness, for which anti-vascular endothelial growth factor (anti-VEGF) is the first-line therapy. Current study describes the profile of patients receiving intravitreal anti-VEGF injections (IVI), and gender variation in Bhutan. The study was designed to inform national health policy.

Study Design: Retrospective cross-sectional study.

Methods: We reviewed the surgical registers of the vitreoretinal (VR) units across Bhutan over three years. Patient demography, clinical findings, diagnostic tests performed, and diagnoses or indications for IVI were logged. A descriptive analysis was performed.

Results: Despite limited availability of anti-VEGF, a total of 381 patients received IVI in operating theatres as mandated by the national guidelines. The majority of patients were males (230, 60.4%, $p = 0.004$). The mean age was 65.2 ± 13.5 years (range 13 years to 90 years), and a median of 69 years. The majority of the treated eyes (117, 30.7%) had BCVA $<3/60$ to light perception (PL), and another 51 eyes (13.4%) had $<6/60$ to $3/60$. The most common indication for IVI was neovascular age-related macular degeneration (nAMD) (168 cases, 42.2%), followed by retinal vein occlusion (RVO) (132 cases, 34.6%), diabetic macular oedema (DMO) and retinopathy (DR) (50 cases, 13.1%), and myopic choroidal neovascular membrane (11 cases, 0.03%).

Conclusion: Limited human resources for managing VR diseases in Bhutan are compounded by economic and geographic challenges. With increasing VR diseases such as nAMD and myopia and complications of systemic diseases such as DR, DMO and RVO, there is a need to improve VR services. Currently, anti-VEGF is procured only for a pooled patients requiring IVI, and patients are lost due to longer waiting periods. Bhutan needs to assess if females are reporting less or are not receiving treatment due to cultural barriers and social stigma.

Keywords: anti-VEGF, Bhutan retinal diseases, diabetic macular oedema, intravitreal injection, neovascular AMD, retinal vein occlusion

Introduction

Vascular diseases such as neovascular age-related macular degeneration (nAMD), diabetic macular oedema (DMO) and diabetic retinopathy (DR), and retinal vein occlusion (RVO) are the major causes of visual impairment and loss of central vision throughout the world.¹ Previously refractory cases were treated with intravitreal injection of the corticosteroids triamcinolone acetonide and dexamethasone.² However, these agents were associated with multiple ocular side effects such as cataract and intraocular pressure spikes.² The pathogeneses of many such diseases is multifactorial. Both inflammatory mediators and vasogenic mediators, such as vascular endothelial growth factors (VEGFs), are activated and create disruption of the retina.^{3,4} As the inner blood-retinal barrier breaks down, fluids and proteins leak into the retina. This leakage creates oedema of the macula and thereby decreases the retinal transparency.²⁻⁵ To counter this effect, anti-VEGFs came into clinical use with much promise. It earned the name of a one day wonder drug for the fast resolution of DMO following intravitreal injection of ranibizumab.⁶ Among anti-

