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

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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.

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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
The number of ziv-afibercept 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 χ² 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 (1–8), median 2. None of the 8 eyes with PDR (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.

**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            | 432              |
| 2   | 53  | M             | NO          | S-NPDR       | 0.48            | 0.22             | 0.4             | 535            | 463            | 525              |
| 3   | 53  | M             | NO          | PDR          | 1.3             | 0.16             | 0.4             | 495            | 298            | 304              |
| 4   | 63  | F             | NO          | PDR          | 0.48            | 0.28             | 0.32            | 428            | 263            | 288              |
| 5   | 64  | M             | NO          | M-NPDR       | 0.48            | 0.3              | 0.08            | 373            | 204            | 221              |
| 6   | 64  | M             | NO          | M-NPDR       | 0.6             | 0.3              | 0              | 356            | 220            | 238              |
| 7   | 62  | M             | NO          | PDR          | 0.6             | 0.1              | 0              | 475            | 208            | 218              |
| 8   | 62  | M             | NO          | PDR          | 0.3             | 0.26             | 0.1             | 367            | 216            | 258              |
| 9   | 63  | M             | NO          | M-NPDR       | 0.6             | 0.48             | 0.42            | 319            | 279            | 270              |
| 10  | 63  | M             | 1 BZ        | PDR          | 0.52            | 0.18             | 0.18            | 346            | 234            | 297              |
| 11  | 59  | M             | NO          | M-NPDR       | 0.6             | 0.2              | 0.48            | 397            | 274            | 278              |
| 12  | 59  | M             | NO          | M-NPDR       | 0.78            | 0.4              | 0.4             | 463            | 320            | 269              |
| 13  | 63  | F             | NO          | S-NPDR       | 0.48            | 0.3              | 0.2             | 574            | 433            | 336              |
| 14  | 63  | F             | 1 BZ        | S-NPDR       | 0.42            | 0.26             | 0.3             | 588            | 351            | 304              |
| 15  | 71  | M             | 1 BZ        | M-NPDR       | 1.5             | 0.78             | 0.78            | 584            | 513            | 513              |
| 16  | 56  | F             | NO          | PDR          | 0.32            | 0.32             | 0.32            | 376            | 213            | 213              |
| 17  | 56  | F             | NO          | PDR          | 0.4             | 0.48             | 0.78            | 306            | 182            | 182              |
| 18  | 65  | F             | NO          | M-NPDR       | 0.5             | 0.18             | 0.18            | 694            | 206            | 206              |
| 19  | 49  | M             | NO          | PDR          | 1               | 0.42             | 0.42            | 397            | 236            | 236              |
| 20  | 49  | M             | NO          | S-NPDR       | 1               | 0.5              | 0.5             | 330            | 193            | 193              |
| 21  | 77  | M             | 7 BZ        | M-NPDR       | 0.78            | 0.32             | 0.32            | 644            | 242            | 242              |
| 22  | 51  | M             | NO          | M-NPDR       | 0.7             | 0.58             | 0.58            | 339            | 192            | 192              |
| 23  | 53  | M             | 1 BZ        | S-NPDR       | 1               | 0.32             | 0.32            | 460            | 274            | 274              |
| 24  | 64  | F             | 4 BZ        | M-NPDR       | 0.6             | 0.48             | 0.48            | 402            | 229            | 229              |
| 25  | 69  | M             | NO          | M-NPDR       | 0.32            | 0.48             | 0.32            | 500            | 403            | 271              |

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, NDR nonproliferative diabetic retinopathy, PDR proliferative diabetic retinopathy, S-NPDR severe NPDR.

BCVA at 6 months ranged from 0.1 to 1.5, median 0.3. The mean baseline BCVA (logMAR) of 0.65 ± 0.3 improved to 0.23 ± 0.17 (p = 0.0004) at 6 and at the last follow-up visit in months were 5.64 ± 0.49 (5–12), respectively. The mean IOP was 15.88 ± 3.53 (9–24) mmHg at baseline and 10.67 ± 1.31 (8–16) mmHg 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 (3–5), 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
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.

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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, WMA; and approval of the manuscript: IZB, WMA.

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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
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