The ROYAL COLLEGE of OPHTHALMOLOGISTS

ARTICLE OPEN

Check for updates

Use of ziv-aflibercept in diabetic macular edema in a Ghanaian population

Imoro Zeba Braimah[1,2] ✉ and Winfried M. Amoaku[3] ✉

AIM: To investigate the use of intravitreal ziv-aflibercept (IVZ) in Ghanaian patients with diabetic macular edema (DME).
METHODS: A retrospective study of patients with DME, who had been treated with IVZ (1.25 mg/0.05 ml), as part of routine clinical practice, on pro re nata basis between 2016 and 2018 who had a minimum follow-up of 6 months was retrieved and analyzed. The primary outcome measure was change in best-corrected visual acuity (BCVA) at 6 months. Secondary outcome measures are change in BCVA at 12 months and at the last follow-up visit, adverse events and change in central macular thickness (CMT).
RESULTS: Twenty-five eyes of 17 patients (11 males) were included in this study. Their mean age was 60.82 ± 7.70 years and the mean duration of follow-up was 9.52 ± 3.31 months. The mean baseline BCVA (logMAR) of 0.65 ± 0.3 improved to 0.34 ± 0.16 ($p < 0.0001$) and 0.22 ± 0.15 ($p = 0.0004$) at 6 and 12 months, respectively. Twelve (48%) eyes had a visual gain of at least three lines at 6 months and 4 of 12 eyes (33.3%) at 1 year. There was a significant reduction in the mean CMT at 6 and 12 months and at the last follow-up visit compared to baseline ($p < 0.0001$). The adverse events recorded were raised intraocular pressure (four eyes) at 3, 6, and 12 months post injection, increased blood pressure in a patient with known systemic hypertension and transient memory loss in one patient.
CONCLUSION: IVZ (1.25 mg) was associated with significant improvement in BCVA and reduction in CMT at 6 and 12 months in eyes with DME. A randomized clinical trial is warranted to assess this potentially cost-effective intervention for DME in low-resource settings.

Eye (2022) 36:40–44; https://doi.org/10.1038/s41433-022-02005-6

INTRODUCTION

Diabetic macular edema (DME) may result in blindness or visual impairment in patients with diabetes mellitus [1–4]. The magnitude of blindness and visual impairment from DME is expected to increase in low- to middle-income countries due to an increasing prevalence of diabetes, combined with inadequate eye care services including access to affordable treatment [5–7]. DME results from the accumulation of fluid in the central retina due to increased permeability of capillaries around the macula caused by vascular endothelial growth factor [8–10].

The Diabetic Retinopathy Clinical Research Network (DRCR.net) has shown in eyes with DME that ranibizumab and aflibercept have similar efficacy that is superior to bevacizumab at 1 year [11, 12]. Aflibercept and ranibizumab are expensive and studies have found bevacizumab to be cost-effective compared to aflibercept and ranibizumab [13]. An intravenous formulation of aflibercept (ziv-aflibercept) is similar in cost to bevacizumab when compounded. There are reports on the safety and efficacy of off-label ziv-aflibercept for the treatment of DME in some populations [14–19]. In this study, we report the use of intravitreal ziv-aflibercept (IVZ) in a Ghanaian population with DME.

METHODS

A retrospective case series of patients with DME treated with IVZ between October 2016 and March 2018 at the Eye Centre, Korle-Bu Teaching Hospital. This study was approved by the Ethics and Protocol Review Committee of the College of Health Sciences, University of Ghana and adhered to the tenets of the Declaration of Helsinki on human subjects.

Case definitions and eligibility criteria

A patient was said to have DME if they met the following criteria: established history of diabetes mellitus (type 1 or 2), documented fasting plasma glucose level >126 mg/dl or non-fasting plasma glucose level >200 mg/dl, clinical examination consistent with DME supported by fluorescein angiography, and other causes of retinopathy excluded.

The inclusion criteria were patients aged 18 years or older, who meet diagnostic criteria for DM, central macula edema with retinal thickness >300 um using SD-optical coherence tomography (OCT), treatment naive or had not received treatment in the last 3 months, and a minimum follow-up of 6 months. Exclusion criteria were intraocular surgery within 3 months in the study eye, laser photocoagulation or intravitreal corticosteroid or anti-VEGF within previous 3 months, or myopia ≥−6.0 dioptres.

