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Ziv-aflibercept and bevacizumab for exudative age-related macular degeneration: A retrospective comparison of clinical outcomes and cost at 1 year

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Abstract:

PURPOSE: The purpose of this study was to compare intravitreal ziv-aflibercept (IVZ) monotherapy to intravitreal bevacizumab (IVB) monotherapy in patients with exudative age-related macular degeneration (eAMD).

MATERIALS AND METHODS: Patients with treatment-naïve eAMD treated with *pro re nata* (PRN) monotherapy of IVZ (1.25 mg/0.05 ml) or IVB (1.25 mg/0.05 ml) with a minimum follow-up of 12 months were retrospectively analyzed. Study outcomes included change in best-corrected visual acuity (BCVA), central macular thickness, mean number of injections, and total medication cost in both the groups at 12 months.

RESULTS: Forty-seven eyes (IVZ, 18/47 [38.3%] and IVB, 29/47 [61.7%]) from 47 treatment-naive patients were included. The change in BCVA for patients receiving IVZ was from 0.61 ± 0.33 logarithm of the minimum angle of resolution (Snellen 20/81; range: 20/38–20/174) to 0.45 ± 0.31 (Snellen 20/56; range: 20/27–20/115) at 1 year (P = 0.02). The total number of injections needed to achieve the resolution of intraretinal or subretinal fluid was 2.6 ± 1.4 and 3.5 ± 1.3 for IVZ and IVB, respectively (P = 0.029). Direct medication cost of IVZ and IVB in our cohort on PRN basis was an average of US$78 (2.6 × US$30) and US$175 (3.5 × US$50), respectively, through 1 year.

CONCLUSION: IVZ-PRN monotherapy resulted in improved visual acuity, reduced treatment burden, and reduced direct medication cost in comparison to IVB-PRN monotherapy through 1 year.

Keywords:

Age-related macular degeneration, antivascular endothelial growth factor, bevacizumab, ziv-aflibercept

Introduction

Age-related macular degeneration (AMD) is the most common cause of blindness in the developed world with a sizable proportion of cases occurring in Asia.[1] In studies from countries including the United States and the United Kingdom where access to antivascular endothelial growth factor (VEGF) medication is readily available, the number of intravitreal anti-VEGF injections for AMD and other retinal diseases continues to steadily rise.[2,3] A similar need for increasing anti-VEGF treatment for exudative age-related macular degeneration (eAMD) is also occurring other parts of the world, especially South and East Asia.[1]

Bevacizumab (Genentech, South San Francisco, USA), which was not initially

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formulated for ophthalmic use, has been used as a lower cost alternative to ranibizumab (Genentech, South San Francisco, USA) with similar visual outcomes in clinical trials for eAMD.[4,5] Aflibercept (Regeneron, Tarrytown, New York, USA) is another anti-VEGF drug that is approved for ocular use in eyes with eAMD. Currently, there are no randomized clinical trials demonstrating visual benefits of aflibercept over bevacizumab or ranibizumab in eAMD, although aflibercept allows for less frequent dosing.[6,7] Further, aflibercept has another theoretical advantage: aflibercept has a higher binding affinity to VEGF and in some case series has demonstrated its efficacy in previously treatment-resistant eyes.[6-9]

Treating physicians, especially in the developing world, face a dilemma whether to choose a more efficacious or a more cost-effective drug because of significant cost differences between these drugs. Bevacizumab costs approximately US$50 a dose when compounded to a 0.05-ml dose compared to ranibizumab and aflibercept, which cost about US$1950.[10-12] These costs are an increasingly significant financial burden for many patients in both the developing and developed world. Ziv-aflibercept (Regeneron, Tarrytown, New York, USA) is an anti-VEGF originally formulated for systemic oncologic use but has been demonstrated to be safe and effective for ophthalmic use.[12,13] Compounded ziv-aflibercept allows for ophthalmic use of a medication with a similar mechanism of action (anti-VEGF trap) to aflibercept but with a cost (US$30) even less than that of bevacizumab.[10] Ziv-aflibercept is a US Food and Drug Administration (FDA)-approved drug for metastatic colon cancer, the same indication for which bevacizumab (Avastin) has FDA approval.[13]

No study to the authors' knowledge has compared the efficacy of ziv-aflibercept to bevacizumab in eAMD. Our study, evaluating treatment-naïve eAMD patients in a real-world setting, compares the effectiveness and cost of patients treated with ziv-aflibercept monotherapy to those treated with bevacizumab monotherapy over 1 year using *pro re nata* (PRN) protocol.

