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Complications of Ziv-Aflibercept in Choroidal and Retinal Vascular Diseases

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Abstract

Introduction: The modern ophthalmology trends are changing rapidly every day with the introduction of much newer studies and research. Numerous anti-vascular endothelial growth factors (VEGF) are utilized as the mainstay in the treatment of intraocular vascular pathologies. The rationale of this study is to add to the literature regarding the safety and efficacy profile of the ziv-aflibercept as there is insubstantial data in patients with intraocular vascular pathologies being treated with this injection with prime focus on the complications of the injection. **Materials and Methods:** A prospective observational study was conducted at Opthalmology Department, Lahore General Hospital, Lahore between 14 August 2018 and 23 December 2019. Patients with choroidal and retinal vascular diseases like diabetic macular edema (DME), age-related macular degeneration (AMD) and retinal vein occlusion (RVO) who had no active infection of eye and had no history of myocardial infarction or cerebrovascular accident were added in this study. **Results:** Best-corrected visual acuity was significantly improved at 4, 8, and 12 weeks as compared to the baseline ($p < 0.05$). At 12 weeks there was statistically significant difference in BCVA changes. Central macular thickness was notably decreased in each 4-week interval comparatively to the baseline values ($p < 0.05$). At 24 weeks follow-up, BCVA and CMT showed notable improvement ($p < 0.05$). **Conclusion:** The use of ziv-aflibercept injection via intravitreal route under aseptic conditions for choroidal and retinal vascular diseases is effective as well as safe with mild and treatable ocular side effects.

Keywords

Ziv-Aflibercept, Anti VEGF, Choroidal Vascular Diseases, Retinal Vascular Diseases

1. Introduction

The modern ophthalmology trends are changing rapidly every day with the introduction of much newer studies and research. Numerous anti-vascular endothelial growth factors (VEGF) are utilized as the mainstay in the treatment of intraocular vascular pathologies. As of not long ago, the selection of medications was restricted to bevacizumab (Avastin) and ranibizumab (Lucentis), the former being more famous by virtue of its lower cost. Aflibercept (Eylea) is another addition to the drug regime, which might offer better effectiveness and a more extended impact.

Aflibercept and Ziv-Aflibercept (Eylea®, Regeneron, Tarrytown, NY, USA) are recombinant fusion proteins, composed of extra-cytoplasmic, native-receptor VEGF-binding sequences from VEGF receptor (VEGFR) 1 and VEGFR 2, 9 and binds VEGF 165 up to 100 times greater than either bevacizumab or ranibizumab, they also bind to the isoforms of VEGF-B and placental growth factor.

Ziv-aflibercept, an anticancer medication having the action of anti-VEGF which was approved to be used against metastatic colorectal carcinoma, has a similar structure and carries similar capacity as aflibercept, however the latter has a lower osmolarity, goes through an alternate filtration process and contains distinctive buffering arrangements that cause less discomfort when infused intravitreally. Keeping in view the financial crises in most of the economically oppressed countries, ziv-aflibercept is a lot less expensive recombinant fusion protein [1] [2] [3]. And Mansour *et al.* also have utilized proof from *in vitro* and *in vivo* studies to address specific worries corresponding to safety profile while using it intraocularly; for example, osmolality contrasts and the danger of prompting changes to retinal morphology [4] [5].

Although there are encouraging results in halting the disease and improvement in the visual outcome, intravitreal injection of anti-VEGF agents may be associated with systemic adverse effects and devastating ocular complications. The rationale of this study is to add to the literature regarding the safety and efficacy profile of the ziv-aflibercept as there is insubstantial data in patients with intraocular vascular pathologies being treated with this injection with prime focus on the complications of the injection.

2. Materials and Methods

A prospective observational study conducted at Opthalmology Department, Lahore General Hospital, Lahore between 14 August 2018 and 23 December 2019.

The Institutional Review Board approved the research, which adhered to the

Declaration of Helsinki's tenets. All patients were well informed about the use of an off label drug and the complications that might occur. A written informed consent was taken from every patient.

Patients with choroidal and retinal vascular diseases like diabetic macular edema (DME), age-related macular degeneration (AMD) and retinal vein occlusion (RVO) who had no active infection of eye and had no history of myocardial infarction or cerebrovascular accident were added in this study.