The recorded characteristics of the patients included age, sex, systemic co-morbidities, and affected eye. Measurements included best-corrected visual acuity (BCVA) as for the Early Treatment Diabetic Retinopathy Study, central macular thickness (CMT), using the three-dimensional OCT (−2000

[1]Department of Surgery (Eye), School of Medicine and Dentistry, Korle-Bu, Ghana. [2]Eye Centre, Korle-Bu Teaching Hospital, Korle-Bu, Ghana. [3]Academic Ophthalmology, DCN, Faculty of Medicine and Health Sciences, University of Nottingham, Nottingham, UK. ✉email: zebaimoro2000@yahoo.com; winfried.amoaku@nottingham.ac.uk

Table 1. Demographic and clinical characteristics of eyes with DME at baseline and follow-up.

	Age	Sex	Prior therapy	Stage of DR	Baseline BCVA	BCVA at 6 months	BCVA at last visit	CMT at baseline	CMT at 6 months	CMT at last visit	Last visit/ months
1	52	F	NO	M-NPDR	0.6	0.2	0.32	488	215	433	12
2	53	M	NO	S-NPDR	0.48	0.22	0.4	535	463	525	8
3	53	M	NO	PDR	1.3	0.16	0.4	495	298	304	7
4	63	F	NO	PDR	0.48	0.28	0.32	428	263	288	16
5	64	M	NO	M-NPDR	0.48	0.3	0.08	373	204	221	12
6	64	M	NO	M-NPDR	0.6	0.3	0	356	220	238	12
7	62	M	NO	PDR	0.6	0.1	0	475	208	218	12
8	62	M	NO	PDR	0.3	0.26	0.1	367	216	258	12
9	63	M	NO	M-NPDR	0.6	0.48	0.42	319	279	270	14
10	63	M	1 BZ	PDR	0.52	0.18	0.18	346	234	297	10
11	59	M	NO	M-NPDR	0.6	0.2	0.48	397	274	278	12
12	59	M	NO	M-NPDR	0.78	0.4	0.4	463	320	269	12
13	63	F	NO	S-NPDR	0.48	0.3	0.2	574	433	336	13
14	63	F	1 BZ	S-NPDR	0.42	0.26	0.3	588	351	304	13
15	71	M	1 BZ	M-NPDR	1.5	0.78	0.78	584	513	513	6
16	56	F	NO	PDR	0.32	0.32	0.32	376	213	213	6
17	56	F	NO	PDR	0.4	0.48	0.78	306	182	182	6
18	65	F	NO	M-NPDR	0.5	0.18	0.18	694	206	206	7
19	49	M	NO	PDR	1	0.42	0.42	397	236	236	6
20	49	M	NO	S-NPDR	1	0.5	0.5	330	193	193	6
21	77	M	7 BZ	M-NPDR	0.78	0.32	0.32	644	242	242	6
22	51	M	NO	M-NPDR	0.7	0.58	0.58	339	192	192	6
23	53	M	1 BZ	S-NPDR	1	0.32	0.32	460	274	274	6
24	64	F	4 BZ	S-NPDR	0.6	0.48	0.48	402	229	229	6
25	69	M	NO	M-NPDR	0.32	0.48	0.32	500	403	271	12

BCVA best-corrected visual acuity, *BZ* bevacizumab, *CMT* central macular thickness, *DME* diabetic macular edema, *DR* diabetic retinopathy, *F* female, *M* male, *M-NPDR* moderate NPDR, *NPDR* nonproliferative diabetic retinopathy, *PDR* proliferative diabetic retinopathy, *S-NPDR* severe NPDR.

Topcon). The number of ziv-aflibercept injections, longest treatment-free interval, and additional treatment whilst on IVZ were also recorded.

Standard procedure for intravitreal injection was followed, with povidone-iodine cleaning.

Outcome measures

The primary outcome measure was the change from baseline in BCVA at 6 months. The secondary outcome measures included change from baseline in BCVA at 3 months, 12 months and at the last follow-up visit; the proportion of eyes that gained at least 5, 10, or 15 letters from baseline; and the change from baseline in CMT at 6 and 12 months.

