# One-year outcome of intravitreal ziv-aflibercept therapy for non-responsive neovascular age-related macular degeneration

Imoro Zeba Braimah,[1,2] Komal Agarwal,[2] Ahmad Mansour,[3,4] Jay Chhablani,[2] on behalf of Ziv-aflibercept Study Group

[1]School of Medicine and Dentistry, College of Health Sciences, University of Ghana, Accra, Ghana
[2]Srimati Kanuri Santhamma Centre for Vitreo Retinal Diseases, KAR Campus, L V Prasad Eye Institute, Hyderabad, Telangana, India
[3]Department of Ophthalmology, American University of Beirut, Beirut, Lebanon
[4]Department of Ophthalmology, Rafic Hariri University Hospital, Beirut, Lebanon

**Correspondence to**
Dr Jay Chhablani, LV Prasad Eye Institute, Banjara Hills, Road no. 2 Hyderabad 500034, India; jay.chhablani@gmail.com

Received 10 February 2017
Revised 24 April 2017
Accepted 30 April 2017
Published Online First 8 June 2017

## ABSTRACT

**Aim** To evaluate 12-month outcome of intravitreal ziv-aflibercept (IVZ) therapy in eyes with neovascular age-related macular degeneration (nAMD) that are non-responsive to bevacizumab and ranibizumab.

**Methods** This retrospective study included 16 eyes (14 patients) with nAMD who were on prior treatment with bevacizumab and ranibizumab and were treated with as-needed IVZ (1.25 mg/0.05 mL) for 12 months. The primary outcome measure was the mean change in best corrected visual acuity (BCVA) and secondary outcome measures included mean change in central macular thickness (CMT), retinal pigment epithelial detachment (RPED) heights, longest treatment free interval, presence of subretinal fluid (SRF) and intraretinal fluid (IRF) and adverse events.

**Results** There was no change in the mean logarithm of minimum angle of resolution (logMAR) BCVA at baseline and following treatment with IVZ therapy (p=0.978). The mean number of IVZ injections during 12 months was 5.9±3.3, and the mean number of antivascular endothelial growth factors (VEGFs) injections prior to switching to IVZ was 8.4±4.7. The mean treatment free interval was longer during IVZ therapy (114.4±67.1 days) compared with 76.3±54.6 days before IVZ therapy (p=0.03). Five (31.25%) eyes had visual gains of at least 0.1 logMAR, 3 (18.75%) eyes had stable BCVA (within 0.1 logMAR) and 8 (50%) eyes had BCVA decline of at least 0.1 logMAR. There was no significant difference in the mean CMT, RPED heights and presence of IRF and SRF at 12 months compared with baseline. No adverse events were noted.

**Conclusion** IVZ increased the treatment free interval in non-responders but no significant change in visual and anatomic outcomes.

## INTRODUCTION

Antivascular endothelial growth factors (anti-VEGF) such as ranibizumab (Lucentis, Novartis, Basel, Switzerland), bevacizumab (Avastin, Genentech, San Francisco, California, USA; used off label for intravitreal injection) and aflibercept (Eylea; Regeneron Pharmaceuticals, Tarrytown, New York, USA) are standard treatments of neovascular age-related macular degeneration (nAMD). Non-response to anti-VEGF therapies do occur and can be attributed to primary failure, secondary failures or due to tachyphylaxis.[1–5] The reported rate of non-response to ranibizumab, bevacizumab and aflibercept in nAMD varies and can occur in up to 21% of eyes.[2–6]

Eyes with active nAMD who are non-responsive to a particular intravitreal anti-VEGF may have favourable response by switching to alternative anti-VEGF.[4 5 7] Aflibercept has shown significant anatomic improvement in non-responders with many eyes having stable[8–14] or improved vision.[9 10 13 15] However, the high cost and the unavailability of aflibercept in many countries are major concerns. Bevacizumab is frequently used in low-income to middle-income countries because of its cost-effectiveness compared with ranibizumab and aflibercept. Ziv-aflibercept (Zaltrap; Regeneron, Tarrytown, New York, USA), an intravenous formulation of aflibercept with comparable cost with bevacizumab, has been found to be safe and effective in short-term reports in patients with nAMD.[16–18]

The effect of ziv-aflibercept in patients with nAMD who are non-responsive to bevacizumab or ranibizumab is unknown. In this retrospective study, we seek to evaluate the 12-month outcome of ziv-aflibercept therapy in eyes with nAMD non-responsive to ranibizumab or bevacizumab.