VEGFs, bevacizumab (AVASTIN, Genentech, Inc.,) was the first agent to be used off-label in 2005. Subsequently, multiple anti-VEGF agents such as pegaptanib sodium (Eyestech/OSI Pharmaceuticals, New York, NY, USA), ranibizumab (Lucentis™, Genentech, Inc., South San Francisco, CA, USA and Novartis Pharma AG, Basel, Switzerland), aflibercept (VEGF-trap eye, Eylea™, Regeneron Pharmaceuticals, Inc., and Bayer Pharma AG, Berlin, Germany), brolucizumab (Beovu™, Novartis Pharma AG, Basel, Switzerland), and faricimab have been developed for the management of various ocular vascular diseases.^{7–11} Although all these agents are used, only pegaptanib, ranibizumab, brolucizumab, aflibercept, and faricimab are approved for use in ophthalmological disorders.^{11–13} Ranibizumab, bevacizumab and brolucizumab specifically target VEGF-A activity, while aflibercept has a broader spectrum of action – VEGF-A, as well as other VEGF family ligands such as VEGF-B, placental growth factor-1 (PlGF-1) and placental growth factor-2 (PlGF-2).^{14,15} Faricimab is a new and the first bispecific monoclonal antibody for intravitreal use neutralising both VEGF and angiopoietin-2/tie-2/ pathway.¹⁶ Due to the prolonged activity, faricimab allows extended intervals between injections of up to three or four months in nAMD and DMO patients, which can be a significant benefit for patients and are an alternative to implanted drug delivery systems.^{17,18} We have previously reported on the surgical management of vitreoretinal (VR) diseases in Bhutan that included 11 classes of major VR surgery, cases who underwent examination under anaesthesia, and a summary of anti-VEGF injections.¹⁹ Currently, regular VR services, and so the IVI, in Bhutan are provided only at the Jigme Dorji Wangchuck (JDW) national referral hospital located in Thimphu, and periodically in the ERRH and CRRH during visits by the retinal specialist. This provides unbalanced services within the country- that is the eastern and central regions have less accessibility. Secondly, anti-VEGFs are not readily available in any hospitals or pharmacy shops in Bhutan. These must be procured as special drugs for specific patients, which takes time and delay the treatment. The aim of the current study is to detail the profile of patients treated with intravitreal anti-VEGFs injections (IVI) for ophthalmological diseases in Bhutan, and review the diagnostic testing done to justify that treatment. The study was designed to inform policy makers in Bhutan and other developing countries in the region about its significance.

Methods

Study Design and Ethics

This was a retrospective, case series study approved by the Research Ethics Board of Health (REBH) (REBH/Approval/2016/083), Ministry of Health, Royal Government of Bhutan, Thimphu, Bhutan. This study adhered to the principles of the Declaration of Helsinki. Informed consent was waived by REBH because this retrospective study collected only de-identified data.

Setting and Participants

In Bhutan the JDW national referral hospital is the only apex national referral and teaching hospital with subspecialty eye-care services. Regular VR surgical and interventional services in the country are provided only at the JDW national referral hospital. All such VR patients across the country are referred there for management. Occasionally the VR surgeon visits Eastern Regional Referral Hospital (ERRH) in Mongar and Central Regional Referral Hospital (CRRH) in Gelephu when the treatment is provided there. The sites for the current study included JDW national referral hospital (in the main), and ERRH and CRRH. All the patients who received IVI in the operation theatres of the JDW national referral hospital, ERRH and CRRH over three years (01 May 2013 until 30 April 2016) were included. The national guidelines mandate that IVI should be administered only in operating theatres with proper aseptic measures. The demographic characteristics of patients receiving the IVI and the VR disease pattern represent the entire citizenry.

Clinical Examination and Data Collection

The clinical workup in the out-patient department (OPD) included taking detailed medical histories of presenting symptoms and diseases, associated systemic diseases, and prior surgical or laser interventions done. Best corrected

visual acuity (BCVA) at presentation was measured using a Snellen chart, and Tumbling E for illiterate patients. Intraocular pressure was measured by Goldmann applanation tonometry or an iCare tonometer, and the anterior and posterior segments were examined under slit-lamp biomicroscopy (BM 900, Haag-Streit, Switzerland), and 90D biomicroscopy and indirect ophthalmoscope (Model 125, Welch Allyn, USA). Macular and retinal nerve fibre (RNFL) scans were measured using a Spectral Domain Optical Coherence Tomography (OCT) (Cirrus-HD 4000, Carl Zeiss Germany). Fundus photographs were taken by a VISUCAM-524 (Carl Zeiss, Germany). Fundus fluorescein angiograms (FFA) were performed when needed to confirm occult diseases. A B-ultra sonogram scan was done when necessary (Sonomed Escalon, Model: VUPAD A/B, USA).

For the current study, the patient registers maintained in the VR operational theatre were reviewed. When necessary, the patient registers maintained by the out-patient department of the VR unit and patient case files were sought for additional data. The data collected included demographic information such as age and gender, residential settings, BCVA, diagnostic tests performed, and diagnoses or indications for IVI.

