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RESEARCH ARTICLE

Retrospective Efficacy and Safety Analysis of Zybev (Biosimilar of Bevacizumab) Use At Tertiary Eye care Centres In India: Spectra Study

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Abstract

Purpose:
The purpose of this study was to evaluate the efficacy and safety profile of intravitreal injection of bevacizumabbiosimilar (Zybev) for various retinal neovascular conditions.
Methods: Retrospective analysis was carried out on 108 injections which were administered with intravitrealZybev injection at different tertiary eye care centers in India. The injections were administered for various indications such as wet age‑related macular degeneration (AMD), diabetic macular edema (DME), and retinal vein occlusion (RVO).
Results: The mean age of the patients was 62.7 ± 8.40 years. A total of 61.1% injections were administered to men and 39.9% to women. The indications for which the injection was administered were DME (43.6%), AMD (28.7 %), and RVO (27.7%). Mean pretreatment BCVA was 0.94 ± 0.29 logMAR with CMT 355.76 ± 54.9 μm and postinjection BCVA at day 30 was 0.81 ± 0.26 logMAR with CMT reducing to 292.20 ± 40.81 μm, indicating statistical significance (P = 0.001 and P < 0.0001, respectively) for all groups. Among the ocular side effects, none of the patients were reported with severe inflammation, endophthalmitis or rise in intraocular pressure (IOP) >21 mm of Hg during follow up period of one month post injection. No systemic adverse events were noted in study population.
Conclusion: This retrospective analysis provides real time evidence regarding the efficacy and safety profile of biosimilar of bevacizumab, Zybev. However, more long term, prospective safety and efficacy studies are still awaited, this short term restropectivedata suggest that Zybev can be effective and safe in the management of ocular conditions including DME, wet AMD and RVO.

Introduction:-

Over last more than a decade, anti-vascular endothelial growth factors (anti-VEGF) have revolutionized the treatment of many retinal diseases .The US FDA has approved three anti‑VEGF drugs i.e. Pegaptanib, Ranibizumab, and Aflibercept for the management of various retinal vascular conditions.[5,6,7] But Bevacizumab is the most commonly used anti‑VEGF drug worldwide for treating these conditions. Bevacizumab which was

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designed to inhibit tumor angiogenesis received US‑FDA approval for its use in colorectal carcinomas. Subsequently, it gained widespread access as an off‑label medication for the treatment of various neovascular disorders. Multiple trials have compared ranibizumab with bevacizumab in multiple treatment regimens for comparative efficacy and safety analysis. The results of all these trials, including the IVAN[3] study, CATT[2] trial, MANTA[4] trial, LUCAS[1] trial, and GEFAL[8] trial, have shown that bevacizumab is noninferior to ranibizumab with a similar safety profile.

Cost of treatment is an important factor that decides patient compliance and success rates of anti VEGF therapy. In one cost effectiveness analysis of anti VEGFs used in patients with decreased vision from DME, treatment costs of aflibercept and ranibizumab would need to decrease by 69% and 80%, respectively to become cost effective. [10]

A retrospective cohort study data from January 1, 2006 to December 31, 2015 in USA, anti VEGF usage trends were analysed over a period of 10 years. Among all injections, despite lacking USFDA approval, 64.6% were of bevacizumab, 22.0% ranibizumab, and 13.4% aflibercept. Interestingly, Ranibizumab use declined after 2014 while both the absolute and relative use of bevacizumab and aflibercept increased. [11]

In India, as per recent survey published by Vitreo Retinal Society of India, 47% is the usage share for Bevacizumab among various anti VEGFs to manage different retinal conditions.[13]

In April 2017, Cadila Healthcare Ltd received marketing authorization for biosimilar of Bevacizumab for all claimed indications (cancer of colon and rectum, breast cancer, non small cell lung cancer ovarian cancer, cancer of fallopian tube and kidney cancer)based on extrapolation of indication in Non Small Cell Lung Cancer (NSCLC) after clinical trial report of phase 3 study.