Ocular adverse events including intraocular inflammation and endophthalmitis, and any systemic adverse event whether drug related or unrelated, were also recorded.

Statistical analysis

SPSS V.24 (IBM, Chicago, Illinois, USA) was used for statistical analyses. Continuous variables were presented as mean and standard deviation. Categorical variables were compared using χ^2 or Fisher's exact test. Pre- and post-injection changes in BCVA, intraocular pressure (IOP), and CMT were compared using paired *t*-test. A p value <0.05 was considered statistically significant.

RESULTS

Twenty-five eyes of 17 patients were included in this study. Six of the 17 patients were females and their mean age ± standard deviation (range) was 60.82 ± 7.70 (49–77) years. The mean duration of follow-up was 9.52 ± 3.31 (6–16) months and 12 eyes had a follow-up duration of at least 12 months. All patients had type 2 diabetes mellitus and the mean duration of disease at presentation was 14.92 ± 6.96 (3–30) years. The co-morbidities (number) among this cohort were systemic hypertension (12), hyperlipidemia (7), and 5 patients had glaucoma. Six eyes had previous injections of bevacizumab prior to IVZ, the mean number of previous anti-VEGF injections was 2.5 ± 2.51 (1–7), median 1. All these eyes had not received injections in the previous 3 months prior to switching to IVZ. Seven eyes were pseudophakic.

Eleven eyes had moderate nonproliferative diabetic retinopathy (M-NPDR), 6 eyes had severe nonproliferative diabetic retinopathy (S-NPDR), and 8 eyes had proliferative diabetic retinopathy (PDR) of which 1 had vitreous hemorrhage. None of the 8 eyes with PDR had been treated with laser photocoagulation at presentation. The demographic and clinical characteristics of the study eyes are summarized in Table 1.

All eyes had 3 monthly IVZ followed by pro re nata treatment except in one patient who had memory loss after the second injection of IVZ where the next (third) injection was deferred till after 2 months following this incident.

The numbers of visits post initiation of IVZ at 6 months, 12 months, and at the last follow-up visit in months were 5.64 ± 0.49 (5–6), 10.67 ± 1.31 (8–12), and 8.6 ± 3.06 (5–16), respectively. The mean numbers of IVZ injections at 6 and 12 months and at the last follow-up visit were 4.72 ± 0.84 (3–6), 6.25 ± 1.42 (4–9), and 5.76 ± 1.88 (3–12), respectively. The maximum treatment-free interval was 2.04 ± 0.98 (1–4) months, median of 2 months at the last follow-up visit. The mean IOP was 15.88 ± 3.53 (9–24) mmHg at baseline and there was no significant difference in the mean IOP in subsequent follow-up visits compared to baseline (Table 2).

Visual outcome

The mean baseline BCVA (logMAR) of 0.65 ± 0.3 improved to 0.34 ± 0.16 ($p < 0.0001$) and 0.23 ± 0.17 ($p = 0.0004$) at 6 and

Table 2. Outcomes of IVZ Injections at 3, 6, 12 months and last visit.