Diagnostic Criteria

OCT was performed universally on all cases who have received IVI. This was an appropriate diagnostic tool to diagnose nAMD, RVO, DMO, myopic choroidal neovascular membrane (mCNVM), cystoid macular oedema, central serous chorioretinopathy and vitreomacular tractions. Polypoidal choroidal vasculopathy (PCV) is best diagnosed via its characteristic nodular dilatations arising from neovascular networks that ramify mainly in the subretinal pigment epithelial space on indocyanine green angiography.^{20,21} However, in the current study the PCV was mainly diagnosed based on the OCT findings such as sharp-peaked retinal pigment epithelial detachment (RPED), subretinal pigment detachment ring-like lesion, multilobular RPED, double-layer sign or shallow, irregular retinal pigment epithelium elevation, thick choroid with dilated Haller's layer vessels, and predominance of subretinal fluid. Other suggestive findings with the coloured fundus photographs were extensive subretinal haemorrhage, and orange nodules.²² The FFA was performed only in difficult or occult cases.

Anti-VEGF Injections

The patients needing IVI were pooled for a scheduled injection day, when a 4 mL vial containing 100 mg bevacizumab was procured and dosing formulation done at 1.25 mg per 0.05 mL, or 2.5 mg per 0.1 mL in tuberculin syringes with 30-gauge (G) needles. So, a single vial would benefit 20 to 25 pooled patients. This approach was practised for economic reasons. The anti-VEGF dosing formulations and intravitreal injections were performed under aseptic measures in the operating theatres. Injections into the bilateral eyes in the same sitting was not performed to avoid complications, notably endophthalmitis.

Statistical Analysis

The data were analysed using MATLAB (2020b, The MathWorks, Natick, MA), including tabulating and checking frequencies of cases and creating figures and tables. Comparisons of the expected and observed frequency of gender used Chi-squared tests.

Results

Demography

A total of 381 patients received IVI over the study period. The majority of patients (230, 60.4%) were males ($p = 0.004$). The mean age at presentation was 65.2 ± 13.5 years (ranging from 13 to 90 years), modal year of 70 years, and median 69 years. [Figure 1](#) shows that the males outnumbered females after about 60 years of age.

Visual Acuity

Majority of the eyes receiving IVI (117 cases, 30.7) had BCVA of less than 3/60 to only perception of light (PL), labelled as blindness according to World Health Organisation (WHO) classification of visual impairment.²³ In 85 eyes, the BCVA