A biosimilar is “essentially the same” as the reference biologic biologics in terms of structure, efficacy, safety, and quality but with some natural variability. Biosimilars being economically more viable, have the potential to reduce health-care costs relative to reference biologics, thereby increasing treatment access for patients who need them.

There has been no analysis on the short‑term safety and efficacy of this new biosimilar in patients with retinal vascular diseases.

Hence this retrospective analysis was aimed to evaluate the 1 month post injection safety and efficacy of this Zybev in various eye conditions.

Method:-

This retrospective analysis is based on feedback received from different tertiary eye care centres across India. All eyes had undergone intravitrealbevacizumab therapy from Aug 2017 to Nov 2017. The indications for the intravitreal injections included vitreoretinal pathologies such as wet AMD, DME, and RVO. Patients with less than 1 month of follow‑up were excluded from the study. Informed consent was taken before starting the procedure for all patients. The feedback received included parameters like BCVA (logMAR) andCMT evaluating OCT (μm), assessed before injection and 1 month after injection. Parameters for safety included severe inflammation or endophthalmitis and IOP rise > 21 mm of Hg reported until 1 month post injection. All patients underwent routine ophthalmic examination including best corrected visual acuity, intraocular pressure (IOP) evaluation by Goldmannapplanation tonometry, slit‑lamp biomicroscopy, indirect ophthalmoscopy, and spectral domain optical coherence tomography (SD‑OCT).

Data were entered into Microsoft Excel data sheet and was analyzed using SPSS 22 version software (IBM). Continuous data were represented as mean and standard deviation. Paired *t*‑test is the test of significance for paired data such as before and after injection. $P < 0.05$ was considered statistically significant.

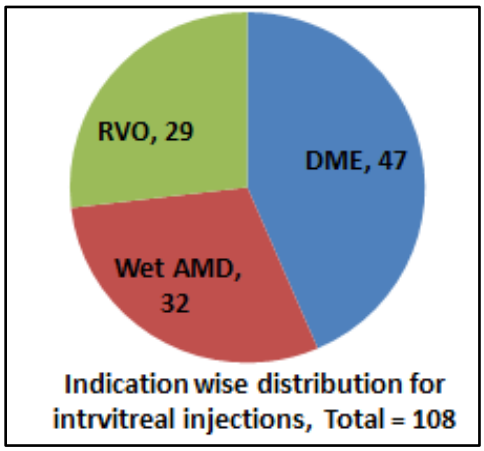
Results:-

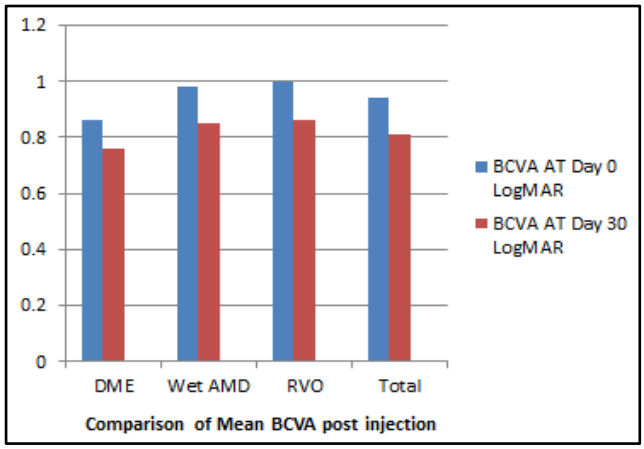
108 eyes of patients with retinal vascular diseases such as diabetic macular edema or DME (47 eyes), wet AMD (32 eyes), and macular edema secondary to RVOs (29 eyes) were enrolled in this study**. [Figure 1]**
The mean age of the patients 62.7 ± 8.40 years. Out of 108 injections administered with intravitrealZybev, 66 were administered to male and 42 to female.