## METHODS

In this retrospective two-centre study (LV Prasad Eye institute, India, and Rafic Hariri University Hospital, Lebanon), patients with nAMD, who are non-responsive to intravitreal bevacizumab and ranibizumab and those who had been treated with intravitreal ziv-aflibercept (IVZ) from April 2014 to January 2016 were included. This study adhered to the tenets of the Declaration of Helsinki and was approved by the institutional review boards (IRBs) of both centres. Off-label use of IVZ was also approved by the IRB of both centres.

Eligible patients are those with active nAMD who were non-responsive to bevacizumab or ranibizumab and switched to IVZ with a minimum follow-up of 12 months. All patients were treated on pro re nata (PRN) basis. Patients were reviewed monthly until the complete response, then every 2 months until the recurrence. Non-response to anti-VEGF in this study was defined as decrease in central macular thickness (CMT) of less than 100 microns, a new or expanding choroidal neovascularisation (CNV) or intraretinal fluid (IRF) or subretinal fluid (SRF) using spectral domain optical coherence tomography (SD-OCT) scanning after 3 monthly anti-VEGF injections.[1 3] All patients with CNV other than nAMD and disciform scar were excluded from this study.

**To cite:** Braimah IZ, Agarwal K, Mansour A, *et al*. *Br J Ophthalmol* 2018;**102**:91–96.

The clinical characteristics of the patients included age, sex, ethnicity, systemic comorbidities, affected eye, type, number and duration of previous anti-VEGF injections at baseline. Best corrected visual acuity (BCVA), CMT, presence of IRF or SRF and height of retinal pigment epithelial detachment (RPED). Longest treatment free interval (longest injection free interval) before switching to IVZ and during 12 months follow-up with IVZ therapy were recorded. The number of ziv-aflibercept injections and additional treatment while on IVZ, if any, were also recorded.

BCVA was assessed by Early Treatment Diabetic Retinopathy Study R chart (Precision Vision, La Salle, Illinois, USA) in Lebanon and Snellen charts in India. CMT is the mean thickness in the central 1000 µm diameter area and was done using optical coherence tomography (OCT) three-dimensional OCT-2000 FA plus Topcon (Topcon, Tokyo, Japan) in Lebanon and Cirrus (Carl Zeiss Meditec, Dublin, California, USA) SD-OCT in India.

IVZ 1.25 mg/0.05 mL was given initially and on PRN basis. Re-treatment criteria for IVZ therapy were persistence of SRF or IRF.

### Statistical analysis

SPSS V.24 was used for statistical analyses. Snellen visual acuities were converted to logarithm of minimum angle of resolution (logMAR) for statistical analysis. BCVAs from the baseline and at 12 months were compared. Categorical variables were compared using $\chi^2$, and continuous variables were compared using the paired sample t-test. A $p<0.05$ was considered statistically significant.

## RESULTS

Sixteen eyes of 14 patients (nine females and five males) with non-responsive active nAMD were treated with IVZ with a follow-up of 12 months. In this series, the mean age was 67.1±11.5 years, with nine Indians and five Caucasians. The patients had the following systemic comorbidities: hypertension (8), diabetes mellitus (5), migraine (3) and dyslipidaemia (2). Four patients had history of cigarette smoking and one had cerebrovascular accident previously. Twelve eyes were phakic, while four eyes had pseudophakia. Representative cases are shown as figures 1 and 2.

The mean (±SD) number of anti-VEGF injections and duration of treatment prior to switching to IVZ therapy were 8.4±4.7 and 920.9±782 days, respectively (tables 1 and 2). There was no change in the mean logMAR BCVA at baseline and at 12 months following treatment with IVZ therapy ($p=0.978$). Only one (6.25%) eye had a Snellen BCVA gain of greater than three lines, while five (31.25%) eyes had visual gain of at least one line at 12 months. Eight (50%) eyes had a Snellen BCVA loss of at least one line and three (18.75%) eyes had a Snellen BCVA