Materials and Methods

Patients with treatment-naïve eAMD were retrospectively analyzed from the clinics of two of the authors (JC and AMM) during the study period from January 2018 to January 2019. All clinical data were collected by JC and AMM at LV Prasad Eye Institute, Hyderabad, India and Rafik Hariri University Hospital, Beirut, Lebanon, respectively. Tenets of the Declaration of Helsinki were followed, and the Institution Review Board approval was obtained from L V Prasad Eye Institute Ethics Committee (Ethics Ref No: LEC 06-15-069). Written informed consent was obtained from all the study patients.

The patients were diagnosed with eAMD based on clinical examination, optical coherence tomography (OCT), and fluorescein angiography on initial visit. Eyes receiving either intravitreal ziv-aflibercept (0.05 ml/1.25 mg) or intravitreal bevacizumab (0.05 ml/1.25 mg) monotherapy with a minimum follow-up of 12 months were included in the study. Patients were excluded if they had prior laser or intravitreal anti-VEGF treatment, other co-existing retinal or uveitic disorders, media opacities precluding fundus view, poor quality OCT scans, or follow-up <1 year. All patients were treated using PRN protocol till the resolution of subretinal or intraretinal fluid on OCT and/or hemorrhage on fundus examination. The pros and cons of ziv-aflibercept and bevacizumab including off-label usage, prior studies, potential complications, and availability of costlier alternative agents were explained to the patients, and the decision to inject either drug was in consultation with the patient. Patients were followed up every 4 weeks till the resolution of intraretinal and/or subretinal fluid following up the duration between visits was increased to 6–8 weeks. Retreatment was done in cases with recurrence of sub- or intraretinal fluid or exudation/new-onset subretinal hemorrhage/drop in best-corrected visual acuity (BCVA) by ≥0.1 logarithm of the minimum angle of resolution (logMAR).

Baseline characteristics including age, gender, treatment status, BCVA (in Snellen chart), and central macular thickness (CMT) were recorded. Total number of ziv-aflibercept and bevacizumab injections, total number of visits, and change in BCVA and CMT through 12 months were calculated. CMT was measured using swept-source OCT (deep range imaging OCT Triton, Topcon, Tokyo, Japan) and spectral-domain OCT (three-dimensional OCT-2000, Topcon, Tokyo, Japan) in India and Lebanon, respectively.

All statistical analysis was performed using SPSS (Version 23; IBM, Armonk, NY, USA). BCVA measured in Snellen chart was later converted to logMAR for statistical analysis. Differences in categorical variables between the two groups were tested using the Fisher's exact test. Paired *t*-test was performed to compare the difference in continuous variables between baseline and final visit in either group. A comparison of study parameters (BCVA, CMT, mean number of injections, and follow-up visits) between the ziv-aflibercept and bevacizumab groups was done using unpaired *t*-test. Multivariate logistic regression analysis was conducted to investigate the baseline factors associated with BCVA at the final visit. $P < 0.05$ was considered to be statistically significant. Cost of each medication dose was estimated at US$30 for ziv-aflibercept and US$50 for bevacizumab based on data from the literature.[10-13]

Results

Forty-seven eyes from 47 treatment-naive eAMD patients were included. Ziv-aflibercept was administered in 38.3% (18/47; India, 10 and Lebanon, 8) of eyes and bevacizumab in 61.7% (29/47; India, 18 and Lebanon, 11). There was no statistically significant difference between baseline characteristics of the two groups [age, gender, baseline BCVA, and baseline CMT; Table 1]. The average age of the patients at presentation (69.7 and 68.3 years) and mean BCVA (logMAR 0.61 and 0.60) was comparable between the ziv-aflibercept and bevacizumab groups, respectively (P = 0.63 and P = 0.93). The average number of visits was 6.5 for both the ziv-aflibercept and bevacizumab groups (P = 0.97) over the course of 1 year [Table 1].