Parameter	Results	Sig. (two-tailed)
Age, mean ± SD (range), years	60.12 ± 7.02 (49–77) 62	–
Number of IVZ injections, mean ± SD (range)		
3 months	2.96 ± 0.2 (2–3), 3	–
6 months	4.72 ± 0.84 (3–6), 5	<0.0001
12 months	6.25 ± 1.42 (4–9), 6	<0.0001
Last visit	5.76 ± 1.88 (3–12), 5	<0.0001
IOP, mean ± SD (range), mmHg		
Baseline	15.88 ± 3.53 (9–24), 15	–
3 months	17.0 ± 3.24 (12–25), 16	0.7311
6 months	16.52 ± 4.6 (6–27), 16	0.9360
12 months ($n = 14$)	18.17 ± 7.94 (11–36), 15.5	0.4468
Last visit	17.32 ± 5.29 (6–27)	0.5021
BCVA, logMAR, mean ± SD (range)		
Baseline	0.65 ± 0.3 (0.3–1.5), 0.6	–
3 months	0.37 ± 0.2 (0.14–0.82), 0.32	0.0004
6 months	0.34 ± 0.16 (0.1–0.78), 0.3	<0.0001
12 months	0.22 ± 0.15 (0–0.48), 0.2	0.0001
Last visit	0.34 ± 0.20 (0–0.78), 0.32	0.0001
BCVA gain at 6 months, frequency (%)		
At least 1 line	22/25 (88.0)	
At least 2 lines	15/25 (60.0)	
At least 3 lines	12/25 (48.0)	
BCVA gain at 12 months, frequency (%)		
At least 1 line	11/12 (91.67)	
At least 2 lines	10/12 (83.33)	
At least 3 lines	4/12 (33.33)	
CMT, mean ± SD (range), μm		
Baseline	449.4 ± 107 (306–694), 428	–
3 months	293.1 ± 117 (146–645), 256	<0.0001
6 months	274.4 ± 91 (182–513), 236	<0.0001
12 months	268.9 ± 61.1 (201–433), 254	<0.0001
Last visit	279.6 ± 89.7 (182–525), 269	<0.0001
Presence of intraretinal fluid, yes/no (%)		
Baseline	25 (100)	–
3 months	18/7 (72.2)	<0.0001
6 months	12/13 (48)	<0.0001
12 months	9/3 (75)	<0.0001
Last visit	14/11 (56)	<0.0001

BCVA best-corrected visual acuity, *CMT* central macular thickness, *IOP* intraocular pressure, *logMAR* logarithm of minimum angle of resolution, *SD* standard deviation, *Sig* significance.

12 months, respectively. There was no significant difference in the mean BCVA at 3 months compared to mean BCVA at 6 months, 12 months and at the last follow-up visit ($p = 1.000$). Twelve (48%) eyes had a visual gain of at least three lines at 6 months and 4 (33.3%) eyes at 1 year. One eye had a visual decline of at least one line at 6 months visit and 2 eyes had visual decline of at least one line at 12 months visit.

CMT measures

There was a significant reduction in the mean CMT at 3, 6, and 12 months and at the last follow-up visit compared to baseline ($p < 0.0001$) (Table 2). All the eyes had intraretinal fluid prior to initiation of IVZ. Intraretinal fluid was still present in 18 (72.2%), 12 (48%), 9 (75%), and 14 (56%) eyes at 3, 6, 12 months and at the last follow-up visit, respectively. Sixteen (83.3%) eyes had subretinal fluid at presentation. Subretinal fluid was still present in 2 eyes only at 1 month post initiation of IVZ but absent in all eyes at 3, 6, and 12 months and at the last follow-up visit.

Adverse events

Four eyes of three patients developed raised IOP whilst receiving treatment with IVZ. One female patient not known to have glaucoma had raised IOP in both eyes at 12 months post initiation of IVZ that was subsequently controlled with Guttae Timolol 0.5% bid. Another female patient known to have glaucoma and on treatment with Guttae Latanoprost 0.005% nocte to both eyes developed raised IOP at 3 months post initiation of IVZ, which was treated with Guttae Timolol 0.5% bid being added to her medications. The third patient who was known to have glaucoma and on Guttae Timolol 0.5% bid and Guttae Latanoprost 0.005% nocte had raised IOP in the eye receiving IVZ at 6 months and Guttae Dorzolamide 20 mg/ml tid was added to the medications.

One patient known to have systemic hypertension on treatment with medications developed severe hypertension at 6 months post initiation of IVZ. The blood pressure was controlled with medications and IVZ injections resumed. A 65-year-old female with systemic hypertension developed memory loss after her second injection of IVZ. The memory loss resolved without sequelae and IVZ injection resumed after 2 months of the episode of the memory loss. One patient had cataract extraction at 11 months due to progressive visual loss attributed to cataract.

DISCUSSION

This retrospective pilot study reports the outcome of using IVZ (1.25 mg) in routine clinical practice in 25 eyes with DME in a West African population. The treatment was well tolerated. Follow-up data were available in all 25 eyes at 6 months and in 12 of 25 at 12 months.

