Ten Years of Intravitreal Bevacizumab : Systemic and Ocular Safety Review at Tertiary Care Centre.

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Introduction :

The first Anti-VEGF which was approved and available for clinical use was Bevacizumab, which was first marketed in 2004 for treatment of colon carcinoma.[1] Later it was realized that this treatment improved the wet Age Related Macular Degeneration (ARMD) in those who had both the diseases and thus systemic Bevacizumab was used for some time for the treatment of wet ARMD.[2] Soon after, ophthalmologists began injecting bevacizumab directly into the vitreous cavity as an off-label use in the treatment of wet AMD.[3] Since then intravitreal Bevacizumab has been used in various other retinal disorders and is now as an established treatment option for wet ARMD, macular edema due to retinal vein occlusion, diabetic retinopathy, uveitis and other diseases. [4]

Safety of intravitreal Bevacizumab has been challenged as it has not passed the rigorous approval process of USFDA for use as an intravitreal injection for the treatment of retinal diseases. However numerous case series and clinical trials over the period of time have established its safety as an intravitreal injection except for few adverse events as reported in literature.[5] Bevacizumab may continue to be a choice for patients and ophthalmologists in coming future because of being equally safe, effective and very cost effective than the contemporary molecules in spite of being "Unlicenced" for ophthalmic use till the exorbitant prices of the "Approved" anti-VEGF molecules are brought down at par to the dosing of Bevacizumab.[6]

Here we are reporting the retrospective analysis of safety of intravitreal anti-VEGF in cases which received intravitreal Bevacizumab for various indications in our institute during the course of 10 years.

Materials and Methods :

Medical records of consecutive subjects who had received intravitreal anti-VEGF during last 10 years for various indications and had completed at least6 weeks of post intervention follow up were retrieved and analysed for the adverse events and comorbid conditions. The institutional ethical committee was intimated for the same and the confidentiality of the subjects was maintained as per the declaration of Helsinki.

As per the protocol, the subjects who require intravitreal anti-VEGF were registered for the day care procedure and the procedure was done in an operation room under aseptic conditions. A fresh vial of Bevacizumab (Inj. Avastin®100mg/4 ml) was utilized for all the subjects planned on a single day and the injection was withdrawn separately for each subject using an insulin syringe with 30g needle. The subjects receivedo.05ml injection Bevacizumab (25mg/ml) + 0.05ml injection Dexamethasone (4mg/ml) under topical anesthesia with aseptic precautions after paracentesis (approximately 0.1ml) done through a self-sealing needle track at the limbus. After all the subjects planned for that day had received the injection, the vial was discarded. The subjects were prescribed eye drop moxifloxacin 4 times a day starting immediately after the procedure as no eye patching was done. The subjects were evaluate on day 1, 14, and at 6 weeks for the therapeutic benefits and any adverse events.

The variables retrieved and included in the study included the demographic details, clinical details regarding the eye condition and the systemic comorbidities as mentioned in the table

1. The details of adverse events post intervention were retrieved for a period of follow up till 6 weeks. The adverse events related to eye conditions were grouped as expected/mild (Non sight threatening) and severe (Sight threatening).

Results :

The average age of the 773 subjects included in the study was 53.1 years (Range 0.1-91 years, Median 55, SD 15.4) and there were 227 (29.4%) female vs 546 (70.6%) males. The premorbid conditions which were seen in the available records are described in the.

The majority of premorbid systemic condition werediabetes mellitus, hypertension and insomnia. Ocular comorbidity was seen in form of cataract in 271 (35.00%) subjects. There were 175 (22.7%) individuals with history of tobacco use in any form past or present.

Looking at the indications of the intravitreal anti-VEGF the most common was diabetic retinopathy (NPDR, n=183, 23.67% and PDR, n=171, 22.12%). The indication in NPDR was macular edema as seen on Optical Coherence Tomography and in PDR it was a preparatory step when proceeding for pars plana vitrectomy. This procedure was done in 115 (14.87%) and 93 (12.3%) subjects for retinal vein occlusion associated macular edema and wet ARMD respectively. Three eyes of neonates with ROP received intravitreal anti-VEGF for aggressive posterior ROP and rigidity of the pupils.

Table 1

Summary of demographics and baseline characteristics of the study population (n=22).								
Characteristic	Value							773
Age (years)	77 (61-90)		53.1 (0.1-91)	55	15.4			
Females	15 (68.2)		227					
Tobacco usea								
Never used tobacco		8	281	36.36364				
Ever used tobacco		2	70	9.090909				
Current tobacco user		3	105	13.63636				
Information not available		9	316	40.90909				
			773					
Medical history								
Cataract		20	271	35.00				
Arterial hypertension			217	28.07				
Insomnia		6	211	27.27				
Hypercholesterolemia		5	176	22.73				
Prostatic benign hyperplasia		5	176	22.73				
Hypothyroidism		5	176	22.73				
Arrhythmia		4	141	18.18				
Diabetes mellitus			554	71.67				
Right bundle branch block		3	105	13.64				
Depression		3	105	13.64				

There was total 337 adverse events noted in the study population over the observation period of 6 weeks which transforms to 47.34 events per 100 injections. Out of these adverse events 315 were of non-serious nature and 51 were sight threatening .