The improvement in acuity for patients treated with ziv-aflibercept was statistically significant, with the average presenting acuity of logMAR 0.61 ± 0.33 (Snellen 20/81; range: 20/38–20/174) to 0.45 ± 0.31 (Snellen 20/56; range: 20/27–20/115). The change in acuity for eyes receiving bevacizumab was not statistically significant with baseline and final logMAR BCVAs of 0.6 ± 0.34 and 0.67 ± 0.44 (P = 0.29). The average CMT for those treated with ziv-aflibercept remained stable over 1 year with initial and final average CMTs of 249 ± 103 microns and 272 ± 92 microns, respectively (P = 0.39). For bevacizumab, a similar anatomic stability was noted with CMTs of 283 ± 139 microns and 243 ± 105 microns (P = 0.18) [Table 2].

The number of injections needed to achieve the resolution of intraretinal, subretinal, or sub-RPE fluid was 2.6 ± 1.4 and 3.5 ± 1.3 for ziv-aflibercept and bevacizumab, respectively (P = 0.029). Based on the number of injections needed, the cost of PRN ziv-aflibercept in our cohort was an average of US$78 (2.6 × US$30) while that of bevacizumab treatment was on average US$175 (3.5 × US$50) [Table 3]. The number of eyes receiving ziv-aflibercept who gained three or more lines of vision was more compared to bevacizumab (5 to 4). However, more number of bevacizumab treated eyes had a final visual acuity >20/40 [Table 4]. Further, in eyes receiving ziv-aflibercept, better baseline BCVA (P < 0.001; confidence interval [CI]: 0.53–1.10), and lower baseline CMT (P = 0.006; CI: 0.002–0.001) were all associated with improved final BCVA. There were no ocular or systemic adverse events related to the intraocular use of ziv-aflibercept and bevacizumab in our cohort.

Discussion

Our study retrospectively compared visual and anatomic outcomes of ziv-aflibercept with bevacizumab for the treatment of eAMD. We found that at 1 year, eyes receiving ziv-aflibercept had a better final visual acuity relative to eyes receiving bevacizumab despite similar baseline visual acuity and fewer treatments. Further, due to the relatively lower cost of ziv-aflibercept, we found that using a PRN protocol led to ziv-aflibercept treatment costing less than half of that for bevacizumab.

Ziv-aflibercept is structurally identical to aflibercept, but ziv-aflibercept preparation has a higher osmolarity and was potentially thought to be toxic to the retina. However, both short-term and long-term clinical studies using a variety of imaging modalities including full-field electroretinography demonstrated the ocular safety profile of ziv-aflibercept.[14,15] Another concern regarding substituting ziv-aflibercept for aflibercept is that 0.05 ml of ziv-aflibercept yields 1.25 mg while the FDA-approved dose of aflibercept is 2 mg in 0.05 ml.[15] However, it is important to note that a 0.5-mg monthly aflibercept treatment arm in the VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD (VIEWS 1 and 2) was noninferior to 0.5 mg of monthly ranibizumab. Extrapolating this to ziv-aflibercept, this may suggest that a dose of 1.25 mg ziv-aflibercept would be at least as effective as 0.5 mg of aflibercept.[11]

Our study suggests that ziv-aflibercept is as effective and possibly even more effective in improving BCVA and comparable to bevacizumab in stabilizing CMT. As a result, ziv-aflibercept maybe a viable alternative to deliver commensurate clinical outcomes while reducing the cost and treatment burden for patients. This information is clinically important as the burden of retinal disease increases globally, especially in developing nations where cost is a major barrier to patients receiving treatment. Previous studies have

Table 1: Baseline characteristics of ziv-aflibercept-treated group and bevacizumab-treated group