The exclusion criteria were only eyed patients, those with uncontrolled diabetes, uncontrolled glaucoma, epiretinal membrane, advanced cataract or vitreomacular traction, and a history of intravitreal injection and/or laser therapy.

3. Sample Size

Sample size of 156 eyes of 136 patients is estimated at 95% confidence level and taking expected prevalence rate is 77.5% (Singh *et al.*, 2017) with 7% margin of error.

$$n = Z^2_{1-\alpha/2} \cdot p \cdot q / d^2$$

$Z^2_{1-\alpha/2}$ confidence level 95% = 1.96.

p = Expected sensitivity = 77.5 %.

Absolute precision = d = 7%.

4. Data Analysis

Data was collected and analyzed by using SPSS version 39.0. Qualitative Variables Subconjunctival Hemorrhage, Anterior Uveitis, Intraocular Inflammation and Cataract were considered.

At presentation, a comprehensive ocular examination was conducted, including best corrected visual acuity (BCVA), anterior segment examination, posterior segment examination using a slit lamp and indirect ophthalmoscope, intraocular pressure measurement, optical coherence tomography (OCT) and fundus fluorescein angiography (FFA). BCVA was determined using Snellen's visual acuity chart and the results were expressed in the logarithm of the minimum angle of resolution (Log MAR) scale. Cirrus 5000 was used for the OCT (Zeiss, Dublin, CA). The thickness of the retina was determined in a 3 mm circle centred on the site of fixation. The central macular thickness (CMT) was determined by the central 1 mm zone used.

All the patients received intravitreal Ziv-aflibercept injections at baseline. Ziv-aflibercept 1.25 mg/0.05mL (ZALTRAP; Regeneron Pharmaceuticals Inc) was injected intravitreally by a single surgeon under aseptic conditions. Topical anesthesia was instilled in the conjunctival sac followed by 5% povidone-iodine solution after that a sterile eyelid retractor was applied. Ziv-aflibercept (1.25 mg/0.05mL) was injected via sclera (3.5 to 4 mm posterior to the limbus) into the mid-vitreous.

At the 1st and 7th post-operative day, all eyes were examined with a slit-lamp to observe any expected complication including intra-ocular inflammation or higher

intra-ocular pressure. All subjects received a minimum of three injections at 4 weekly intervals. At 4, 8, 12 and 24-week follow-ups the BCVA, slit lamp examination with intraocular pressure measurement, fundoscopy and OCT were repeated.

At each follow-up appointment, any probable ocular or systemic complications associated with the injections were noted.

5. Results

Primarily 162 eyes of 141 patients met our inclusion criteria. Of all the patients, 5 patients (7 eyes) lost to follow-up. So a total of 156 eyes of 136 patients completed whole duration of study and were included in the results. 15 patients had bilateral injections (See Table 1, Figure 1).

The mean baseline CMT was 493 μm (±102 μm). The mean baseline BCVA (logMAR) was 0.78 (Snellen chart equivalent to 6/36).

Best-corrected visual acuity was significantly improved at 4, 8, and 12 weeks as compared to the baseline ($p < 0.05$). At 12 weeks there was statistically significant difference in BCVA changes.

Central macular thickness was notably decreased in each 4-week interval comparatively to the baseline values ($p < 0.05$).

At 24 weeks follow-up, BCVA and CMT showed notable improvement ($p < 0.05$).

In our study, 10 eyes had subconjunctival hemorrhage, 5 eyes showed signs of anterior uveitis, 3 eyes experienced sterile intraocular inflammation while 2 eyes showed significant progression of cataract. Endophthalmitis, vitreous hemorrhage and retinal detachment was not observed in any eye of the patients (See Table 2, Figure 2).

Table 1. Complications.

Bilateral injections	15 (9.62%)
Unilateral injections	141 (90.38%)

Table 2. Rate of complications in operated eyes.