We observed improvement in BCVA at 12 weeks (−0.28 ± 0.28) using 1.25 mg IVZ and this mean change was maintained at 6 months (−0.31 ± 0.28), 12 months (−0.31 ± 0.17), and at the final follow-up visit (−0.31 ± 0.29). The improvement in BCVA was accompanied by a significant reduction in the mean CMT at 3, 6, and 12 months and at the last follow-up visit compared to baseline ($p < 0.0001$). An IOP elevation at 3, 6, and 12 months after IVZ was observed in some eyes, which was satisfactorily controlled. We did not observe other serious adverse events associated with IVZ use in eyes with DME in this study.

In low- and middle-income countries, the use of anti-VEGF to treat diabetic macula edema results in a considerable cost for patients and their families. The cost of compounded bevacizumab and IVZ is similar. Compounded bevacizumab has been found to be more cost-effective than aflibercept or ranibizumab [13]. As the treatment with anti-VEGF is not covered by the National Health Insurance Schemes in many developing and low-middle countries including Ghana, costs to patients can lead to infrequent use of anti-VEGF and frequent loss to follow-up. The visual and anatomic response to anti-VEGF in routine clinical practice may not be as good as that observed in clinical trials especially in developing countries where out of pocket payment is frequent [20].

A limitation of this study is that it is a retrospective case series, with a small number of eyes. However, it demonstrates the potential use of affordable IVZ in a West African population. A randomized control study of the safety and efficacy of IVZ in DME is recommended.

In conclusion, IVZ (1.25 mg) may be associated with significant improvement in BCVA and a significant reduction in CMT in eyes

with DME at 6 and 12 months. Prospective randomized studies are required to support these findings.

SUMMARY

What was known about this topic

- In eyes with DME Ranibizumab and aflibercept have similar efficacy that is superior to bevacizumab at 1 year.
- Off-label use of bevacizumab has been found to be cost-effective compared to aflibercept and ranibizumab.
- Ziv-aflibercept is similar in cost to bevacizumab when compounded.
- The safety and efficacy of ziv-aflibercept for the treatment of DME has been reported in other populations.

What this study adds

- This retrospective study reports the outcome of using IVZ (1.25 mg) in routine clinical practice in 25 eyes with DME in a West African population.
- IVZ was associated with significant improvement in BCVA and reduction in CMT at 6 and 12 months in Ghanaian eyes with DME and the treatment was well tolerated.

DATA AVAILABILITY

No data repository in Ghana. The datasets used in this study are available from the principal investigator, IZB, on reasonable request.