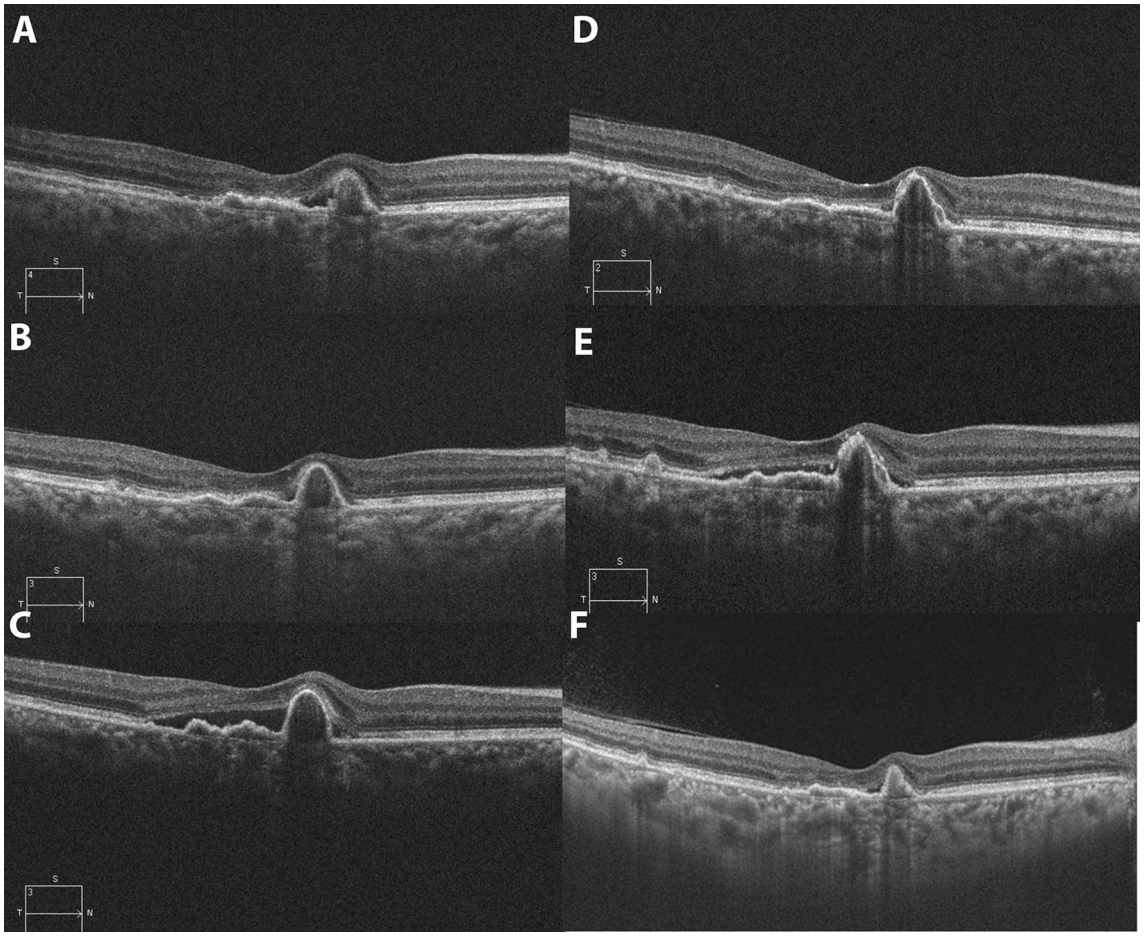


**Figure 1** A 55-year-old female presented with vision loss in her right eye. She has received 3 monthly intravitreal bevacizumab injections without any significant improvement. Her visual acuity was 20/40 with persistent subretinal fluid (SRF) (A). She underwent single intravitreal ziv-aflibercept (IVZ) injection (1.25 mg/0.05 mL) and improved to 20/25 with complete resolution of SRF (B). She was on regular follow-up and had a recurrence (C) 4 months after the first IVZ and responded well to two more monthly IVZ injections (D). Four months after third IVZ injection, she had another recurrence (E) for which she was injected with 2 monthly IVZ injections. She maintained visual acuity of 20/25 at 12-month follow-up (F).