Subconjunctival Hemorrhage	10
Anterior Uveitis	5
Intraocular Inflammation	3
Cataract	2

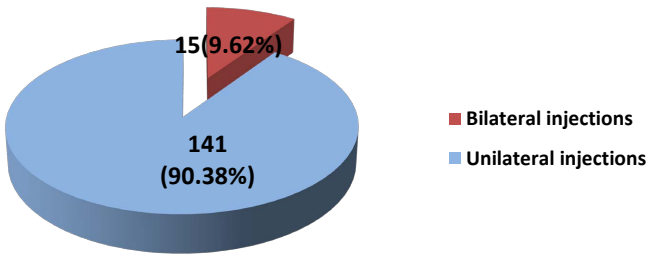

Figure 1. Complications.

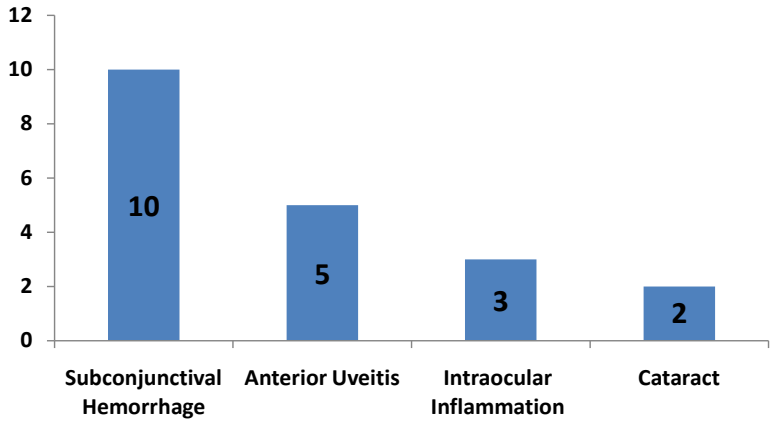

Figure 2. Rate of complications in operated eyes.

6. Discussion

Ziv-aflibercept has similar molecular structure as Aflibercept. However, the manufacturing process of Aflibercept involves more robust purification and use of buffers which causes less ocular irritation and toxicity [6].

A study was conducted to assess the role of ziv-aflibercept in 34 eyes of 26 patients with refractory DME after a mean of 5.93 injections of bevacizumab, aflibercept, ranibizumab and triamcinolone acetonide. The patients were injected with 1.25 mg/0.05mL ziv-aflibercept after a washout period of 4 to 6 weeks on a PRN (pro re nata) basis with a mean of 2.03 injections during the course of 3 months. Visual acuity got better (Δ (Change) − 0.17 logMAR) ($p = 0.084$) and CMT decreased towards normal values significantly (mean of 513.79 μm before and 426.76 μm at 2 months after switch to ziv-aflibercept; $p = 0.006$) without any reported adverse ocular effects [7].

Not to mention, there is much limited data available about the safety profile and complications of ziv-aflibercept. Apart from the systemic complications, there are some similar ocular complications that might be expected when administering intravitreal anti-VEGF drugs [4]. These complications can occur irrespective of the underlying ocular association.

6.1. Endophthalmitis

Infectious endophthalmitis remains one of the most notorious complications of intravitreal injections. Several clinical trials with anti-VEGF therapy have suggested that the incidence of endophthalmitis per patient has been reported to range from 0.019% to 1.6% [5] [6].

However, there are precautionary measures taken to combat this devastating complication which includes: treatment of active external infections like significant blepharitis and eyelid abnormalities such as ectropion which pose a threat of developing endophthalmitis. Proper sterilization is mandatory to reduce the risk. The use of 5% povidone-iodine in the conjunctival fornices is an acceptable and widely used universal practice which is a strong recommendation for preventing endophthalmitis [7].

Considering this common devastating outcome of endophthalmitis after intravitreal injection, and the importance of immediate treatment, we instructed all patients to report promptly at the first sign of any visual disturbance or ocular pain.

6.2. Intraocular Inflammation

Intraocular inflammation is considered as one of the commonest ocular adverse events associated with intraocular anti-VEGF drugs [8].

It is challenging and difficult to differentiate sterile intraocular inflammation from infectious endophthalmitis. A study was conducted in which the time of presentation, presence of pain, and the severity of clinical findings were supportive [9].