REFERENCES

1. Diabetes Control and Complications Trial Research Group. Progression of retinopathy with intensive versus conventional treatment in the Diabetes Control and Complications Trial. Ophthalmology. 1995;102:647–61.
2. Klein R, Klein BE, Moss SE, Cruickshanks KJ. The Wisconsin Epidemiologic Study of Diabetic Retinopathy. XV. The long-term incidence of macular edema. Ophthalmology. 1995;102:7–16.
3. Lee R, Wong TY, Sabanayagam C. Epidemiology of diabetic retinopathy, diabetic macular edema and related vision loss. Eye Vis. 2015;2:17.
4. Chen E, Looman M, Laouri M, Gallagher M, Van Nuys K, Lakdawalla D, et al. Burden of illness of diabetic macular edema: literature review. Curr Med Res Opin. 2010;26:1587–97.
5. Pascolini D, Mariotti SP. Global estimates of visual impairment: 2010. Br J Ophthalmol. 2012;96:614–8.
6. Hussain N, Khanna R, Hussain A. Trend of retinal diseases in developing countries. Expert Rev Ophthalmol. 2008;3:43–50.
7. Dalal S, Beunza JJ, Volmink J, Adebamowo C, Bajunirwe F, Njelekela M, et al. Non-communicable diseases in sub-Saharan Africa: what we know now. Int J Epidemiol. 2011;40:885–901.
8. Bresnick GH. Diabetic maculopathy. A critical review highlighting diffuse macular edema. Ophthalmology. 1983;90:1301–17.
9. Ho AC, Scott IU, Kim SJ, Brown GC, Brown MM, Ip MS, et al. Anti-vascular endothelial growth factor pharmacotherapy for diabetic macular edema: a report by the American Academy of Ophthalmology. Ophthalmology. 2012;119:2179–88.
10. Wang S, Park JK, Duh EJ. Novel targets against retinal angiogenesis in diabetic retinopathy. Curr Diab Rep. 2012;12:355–63.
11. Wells JA, Glassman AR, Ayala AR, Jampol LM, Aiello LP, Antoszyk AN, et al. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema. N Engl J Med. 2015;372:1193–203.
12. Wells JA, Glassman AR, Ayala AR, Jampol LM, Bressler NM, Bressler SB, et al. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema: two-year results from a comparative effectiveness randomized clinical trial. Ophthalmology. 2016;123:1351–9.
13. Ross EL, Hutton DW, Stein JD, Bressler NM, Jampol LM, Glassman AR. Cost-effectiveness of aflibercept, bevacizumab, and ranibizumab for diabetic macular edema treatment: analysis from the Diabetic Retinopathy Clinical Research Network Comparative Effectiveness Trial. JAMA Ophthalmol. 2016;134:888–96.
14. Andrade GC, Dias JR, Maia A, Farah ME, Meyer CH, Rodrigues EB. Intravitreal injections of ziv-aflibercept for diabetic macular edema: a pilot study. Retin (Phila, PA). 2016;36:1640–5.
15. Ashraf M, El Kayal H, Souka AAR. Comparison between the short-term outcomes of bevacizumab and ziv-aflibercept in the treatment of primary diabetic macular oedema. Acta Ophthalmol. 2017;95:e803–e4.
16. Ashraf M, Souka AA, El Kayal H, El Manhaly M, Abdallah MH. Three-month outcomes of ziv-aflibercept in the treatment of diabetic macular oedema. Acta Ophthalmol. 2016;94:e669.
17. Mansour AM, Dedhia C, Chhablani J. Three-month outcome of intravitreal ziv-aflibercept in eyes with diabetic macular oedema. Br J Ophthalmol. 2017;101:166–9.
18. Baghi A, Jabbarpoor Bonyadi MH, Ramezani A, Azarmina M, Moradian S, Dehghan MH, et al. Two doses of intravitreal ziv-aflibercept versus bevacizumab in treatment of diabetic macular edema: a three-armed, double-blind randomized trial. Ophthalmol Retina. 2017;1:103–10.
19. Jabbarpoor Bonyadi MH, Baghi A, Ramezani A, Yaseri M, Soheilian M. One-year results of a trial comparing 2 doses of intravitreal ziv-aflibercept versus bevacizumab for treatment of diabetic macular edema. Ophthalmol Retina. 2018;2:428–40.
20. Maggio E, Sartore M, Attanasio M, Maraone G, Guerriero M, Polito A, et al. Anti-vascular endothelial growth factor treatment for diabetic macular edema in a real-world clinical setting. Am J Ophthalmol. 2018;195:209–22.

ACKNOWLEDGEMENTS

The authors would like to thank the staff of the medical records department, treatment room, and outpatient clinic of the Eye Centre, Korle-Bu Teaching Hospital, for their support during the conduct of this study. We express our gratitude to participants who voluntarily consented for their images to be included in this study.

AUTHOR CONTRIBUTIONS

Designed the study: IZB, WMA; conducted the study: IZB, WMA; retrieved and analyzed the data: IZB; data interpretation: IZB and WMA; preparation of the manuscript: IZB and WMA; critical review of the manuscript: IZB, WMA; and approval of the manuscript: IZB, WMA.

FUNDING

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. The publication costs for this article were funded by The Queen Elizabeth Diamond Jubilee Trust through the Commonwealth Eye Health Consortium. The funding body did not participate in the design of the study, data collection and analysis, interpretation of data and writing of the manuscript. WMA has had grant support from Bayer (2018–2022), Boehringer Ingelheim (2019–2022), Novartis (2019–2021), Roche (2021–2022), and is currently under negotiation for an NHIR i4i Grant (2022–2025). He has also received honoraria for lectures from Allergan and Novartis.

COMPETING INTERESTS

The authors declare no competing interests.

CONSENT FOR PUBLICATION

Written informed consent for publication was obtained from patients included in this article. Data were retrospectively obtained and anonymized.

ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to Imoro Zeba Braimah or Winfried M. Amoaku.