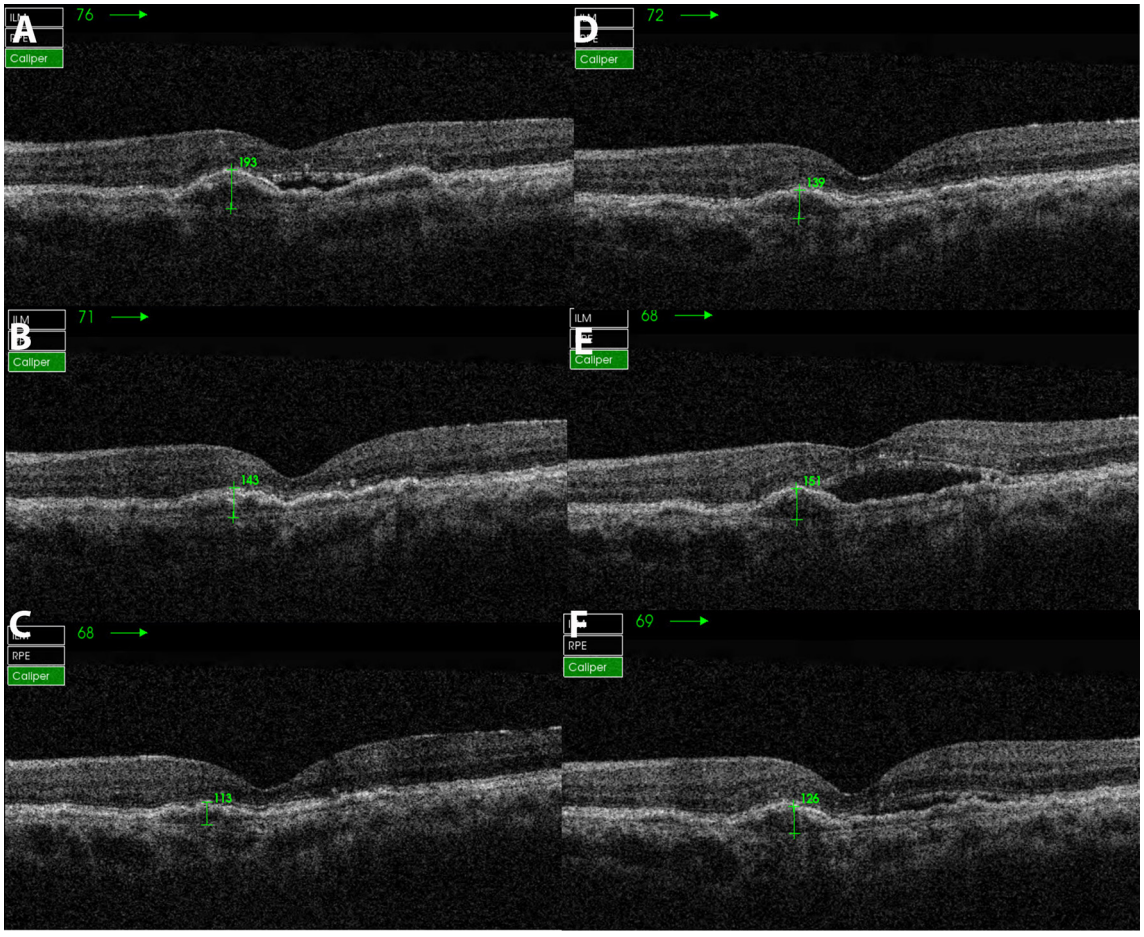


**Figure 2** A 63-year-old male presented with a history of seven intravitreal ranibizumab injections and eight intravitreal bevacizumab injections for choroidal neovascularisation in his left eye. His visual acuity was 20/30 with active choroidal neovascularisation (A). He underwent 2 monthly intravitreal ziv-aflibercept (IVZ) (1.25 mg/0.05 mL) and recovered to 20/25 with no activity on optical coherence tomography (OCT) scan (B). He was under regular follow-up (C and D) and had recurrence at 8 months (E) with visual acuity of 20/63. He was treated with two IVZ injections and recovered visual acuity to 20/40 with improvement on OCT scan (F) with persistent activity.

loss of aleast 3 lines at 12 months. There was no statistically significant difference between the mean CMT at the final examination (248.7±146.5) compared with baseline (254.6±139.3) (p=0.830).

Twelve of the 16 eyes had RPED at baseline. There was a reduction in the RPED height in 9 of the 12 eyes. Of the nine eyes with reduction in RPED heights, 3 (33.3%) had improvement in VA of at least 0.1 logMAR (approximately one line), 4 (44.4%) had vision worsened by at least 0.1 logMAR (approximately one line) and vision was maintained in 2 (22.2%). There was a reduction in the mean height of RPED at 12 months (162.69±183.4 µm) compared with baseline (198.69±210.4 µm) (p=0.075). There was a reduction in the presence of IRF and SRF at 12 months compared with baseline although the differences were not statistically significant (table 1).

The mean number of IVZ injections per eye at 12 months was 5.9±3.3, and two eyes received additional treatment: intravitreal bevacizumab in one eye because of unavailability of IVZ and in combination with PDT in another eye due to poor response to IVZ.

The mean treatment free interval was longer during IVZ therapy (114.4±67.1 days) compared with 76.3±54.6 days before IVZ therapy (p=0.03). Median treatment free interval increased from 60 days before IVZ therapy to 90 days during IVZ therapy.

## DISCUSSION

Eyes with nAMD who are non-responsive to a particular anti-VEGF may respond favourably by switching to another anti-VEGF. Although there was significantly longer treatment free interval in this cohort of eyes who were switched to IVZ therapy, only one-third of eyes had improved Snellen visual acuity of at least one line, while 50% of the eyes had Snellen visual acuity loss of at least one line, at 1 year.