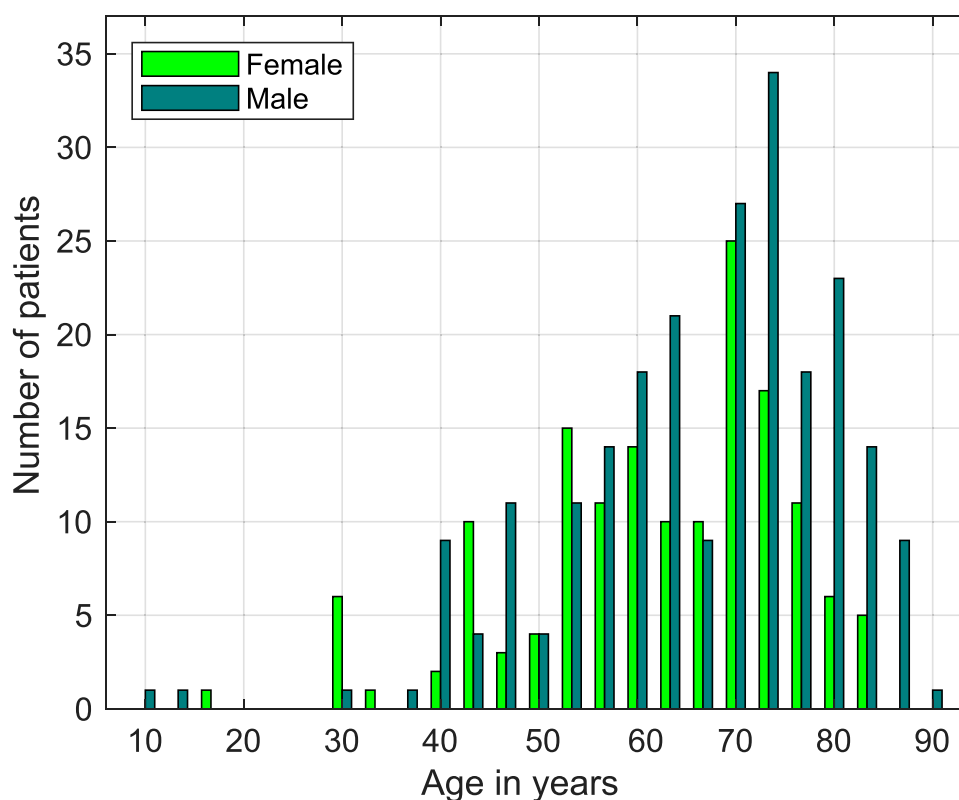


Figure 1 Age distribution of the male and female patients in years. It shows male predominance after 60 years of age.

was not assessable. This included patients who were not cooperative in measuring BCVA, people with special needs and in some cases a lack of data. The details of the BCVA are shown in [Table 1](#).

Intravitreal Anti-VEGF Injections

nAMD was the most common indication for the IVI accounting for 168 cases (44.2%). This was followed by RVO in 132 cases (34.6%). Within the RVO subgroup, branch RVO (BRVO) was the most common subgroup with 70 cases (53.0%), followed by central RVO (CRVO) in 55 cases (41.7%), and hemi-central RVO (HCRVO) in 7 cases (5.3%). Only 50 cases (13.1%) receiving IVI had DR or DMO, 11 cases (0.03%) had mCNVM, and 6 cases (0.02%) had PCV. Other indications for anti-VEGF injections are shown in [Table 2](#).

Table 1 Best Corrected Visual Acuity at Presentation

Visual Acuity Based on WHO Classification of Blindness	n, Patients	%
≥ 6/18	21	5.5
< 6/18–6/60	107	28.1
< 6/60–3/60	51	13.4
< 3/60 – Perception of Light (PL)	117	30.7
Not Assessable (NA)	85	22.3
No Perception of Light (NPL)	0	0
Total	381	100

Table 2 Indications of Anti-VEGF Injection

Diseases	n, Patients	%
Neovascular AMD	168	44.2
Retinal Vein Occlusion	132	34.6
Diabetic Macular Oedema	50	13.1
Myopic CNVM (mCNVM)	11	0.03
Polypoidal Choroidal Vasculopathy (PCV)	6	0.02
Neovascular Glaucoma	4	0.01
Others*	10	0.03
Total	381	100.0

Notes: *Others include Cystoid macular oedema, Central serous chorioretinopathy and Vitreomacular traction.

Abbreviations: AMD, Age-related macular degeneration; CNVM, Choroidal neovascular membrane.

Discussion

To summarise the vital results, male preponderance was significant ($p = 0.004$), 30.7% of the study eyes were legally blind, 13.4% had severe visual impairment (VI) and 28.1% had moderate VI as per the WHO classification of VI.²³ nAMD was the most common indication for IVI, followed by RVO, DMO/DR, mCNVM, PCV, and neovascular glaucoma.

A study on the pattern and presentation of VR diseases in Bhutan in the same period reported that majority of patients were males, 1544/2913.²⁴ Similar results were found with the surgical management of VR diseases,¹⁹ and neuro-ophthalmological cases presenting to the VR clinics reported earlier.²⁵ A meta-analysis of eye surgical services in developing countries has shown that females receive fewer surgical or interventional services than the males,²⁶ as was seen with receiving IVI in the current study.

The national VR unit was established in Bhutan only in early 2012.²⁷ Prior to that, VR cases were referred to India or Nepal for treatment. However, most patients were reluctant to go out of the country for the treatment because of the communication gap in foreign lands. This partly encouraged some patients to seek to traditional or indigenous methods of healing. Some even sought local healers or witchcraft practice with false hope, resulting in irreversible loss of vision and even loss of eyes, while most cases did not receive any treatment and accepted it as their destiny. The global prevalence of AMD and gender disparity reported that AMD is more common among females, and they were being more heavily impacted with visual impairment and disability.²⁸ This is attributed to higher level of lipid and apolipoprotein in females.²⁹ However, in Bhutan we found that the number of females reporting as well as receiving IVI was significantly lower. The concerned authorities must investigate if the females are not reporting and coming forward for treatment because of cultural barriers and social stigma. The hidden higher prevalence of AMD among females, if there is any, must be addressed. A contrasting finding is that the female life expectancy (74.4 years) is longer than that of males (72.0 years) in Bhutan,³⁰ indicating that there should be more females than males in the elderly group. But in our study, there are more males reporting and receiving IVI. This further supports the need for a population-based survey or community screening to see if there are more females with retinal vascular diseases not reporting for treatment.