	Ziv-aflibercept-treated group (n=18)	Bevacizumab-treated group (n=29)	P
Age (years)	69.7±9.5	68.3±9.8	0.63
Male gender (%)	8 (44.4)	15 (51.7)	0.77
Treatment-naïve (%)	18 (100)	29 (100)	1.0
Baseline BCVA (LogMAR)	0.61±0.33 (Snellen 20/81; range 20/38-20/174)	0.60±0.34 (Snellen 20/56; range 20/27-20/115)	0.93
Baseline CMT (μm)	249±103	283±139	0.38
Number of visit	6.5±2.6	6.5±2.3	0.97

BCVA=Best-corrected visual acuity; LogMAR=Logarithm of minimal angle of resolution; CMT=Central macular thickness

Table 2: Comparison of values between the initial and final presentations in both the groups

	Initial presentation		Final presentation
Ziv-aflibercept			
BCVA (log MAR)	0.61±0.33		0.45±0.31
P		0.020	
CMT (μm)	249±103		272±92
P		0.39	
Bevacizumab			
BCVA (log MAR)	0.60±0.34		0.67±0.44
P		0.29	
CMT (μm)	283±139		243±105
P		0.18	

BCVA=Best-corrected visual acuity; Log MAR=Log minimal angle of resolution; CMT=Central macular thickness

Table 3: Average number of injections for ziv-aflibercept and bevacizumab as well as average direct cost of each medication

Medication	Ziv-aflibercept	Bevacizumab	*P*
Number of injections	2.6±1.4	3.5±1.3	0.029
Direct medication cost	US$78	US$175	

Table 4: Comparison of visual acuity gains and losses between medications

	Ziv-aflibercept eyes	Bevacizumab
Final visual acuity >20/40	2	5
Three lines or greater improvement	5	4
Three lines or greater decline in vision	1	6

shown the efficacy of ziv-aflibercept to treat eAMD with improved visual acuity as well as improved CMT.[14]

Our study has the limitations of a relatively low number of eyes, its retrospective nature, and the use of a PRN protocol. The low number and retrospective nature reflect the need for randomized clinical trials as well as the barrier many face in obtaining compounded medications in the developing world.[16] Limited availability of ziv-aflibercept compared to bevacizumab was the main reason for the small number of eyes in this group. The modified PRN protocol is also a limitation as there is growing evidence that treat and extend may yield superior visual acuities to PRN.[17] However, no randomized clinical trials have directly compared PRN versus treat-and-extend protocols.[18] Further, our study retrospectively selected patients treated with PRN monotherapy in real-life settings. Thus, it is likely that these eyes were good responders which are reflected in the lower treatment frequency relative to prospective randomized clinical trials.[4,5] Patient selection issues may also explain why there appears to be a discrepancy in bevacizumab having more eyes with acuity >20/40 but many more eyes with three lines of vision loss or more. Finally, given the low numbers, no meaningful information on safety of the medications can be obtained from this study.

Despite our limitations, our study is the first to provide evidence that ziv-aflibercept is an acceptable, cost-effective, and possibly even more effective medication when compared with bevacizumab, the most commonly used anti-VEGF medication in the United States.[2] In addition, using an as needed treatment protocol allows for less frequent treatments with ziv-aflibercept relative to bevacizumab. The possibly lower treatment burden along with a medicine that is 60% the cost of bevacizumab may potentially improve access and outcomes for many patients who otherwise have limited options. Further, as bevacizumab has experienced concerns for counterfeit medication in the supply chain, ziv-aflibercept may also be an ever-important alternative.[16] Despite the comparative efficacy design of this retrospective study, randomized controlled trials will be necessary with significantly larger number of patients to validate the efficacy and safety of ziv-aflibercept compared to bevacizumab which has a nearly 14-year history of efficacy and safety. We hope this study moves us closer toward such a comparative trial because the possibility of a medication that not only has similar effectiveness but also may decrease both costs and treatment burden may change the paradigm of anti-VEGF treatment globally.

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Conflicts of interest

The authors declare that there are no conflicts of interests of this paper.

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