Aflibercept has shown good response to non-responders of other anti-VEGF therapy in eyes with nAMD.[8–14 19–22] While several reports have demonstrated good anatomic response with unchanged visual acuity on switching to aflibercept in non-responders,[8 11 12 14 20 21] other reports have demonstrated in addition a significant improvement in visual acuity.[9 10 13 19 22] In a retrospective review of 189 eyes (155 non-responders) with nAMD on treatment with ranibizumab and bevacizumab and switched to aflibercept, Chan *et al* reported significant improvement in visual acuity, IRF and SRF and RPED heights, and volume at 6 months after the switch to aflibercept.[9] Similarly, Chang *et al* noted improvement in visual acuity and central retinal thickness at 12 months after the switch to aflibercept.[10] Hariri *et al* reported significant improvement in both the anatomic and visual outcome after 3 monthly injections of aflibercept in patients with suboptimal response to ranibizumab

**Table 1** Clinical characteristics of eyes non-responsive to bevacizumab or ranibizumab

| Parameter | Results | Sig. (two tailed) |
|---|---|---|
| No. of eyes | 16 | – |
| Affected eye (right/left) | 7/9 | – |
| Age, mean±SD(CI)(range), years | 67.1±11.5(60.9 to 73.2)(55–87) | – |
| Sex (M/F) | 5/11 | – |
| Race (Caucasian/Indian) | 6/10 | – |
| Previous treatment duration at baseline, mean±SD(CI)(range) | 920.9±782(504.5 to 1337.3)(110–2640) | – |
| Lens status, no. of eyes | | |
| Clear | 4 | |
| Cataract | 8 | |
| PCIOL (posterior chamber intraocular lens) | 4 | |
| Previous treatment per eye, mean±SD (median, range) | | |
| Overall | 8.4±4.7 (8, 2–19) | |
| Bevacizumab | 6.1±3.8 (5.5, 2–18) | |
| Ranibizumab | 2±2.6 (0.5, 0–7) | |
| PDT (photodyanamic therapy) | 0.25±0.4 (0, 0–1) | – |
| No. of Intravitreal ziv-aflibercept injections per eye at 12 months, mean±SD(CI)(range) | 5.9±3.2(4.2 to 7.6)(2–9) | – |
| Additional treatment on intravitreal ziv-aflibercept, frequency (%) | | |
| PDT | 3/16 (18.75) | |
| Bevacizumab | 1/16 (6.25) | |
| Ranibizumab | 1/16 (6.25) | |
| Focal laser | 1/16 (6.25) | |
| Longest treatment free interval, mean±SD(CI)(range), days | | 0.032* |
| Prior to intravitreal ziv-aflibercept | 76.3±54.6(47.2–105.3)(0–180) | |
| During intravitreal ziv-aflibercept therapy at 12 months | 114.4±67.1(78.6 to 150.1)(40–270) | |
| BCVA, logMAR, mean±SD(CI)(range) | | 0.978* |
| Baseline | 0.60±0.59(0.29 to 0.92)(0.1–2.2) | |
| 12 months | 0.60±0.45(0.36 to 0.84)(0–1.5) | |
| Visual acuity gain at 12 months, frequency (%) | | |
| At least one line | 5/16 (31.25) | |
| At least two lines | 2/16 (12.5) | |
| At least three lines | 1/16 (6.25) | |
| Visual acuity loss at 12 months, frequency (%) | | |
| At least one line | 8/16 (50) | |
| At least two lines | 5/16 (31.25) | |
| At least three lines | 3/16 (18.75) | |
| CMT, mean±SD, (range), (µm) | | .830* |
| Baseline | 254.6±139.3(180.5–328.8)(100–572) | |
| 12 months | 248.7±146.5(170.7–326.7)(54–655) | |
| Presence of IRF, yes/no (%) | | 0.611† |
| Baseline | 8/8 (50) | |
| 12 months | 5/11 (31) | |
| Presence of SRF, yes/no (%) | | 0.119† |
| Baseline | 12/4 (75) | |
| 12 months | 5/11 (31) | |
| RPED height, mean±SD(CI),(range), µm | | 0.075* |
| Baseline | 198.69±210.4(86.6 to 310.7),(0–807) | |
| 12 months | 162.69±183.4(64.5 to 259.9),(0–762) | |

*aired sample t-test.
†$\chi^2$.
BCVA, best corrected visual acuity; CMT, central macular thickness; IRF, intraretinal fluid; logMAR, logarithm of minimum angle of resolution; RPED, retinal pigment epithelial detachment; SRF, subretinal fluid.

and bevacizumab.[13] In this cohort of our patients, there was no significant improvement in visual acuity at 12 months following switch to IVZ. Similarly, others did not find significant improvement in visual acuity in their group of patients who had been switched to aflibercept.[8 11 12 14 20 21 23] The lack of significant improvement in anatomic and visual outcome in this series may be attributed to the chronic nature of their disease as confirmed by a long mean duration of follow-up of 921 days prior to switching to IVZ therapy.