The symptoms began within 1 - 6 days after injection in the patients who developed endophthalmitis and less than 1 day in the acute intraocular inflammation group. The anterior chamber reaction was severe in all endophthalmitis cases along with keratic precipitates, hypopyon, fibrin, or anterior synechiae. None of the signs was present in acute intraocular inflammation [10].

Although acute intraocular inflammation has milder symptoms in comparison to endophthalmitis, surgeons should always be vigilant about every case of uveitis after intravitreal anti-VEGF injection as suspected endophthalmitis and should administer intravitreal antibiotics whenever there are high clinical suspicions.

6.3. Raised Intraocular Pressure

Acute elevation of intraocular pressure (IOP) which lasts a few hours at most after intravitreal injection is mostly injection-procedure-related [11]. Patients with pre-existing glaucoma have higher rates of IOP elevation compared with those without pre-existing glaucoma [12].

Several theories, including an inflammatory mechanism or trabeculitis, a pharmacologic effect of VEGF blockade, impaired outflow leading to protein aggregates/silicone droplet debris, and adversely affecting the outflow pathways due to the repeated trauma and or IOP spikes associated with the injection procedure, have been proposed for the possible reasons of sustained IOP elevation after intravitreal anti-VEGF injections [12].

Routine monitoring of IOP is recommended for all patients receiving intraocular Anti-VEGF drugs.

6.4. Ocular Hemorrhage

Ocular hemorrhage following the use of intravitreal anti-VEGF drugs has been encountered in various studies [12]. Subconjunctival hemorrhage has been promulgated to take place in nearly 10% of injections, with increased risk in patients who were on aspirin therapy [13].

Massive choroidal detachment/hemorrhage and massive subretinal hemorrhage have been reported after intravitrealAnti-VEGF injections [14] [15].

6.5. Rhegmatogenous Retinal Detachment

There is a low (0% to 0.67%) overall incidence of rhegmatogenous retinal detachment (RRD) after intravitreal anti-VEGF injection [16].

An induction of posterior vitreous detachment or an incorrect technique of injection has been postulated as noticeable etiology of RRD after intravitreal injection [17].

Precautionary measures that must be practiced to avoid RRD are precise and appropriate site of injection that is 3.5 to 4 mm posterior to the limbus, tunneled insertion of the needle to circumvent vitreous wick or reflux and use of smaller gauge needles.

During this study, 3 eyes (3.7%) showed signs of sterile intraocular inflammation after ziv-aflibercept injection. The number is significant and difference in manufacturing process of ziv-aflibercept may explain this incidence. All of the three patients were managed medically and none of them had reduction in final BCVA as compared to the baseline.

It has been predicted that owing to its hypertonic nature, Ziv-aflibercept can cause retinal toxicity as well as damage to the crystalline lens [17]. Some studies showed that it can cause toxic effects on mitochondrial activity in retinal pigment epithelium (RPE) cells [17]. In our study, however, we have not experienced any case of retinal toxicity. Significant cataract progression was observed in 02 eyes (2.5%) while 10 eyes had subconjunctival hemorrhage and 05 eyes experienced anterior uveitis.

One of the major concerns for compounded intravitreal injections is the risk of endophthalmitis. However, in our study, we have not experienced any case of endophthalmitis in any of the treatment groups. Previous multiple studies also showed the safety of compounded intravitreal injections. So by following the basic protocols of medication manipulation and sterility of the injection site, the chances of endophthalmitis are not greater than non-compounded intravitreal injections.

7. Conclusions

In our study, out of 156 eyes of 136 patients, 10 eyes had subconjunctival hemorrhage which resolved spontaneously within a period of 2 weeks while 5 eyes showed signs of anterior uveitis which was mild and responded well to topical steroids. Only one eye showed repeated episode of anterior uveitis with three subsequent intravitreal doses of ziv-aflibercept but the patient responded well to systemic as well as topical steroids. Sterile intraocular inflammation was observed in 3 eyes which were treated with mild/weak/less potent topical steroids while 2 eyes showed significant progression of cataract. None of the eyes showed signs of endophthalmitis, vitreous hemorrhage and retinal detachment.

In conclusion, the use of ziv-aflibercept injection via intravitreal route under aseptic conditions for choroidal and retinal vascular diseases is effective as well as safe with mild and treatable ocular side effects.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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