AMD was reported as the fourth most common VR disease in Bhutan, next to hypertensive retinopathy, refractive errors referred for retinal evaluation, and DR or clinically significant macular oedema (CSMO).²⁴ So, it is apparent that IVI was most commonly administered to nAMD cases. Another study on the profile of AMD in Bhutan reported that half of AMD cases were in advanced stages needing treatment, and one-third of those with advanced diseases already had disciform scar at their first presentation.³¹ Similarly, the drop-out rates for follow-up are high. The reasons for such late presentation and poor follow-up or medical adherence are many. First, lack of knowledge of the public on diseases and

treatment options available. Secondly, lack of accessibility to services – the regular VR service is provided only at the JDW national referral hospital located in the north-west part of the country and the patients from the central and eastern regions have to travel all the way against difficult terrain, poor road conditions and transport limitations to avail the treatment. Other reasons include poor referral systems, communication gaps between the peripheral and referral hospitals, negative influence of the local healers, and long waiting periods for anti-VEGF. In India too, nAMD was the most common indication for anti-VEGF injections, followed by DMO, RVO and mCNVM.³² On contrary, RVO was the most common indication in Nigeria, followed by DMO, and proliferative DR.³³

Co-existent hypertension and diabetes mellitus, the complications of which result to many ocular vascular diseases, is common in Bhutan.³⁴ The WHO has reported that 28% of total mortality in Bhutan was due to cardiovascular disease, and another 17% due to other non-communicable diseases.³⁵ For these morbidities, the risk factors include harmful use of alcohol, high salt intake, unhealthy diet, physical inactivity, and tobacco use.³⁶ Considering hypertensive retinopathy and diabetes mellitus as risk factors for RVO,³⁷ and both being common among the Bhutanese population, RVO cases received the second highest number of IVI. Similarly, RVO cases also were the second most common indication to receive retinal laser therapy in the country, second only to DR/DMO.³⁸ Here only 50 DMO cases (13.1% of all IVI) received IVI in the study population although DR and DMO was the third most common VR disease in Bhutan, and second most common in a similar study conducted in Nepal.³⁹ This is because only the central DMO, and DMO nasal to the fovea, were treated with IVI. Very severe DR not responding to panretinal photocoagulation (PRP) were also first treated with the IVI to reduce retinal oedema after which PRP was performed successfully. Commonly, DR cases were managed with PRP to such a rate that PRP was the most common type of retinal laser therapy performed in Bhutan.³⁸ Off-centre DMO (except DMO nasal to the fovea) was managed with focal, grid or modified grid laser therapies. It is reported that 25.6% of diabetes patients presented 5–10 years after diagnosis, 19.9% after 10–20 years and 2.3% presented only after 20 years for the first time for their eye/retinal check-up. The study also reported that 12.5% of DR cases had proliferative DR at their first presentation for retinal evaluation.⁴⁰