A longer treatment free interval will result in a reduction in cost of the therapy for the patients and the health system as well as the reduction in risk associated with frequent injections.[9 23] Chan

**Table 2** Clinical characteristics of individual study eye

| | Age | Sex | Details of previous treatment | Baseline BCVA (logMAR) | Final BCVA (logMAR) | Baseline CRT (microns) | Final CRT (microns) | Baseline PED HEIGHT (microns) | Final PED HEIGHT (microns) | Baseline treatment free interval (days) | Final treatment free interval (days) | Number of IVZ injections at 1 year |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 85 | M | 6B+2A | 1.6 | 1.5 | 303 | 220 | 202 | 144 | 30 | 60 | 5 |
| 2 | 70 | F | 2B | 2.2 | 1.0 | 466 | 285 | 807 | 762 | 0 | 60 | 12 |
| 3 | 80 | F | 18B+1R | 0.4 | 0.4 | 226 | 169 | 324 | 215 | 30 | 40 | 12 |
| 4 | 87 | M | 6B+2A | 1.1 | 1.1 | 312 | 219 | 392 | 211 | 0 | 60 | 11 |
| 5 | 63 | F | 8B+7R | 0.3 | 0.5 | 216 | 175 | 161 | 134 | 50 | 60 | 6 |
| 6 | 63 | F | 8B+7R | 0.18 | 0.3 | 174 | 273 | 193 | 151 | 50 | 240 | 4 |
| 7 | 59 | M | 4B+5R | 0.48 | 0.6 | 236 | 209 | 113 | 120 | 140 | 130 | 4 |
| 8 | 63 | F | 7B+3R, PDT | 0.3 | 0.18 | 138 | 179 | 0 | 0 | 140 | 100 | 4 |
| 9 | 63 | F | 8B+1R, PDT | 0.18 | 0.18 | 140 | 151 | 0 | 0 | 150 | 90 | 3 |
| 10 | 57 | F | 3B | 0.1 | 0 | 346 | 202 | 52 | 59 | 60 | 90 | 4 |
| 11 | 55 | F | 4B+4R, PDT | 0.4 | 0.6 | 430 | 466 | 390 | 266 | 180 | 270 | 3 |
| 12 | 75 | M | 8B | 1.0 | 1.3 | 572 | 655 | 0 | 0 | 120 | 60 | 8 |
| 13 | 55 | F | 4R+4B | 0.6 | 1.0 | 150 | 54 | 184 | 117 | 90 | 180 | 2 |
| 14 | 55 | F | 3B | 0.3 | 0.1 | 100 | 96 | 268 | 164 | 60 | 120 | 5 |
| 15 | 84 | F | 4B | 0.3 | 0.6 | 123 | 370 | 93 | 252 | 60 | 150 | 6 |
| 16 | 59 | M | 5B | 0.18 | 0.3 | 142 | 256 | 0 | 0 | 60 | 120 | 3 |

B, intravitreal bevacizumab (1.25 mg/0.05 mL); BCVA, best corrected visual acuity; CRT, central retinal thickness; IVZ, intravitreal ziv-aflibercept (1.25 mg/0.05 mL); logMAR, logarithm of minimum angle of resolution; RPED, retinal pigment epithelial detachment; R, intravitreal ranibizumab (0.5 mg/0.05 mL).

*et al* reported a longer clinical benefit of aflibercept compared with ranibizumab and bevacizumab in their cohort of non-responders, and this could lead to reduction in the treatment burden and total cost of treatment with aflibercept due to greater interval between injections.[9] Similarly, Yonekawa *et al* observed extension of treatment interval on switching to aflibercept in patients with refractory nAMD.[14] Hatz and Prünte have reported that the maximum recurrence-free treatment interval after switching from ranibizumab to aflibercept increased to at least 6 weeks in 35% of patients at 6 months after the switch using a treat and extend protocol although visual acuity remained unchanged.[23] In our cohort of patients who had been switched to IVZ therapy, 94% of eyes had treatment free interval of at least 60 days at 12 months after the switch. The extension of the treatment interval on switching to IVZ injection could be attributed to the natural history of the disease as our cohort had a long duration of treatment. Patients need less injections as the duration of disease and treatment increases. Compounded ziv-aflibercept is much less expensive compared with aflibercept (US$50 vs US$1980) and hence may lead to an almost 98% lower cost of treatment to individuals and the health system. This will be particularly beneficial in low-income to middle-income countries.