BCVA findings:-

The mean BCVA of all the indications improved from baseline (0.94 ± 0.29 logMAR) to day 30 was 0.81 ± 0.26 logMAR, *P* = 0.001). The mean BCVA of DME Group improved frombaseline (logMAR 0.86 ± 0.32) to day 30 (logMAR 0.76 ± 0.29,*P*= 0.1). Of wet AMD Group improved from baseline (logMAR0.98 ± 0.25) to day 30 (logMAR 0.85 ± 0.25, *P* = 0.16); and ofRVO Group improved from baseline (logMAR 1.0± 0.24) to day30 (logMAR 0.86 ± 0.23, *P*= 0.010**). [Figure 2]**

Figure 1.Figure 2.

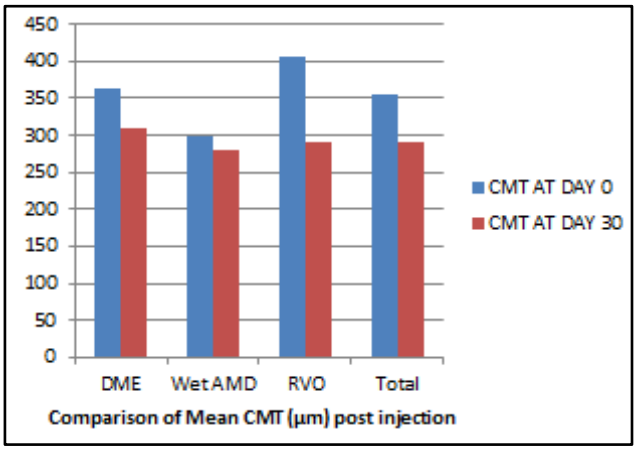


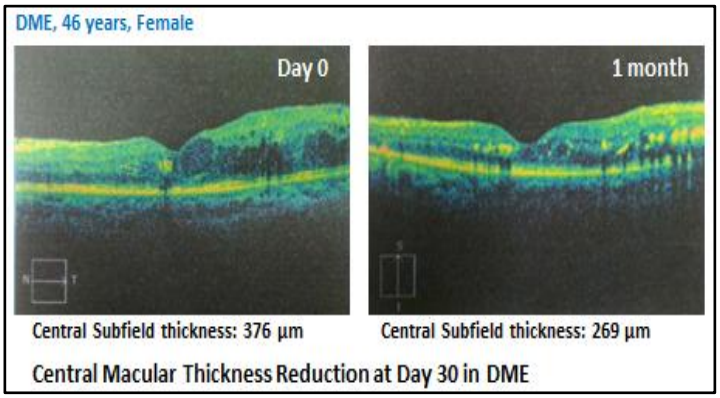


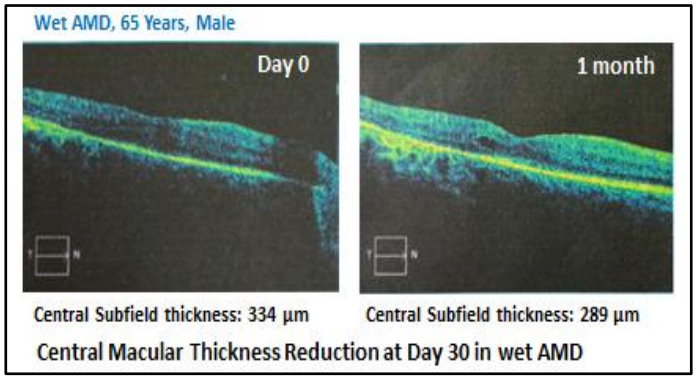
Optical coherence tomography findings:

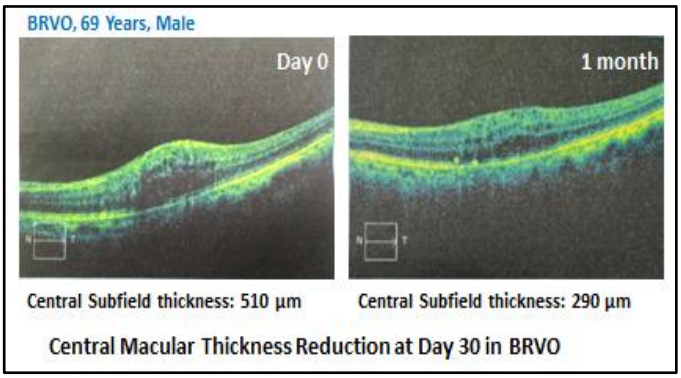
Of 108 eyes, at baseline and day 30, the mean central macular thickness (CMT) improved from 355.76 ± 54.9 µmto 292.20 ± 40.81 µm (*P* < 0.001). In DME Group, the mean CMT improved from 364.4 ± 47.3 µm to 310.7 ± 50.6 µm (*P* < 0.001). In wet AMD Group, the mean CMT improved from 298.1 ± 31.7 µm to 279.2 ± 31.3 µm (*P* = 0.019). In RVO Group, the mean CMT improved from 405.24 ± 18 µm to 291.4 ± 18.8 µm (*P* < 0.001). **[Figure 3]**

Figure 3.









Discussion:-

The introduction of anti VEGF agents has brought revolutionary change in the management of various neovascular retinal conditions including wet AMD, DME and RVO. Off late, the increasing use of anti VEGF agents has markedly improved the visual prognosis for these patients. Bevacizumab and Ranibizumab, both molecules are derived from the same murine monoclonal antibody against VEGF. Ranibizumab, the corresponding Fab fragment of the full-length anti-VEGF antibody, was specifically designed and approved for intravitreal treatment of exudative AMD. Bevacizumab on the other hand is a humanized monoclonal full-length antibody to VEGF and is approved for the systemic intravenous treatment of metastatic colorectal cancers but is not yet approved for injection into the eye. The first report of intravitrealbevacizumab administration for neovascular AMD was published in 2005.[12] Thereafter number of randomized, controlled trials conducted worldwide (IVAN , CATT, MANTA , LUCAS, GEFAL)[3,2,4,1,8] on thousands of patients have shown intravitrealbevacizumab to be noninferior to ranibizumab in terms of efficacy and safety.

According to one retrospective analysis by Rayess et al, out of 503,890 anti-VEGF injection, 153,812 were of bevacizumaband the rate of endophthalmitis risk for bevacizumab, ranibizumab and aflibercept were 0.039%, 0.035%, 0.035% respectively.[9]

Treatment of neovascular retinal conditions incurs high individual, medical and societal costs, all of which should be considered in its management. Lowering the cost of therapy will reduce the economic burden on the individual patients, their families and society, which includes direct medical costs and indirect costs such as work disability and premature retirement. In a country like India, the high cost of treatment is an important limiting factor for treatment compliance to anti VEGF agents. In this respect, the advent of biosimilars provides potential for reduction of pressure on healthcare budget.

When compared to biologics or reference products, the active substance of a biosimilar and its reference product is the same, although there may be slight differences due to the complexities of the production process. As both the reference product and the biosimilar have a degree of natural variability, studies are undertaken to ensure that these differences do not affect the biosimilar's safety.

The limitation of this study is short term outcome of 1 month for analysis. Another limitation is related to the retrospective nature of the study and the fact that intravitreal injection practices were not mentioned.

However, the promising short‑term safety and efficacy data from this retrospective study warrants more number of prospective, randomized studies with repeat injections and larger sample sizes to evaluate long term efficacy and safety of this biosimilar.

Conclusion:-

Intravitreal injection of Zybev (biosimilar of Bevacizumab) was tolerated well over a period of one month with improvement in BCVA and CMT. This short term retrospective analysis suggests this biosimilar can be effective and safe in the management of various retinal neovascular conditions as well.

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