The most common AE was conjunctival haemorrhage which resolved in 2-week time with no added intervention. The serious and sight threatening AE were endophthalmitis (n=2, 0.25%) and cataract formation (n=21, 2.7%). The two cases which had endophthalmitis were with deranged renal functions and were on haemodialysis. The subjects with post injection cataract formation were supposedly needle injury to the crystalline lens during the intravitreal injection or paracentesis.

Discussion :

The purpose of the analysis was to evaluate and report the adverse events associated with the intravitreal Bevacizumab

Eye disease for which Anti-VEGF was given	n	(%)
Age Related Macular Degeneration	93	12.03
Branch Retinal Vein Occlusion	91	11.77
Capillary hemangioma of optic nerve head withmacular edema	3	0.39
Central retinal vein occlusion	24	3.10
Central serous chorioretinopathy	9	1.16
Eale's Disease	91	11.77
Macular edema	40	5.17
Non-proliferative diabetic retinopathy	183	23.67
Neovascular glaucoma	11	1.42
Pars Planitis	15	1.94
proliferative diabetic retinopathy	171	22.12
Pseudophakic CME	3	0.39
Retinopathy of Prematurity	3	0.39
subretinal neovascular membrane	24	3.10
Toxiplasmosis SRNVM	9	1.16
Traumatic subretinal bleed	3	0.39

wherein the drug was aspirated from a fresh single vial using multiple punctures on a single day.

Injection bevacizumab is commonly used by ophthalmologists widely over the world as acost-effective substitute to "Approved" anti-VEGF molecules. This practice will continue till the "approved" molecules are available at a comparable price,unfortunately this does not appear to be a possibility in coming future. Thus, it is of importance to investigate and innovate safe practices for use of multidose vials to keep this affordable and effective option available for patients. This

Table 2 : Adverse events as seen in the subjects included in the study

Outcome	Frequency	AE rate per 100 injections
Total	366	47.34799483
seriousness category		
Non sight threatning	315	40.75032342
Sight threatning	51	6.59767141
Eye inflammation/Endophthalmitis	2	0.258732212
Conjunctival hemorrhage	182.428	23.6
Conjunctival hyperemia	34.785	4.5
Eye pain	27.828	3.6
Conjunctivitis	20.871	2.7
Cataract/nuclear cataractc	20.871	2.7
Ocular hypertension	13.914	1.8
Systemic reactions	0	0
Hypertension	20.871	2.7
Headache	13.914	1.8

requirement is even more relevant for a country like India as majority of individuals have to afford the treatment out of their pocket as less than 20% population has insurance cover.[7]

Bevacizumab as an intravitreal injection to treat retinal diseases got a setback in 2016 when the Drug Controller General India issued an advisory, banning the use of Bevacizumab (inj. Avastin) as intravitreal injection after reports of few cases of eye infection following its use appeared. Though this ban was revoked 2 months after a committee recommended that there is enough evidence that this drug is very useful and cost effective when compared to the "approved"drugs.[8] A guideline has been published by the joint committee of AIOS and VRSI indicating the management of DME. Since then, the ophthalmologists are less keen to use Bevacizumab for their patients because of the apprehension of being on the wrong side of the law.[8]

Our study has looked at the adverse effects as seen up to 6 weeks after the intravitreal injection of Bevacizumab 1.25 mg in a large subset of patients with a wide age spectrum and indications. Though we have not evaluated the efficacy of this procedure as there is enough conclusive evidence (over 2500 publications) and hence that was not the immediate need. However, the outcomes of our study demonstrate that the multidose vial of Bevacizumab can be used safely in multiple subjects with adverse events attributable mainly to the injection technique rather than the use of single source for multiple subjects. There were two cases of endophthalmitis (incidence rate of 0.25 per 100 injections) in subjects who were having compromised renal functions and were on haemodialysis, which itself has been reported to be a risk for endophthalmitis with[10] or without concurrent intraocular procedure.[11] Thus, the cause of endophthalmitis may not be the injection itself. There was an accelerated cataract formation in 21 subjects (incidence rate of 2.1 per 100 injections) within 6 weeks of the injection and this commonly occurs due to direct needle injury to the crystalline lens and cannot be attributed to the multidose vial use.

Thus, the present study shows that a single vial of injection Bevacizumab (Injection Avastin, 100mg/4ml) can be used in more than 1 patient on a single day and multiple punctures using aseptic technique and the practice is safe. Further comparative prospective studies may be conducted for head-to-head comparison of multidose vial vs single dose vials of available biosimilars so that the cost effectiveness of the multidose vial is available for future patients and ophthalmologists do not have any hesitation with support of robust scientific evidence supporting this practice.

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Safety Outcomes of Brolucizumab in Neovascular Age-Related Macular Degeneration Results from the IRIS Registry and Komodo Healthcare Map

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Key Points

Question What are the incidence rates and risk factors for intraocular inflammation (IOI) and/or retinal vascular occlusion (RO) after brolucizumab treatment for neovascular age-related macular degeneration (AMD) in clinical practice?

Findings In this cohort study of patient eyes with neovascular AMD treated with brolucizumab, the incidence rate for any form of IOI and/or RO was approximately 2.4%. A history of IOI and/or RO was a key risk factor for IOI and/or RO after brolucizumab treatment initiation.

Meaning These early findings explore potential risk factors for inflammation-associated adverse events that may occur following real-world treatment with brolucizumab.