Aflibercept has been reported to be effective in treatment-resistant RPEDs, although the long-term visual gain on flattening or reduction in RPED height is unknown.[12 24–26] Patel *et al* reported near complete or complete flattening of RPED in three eyes with persistent RPED despite repeated injections with ranibizumab after 3 months of switching to aflibercept.[26] All three eyes had improvement in their visual acuity.[26] Broadhead *et al* reported significant reduction in RPED heights after 48 weeks of switching to aflibercept in eyes with treatment-resistant nAMD.[24] The authors did not find significant correlation between reduction in RPED height and visual acuity changes.[24] In this study visual acuity improved or was maintained in 56% of eyes who had reduction in RPED heights at 12 months.

Limitations of our study include small sample size and retrospective nature. We did not evaluate OCT features to assess poor response in detail. 'Non-response to previous anti-VEGF therapy probably could be due to under treatment (mean 8.4 injections), due to lack of standardised protocol.' Finally, the treatment protocol was as-needed, which has been previously shown to lead to a poorer visual outcome compared with 'treat and extend' or 'monthly'.[27]

In conclusion, we report IVZ therapy as safe and effective in eyes with nAMD who are non-responsive to bevacizumab or ranibizumab. IVZ therapy extended the treatment free interval with maintenance of visual and anatomical outcome in such difficult situations. Off-label IVZ therapy can be considered as affordable and effective alternative to high-cost, approved anti-VEGF therapies, especially in low-income countries. Studies with larger sample size and longer follow-up are warranted.

**Contributors** Design of the study (JC and KA) and conducted the study (KA, AM and JC); collection (KA, AM and CD), management (JC, AM and KA), analysis (IZB and JC) and interpretation of the data (IZB, JC and AM); and preparation (IZB, JC, KA and AM), review (IZB, JC, KA and AM) or approval (IZB, JC, KA and AM) of the manuscript.

**Competing interests** None declared.

**Patient consent** Obtained.

**Ethics approval** L V Prasad Eye Institute.

**Provenance and peer review** Not commissioned; externally peer reviewed.



## REFERENCES

1 Amoaku WM, Chakravarthy U, Gale R, *et al*. Defining response to anti-VEGF therapies in Neovascular AMD. *Eye* 2015;29:721–31.
2 Eghøj MS, Sørensen TL. Tachyphylaxis during treatment of exudative age-related macular degeneration with ranibizumab. *Br J Ophthalmol* 2012;96:21–3.
3 Krebs I, Glittenberg C, Ansari-Shahrezaei S, *et al*. Non-responders to treatment with antagonists of vascular endothelial growth factor in age-related macular degeneration. *Br J Ophthalmol* 2013;97:1443–6.
4 Gasperini JL, Fawzi AA, Khondkaryan A, *et al*. Bevacizumab and ranibizumab tachyphylaxis in the treatment of choroidal neovascularisation. *Br J Ophthalmol* 2012;96:14–20.
5 Nagai N, Suzuki M, Uchida A, *et al*. Non-responsiveness to intravitreal aflibercept treatment in neovascular age-related macular degeneration: implications of serous pigment epithelial detachment. *Sci Rep* 2016;6:29619.