Although moderate to high myopic cases referred for retinal evaluation was the second most common reason for attending VR clinics in Bhutan, next to hypertensive retinopathy,²⁴ only a small percentage of anti-VEGF injections was given to cases of myopic CNVM (mCNVM). This is because the prevalence of mCNVM among the study group of myopia was only 0.4%.⁴¹ Other studies have reported that mCNVM occurs in approximately 5–10% of highly myopic patients, and 0.04–0.05% of the general population.^{42,43} PCV is common chorioretinal disorder among the Asian populations.⁴⁴ It has been estimated that up to 50% of nAMD cases among the Asians are of the PCV subtype, whereas this proportion among the white populations is estimated to range between 10% and 20%.^{45,46} In Bhutan, 8.1% of advanced AMD were comprised of PCV, and among them 73.7% of them (14/19 cases) were younger than 50 years.³¹ This is highly concerning for a country like Bhutan with a small reserve of working age population and limited human resources. Yet only 6 of 19 PCV cases received IVI, that is, 68.4% of them did not receive treatment. Sadly, they may turn up later with worsened disease not being amenable to the treatment. With these concerns, it was also deliberated that community screening of AMD along with PCV cases might be helpful in Bhutan.⁴⁷ However, until today, it seems there are no large-scale screening programs for AMD like those that exist for DR and retinopathy of prematurity.

We avoided bilateral IVI in the same sitting because there have been incidences of bilateral endophthalmitis following bilateral anti-VEGF injections.⁴⁸ It is also reported that the cumulative rate of infective endophthalmitis increases with the number of IVI.⁴⁹ Therefore, it is a wise step to inject fellow eye a day later than to have bilateral IVI and devastating bilateral endophthalmitis. We also practise giving IVI in the operating theatres because multi-centre study has proven lower endophthalmitis rate with this approach than giving IVI in the out-patient department.⁵⁰

It is common that younger patients have poor medical adherence.⁵¹ So the treating physicians and the healthcare professionals have to give extra effort to teach them about diseases and ensure the importance of timely medications. Additionally, the general population in Bhutan are illiterate and have poor knowledge of diseases or treatment options. Although health education is provided at all levels of healthcare centres in Bhutan there is a need to improve the program. It may be effective to disseminate health advocacy information in the local languages or dialects so the common people are able to understand the message. Involving local leaders and local government bodies may prove more effective. Broadcasting the materials through the national television channels, or even targeting the younger

generations through the mobile phone applications they use, may be helpful. For regionally balanced delivery of the services, Bhutan needs to extend its regular VR services to the ERRH and CRRH, or at least improve community screening and effective referral system.

New approaches to screening and management of the AMD cases may allow for expansion of high-quality convenient care and increasing patient coverage.⁵² The public transport system in Bhutan is challenged by difficult terrain, poor quality of roads and infrequent services. Additionally, it is interrupted during the monsoon season by landslides, falling boulders and swollen rivers and streams, and by snowfall during winter. Therefore, proper patient transport is a must for successful health program. Bhutan also needs to, tactfully, lower the influence of local healers and encourage people to seek proper medical advice. Although Bhutan still struggles to provide basic medical provision and low-cost treatment, it may be worth identifying patients with poor medical adherence and provide longer acting anti-VEGF treatment such as faricimab, which can extend the intervals between successive injections to 4 to 6 months.^{17,18}

This study is limited by being a retrospective study and having a small number of subjects. Visual acuity was not assessable in 85 patients. Being a cross-sectional study, we also did not follow up the patients to understand the outcome of the anti-VEGF treatment. We have considered the BCVA only in the treated eyes, not the fellow eyes, so we could not report if the patients were legally blind. We have a plan to conduct a prospective study overcoming all the limitations.

Conclusions

Currently a regular VR service is provided only at the JDW national referral hospital, so there is high risk that the patients from the eastern and central regions miss out on treatment and regular follow up. So regular services need to be expanded to the eastern and central regional referral hospitals. Secondly, VR diseases secondary to systemic diseases such as RVO, DR and DMO are common. There is an urgent need for strategic control and management of non-communicable diseases and prevent blindness and visual impairment from their complications. Anti-VEGF should be readily available to reduce waiting periods to reduce losing patients. Additionally, there is a need to investigate if females are not reporting for treatment because of cultural barriers and other social stigma.

Data Sharing Statement

The data and material are available from the corresponding author.

Ethical Approval, Informed Consent and Consent for Publication

The study was approved by the Research Ethics Board of Health (REBH) (REBH/Approval/2016/083), Ministry of Health, Royal Government of Bhutan, and was conducted as per the REBH guidelines and tenets of the Declaration of Helsinki. The consent was waived by REBH as the retrospective study collected only the de-identified data.

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Disclosure

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