6 Suzuki M, Nagai N, Izumi-Nagai K, *et al*. Predictive factors for non-response to intravitreal ranibizumab treatment in age-related macular degeneration. *Br J Ophthalmol* 2014;98:1186–91.
7 Singh RP, Srivastava SK, Ehlers JP, *et al*. A single-arm, investigator-initiated study of the efficacy, safety, and tolerability of intravitreal aflibercept injection in subjects with exudative age-related macular degeneration previously treated with ranibizumab or bevacizumab (ASSESS study): 12-month analysis. *Clin Ophthalmol* 2015;9:1759–66.
8 Bakall B, Folk JC, Boldt HC, *et al*. Aflibercept therapy for exudative age-related macular degeneration resistant to bevacizumab and ranibizumab. *Am J Ophthalmol* 2013;156:15–22.
9 Chan CK, Jain A, Sadda S, *et al*. Optical coherence tomographic and visual results at six months after transitioning to aflibercept for patients on prior ranibizumab or bevacizumab treatment for exudative age-related macular degeneration (an american Ophthalmological Society thesis). *Trans Am Ophthalmol Soc* 2014;112:160–98.
10 Chang AA, Broadhead GK, Hong T, *et al*. Intravitreal aflibercept for treatment-resistant neovascular age-related macular degeneration: 12-month safety and efficacy outcomes. *Ophthalmic Res* 2015;55:84–90.
11 Gharbiya M, Iannetti L, Parisi F, *et al*. Visual and anatomical outcomes of intravitreal aflibercept for treatment-resistant neovascular age-related macular degeneration. *Biomed Res Int* 2014;2014:1–7.
12 Gokce G, Durukan AH, Koylu MT, *et al*. Efficacy of aflibercept on exudative age-related macular degeneration in patients exhibiting complete ranibizumab resistance and tachyphylaxis. *Arq Bras Oftalmol* 2016;79:384–9.
13 Hariri A, Diniz B, Fou LV, *et al*. Quantitative OCT subanalysis of eyes with choroidal neovascularization switched from multiple injections of bevacizumab or ranibizumab to intravitreal aflibercept. *Ophthalmic Surg Lasers Imaging Retina* 2015;46:195–200.
14 Yonekawa Y, Andreoli C, Miller JB, *et al*. Conversion to aflibercept for chronic refractory or recurrent neovascular age-related macular degeneration. *Am J Ophthalmol* 2013;156:29–35.
15 Chang AA, Li H, Broadhead GK, *et al*. Intravitreal aflibercept for treatment-resistant neovascular age-related macular degeneration. *Ophthalmology* 2014;121:188–92.
16 Chhablani J, Narayanan R, Mathai A, *et al*. Short-term safety profile of intravitreal ziv-aflibercept. *Retina* 2016;36:1126–31.
17 Mansour AM, Al-Ghadban SI, Yunis MH, *et al*. Ziv-aflibercept in macular disease. *Br J Ophthalmol* 2015;99:1055–9.
18 Mansour AM, Chhablani J, Antonios RS, *et al*. Three-month outcome of ziv-aflibercept for exudative age-related macular degeneration. *Br J Ophthalmol* 2016;100:1629–33.
19 Aghdam KA, Pielen A, Framme C, *et al*. Visual and anatomic outcomes after conversion to aflibercept in neovascular age-related macular degeneration: 12-month results. *Eur J Ophthalmol* 2016;26:473–8.
20 Ho VY, Yeh S, Olsen TW, *et al*. Short-term outcomes of aflibercept for neovascular age-related macular degeneration in eyes previously treated with other vascular endothelial growth factor inhibitors. *Am J Ophthalmol* 2013;156:23–8.
21 Pfau M, Fassnacht-Riederle HM, Freiberg FJ, *et al*. [Switching Therapy from Ranibizumab and/or Bevacizumab to Aflibercept in Neovascular Age-Related Macular Degeneration (AMD): One-Year Results]. *Klin Monbl Augenheilkd* 2016;233:945–50.
22 Seguin-Greenstein S, Lightman S, Tomkins-Netzer O. A Meta-analysis of studies evaluating visual and anatomical outcomes in patients with treatment resistant neovascular Age-Related Macular Degeneration following switching to treatment with aflibercept. *J Ophthalmol* 2016;2016:4095852.
23 Hatz K, Prünte C. Intravitreal aflibercept in neovascular age-related macular degeneration with limited response to ranibizumab: a treat-and-extend trial. *Retina* 2017;37:1185–92.
24 Broadhead GK, Hong T, Zhu M, *et al*. Response of pigment epithelial detachments to intravitreal aflibercept among patients with treatment-resistant neovascular age-related macular degeneration. *Retina* 2015;35:975–81.
25 Kanesa-Thasan A, Grewal DS, Gill MK, *et al*. Quantification of change in pigment epithelial detachment volume and morphology after transition to Intravitreal Aflibercept in eyes with recalcitrant neovascular AMD: 18-month results. *Ophthalmic Surg Lasers Imaging Retina* 2015;46:638–41.
26 Patel KH, Chow CC, Rathod R, *et al*. Rapid response of retinal pigment epithelial detachments to intravitreal aflibercept in neovascular age-related macular degeneration refractory to bevacizumab and ranibizumab. *Eye* 2013;27:663–8.
27 Chin-Yee D, Eck T, Fowler S, *et al*. A systematic review of as needed versus treat and extend ranibizumab or bevacizumab treatment regimens for neovascular age-related macular degeneration. *Br J Ophthalmol* 2016;100.