

Long-term outcome of treat and extend intravitreal ziv-aflibercept therapy

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ABSTRACT

Aim To assess the 30-month outcome of treat and extend (TAE) intravitreal ziv-aflibercept therapy in eyes with macular diseases.

Methods In this prospective study, consecutive subjects received intravitreal 0.05 mL ziv-aflibercept (1.25 mg) injections for various macular diseases. Outcome measures were best-corrected visual acuity (BCVA) (logarithm of the minimum angle of resolution) and central macular thickness (CMT) on spectral domain optical coherence tomography. Paired comparison was done using Wilcoxon signed-rank test calculator.

Results Fifty-three eyes of 48 subjects (33 naïve eyes) received intravitreal ziv-aflibercept and were followed between 12 and 30 months following TAE included neovascular age-related macular degeneration (nAMD) (35 eyes) and diabetic macular oedema (DMO) (18 eyes). In eyes with nAMD, CMT decreased by 107.8 µm at the 30-month follow-up ($p=0.012$) with BCVA gain of 0.52 ($p=0.001$). In eyes with DMO, CMT decreased by 224.3 µm at the 30-month follow-up ($p=0.027$) with BCVA gain of 0.46 ($p=0.042$). Combining all disease categories, the mean number of injections was 9.2 at month 12, 2.5 between 12 and 18 months, 1.6 between 18 and 24 months and 1.0 between 24 and 30 months.

Conclusions Using TAE regimen, intravitreal ziv-aflibercept appeared efficacious at managing retinal disease through month 30 using the TAE regimen.

Vascular endothelial growth factor (VEGF) antagonists usage follows regimens based on drug half-life, disease severity and activity, ophthalmologist preference, affordability and patient compliance. Fixed dosing consists of injections at present intervals. Pro re nata (PRN) regimen consists of as-needed injections after loading phase with monthly monitoring visits. Treat and extend (TAE) consists of loading phase until fluid resolution, followed by 2-week extension intervals until the next injection. TAE was first introduced by Spaide and Freund in 2007 for neovascular age-related macular degeneration (nAMD) aiming to reduce treatment burden, and this approach was extended to other diseases.¹ Ziv-aflibercept (Sanofi and Regeneron Pharmaceuticals Tarrytown, New York, USA) is the off-label, equivalent to the approved aflibercept (Eylea, Regeneron, Tarrytown, New York, USA), for the treatment of nAMD and diabetic macular oedema (DMO). A number of clinical reports dealt with a short to medium term of intravitreal ziv-aflibercept therapy^{2,3} using PRN methodology⁴⁻⁶ or a mixture of PRN and

TAE.⁷ Emerging recent literature focuses on the clinical efficacy of TAE protocols in ranibizumab and aflibercept in various macular disorders.⁸⁻¹⁰ We present the 30-month visual and anatomic results of intravitreal ziv-aflibercept (1.25 mg) therapy following TAE regimen.

METHODS

This prospective non-randomised one-centre study examined the efficacy of ziv-aflibercept from March 2015 to February 2018, was approved by the institutional review committee and adhered to the tenets of the Declaration of Helsinki. All patients signed a formal consent for this off-label protocol. Inclusion criteria included a treatment with ziv-aflibercept for at least 1 year by TAE for various macular diseases (nAMD and DMO). Exclusion criteria included use of other intravitreal therapies during the study period, prior vitreoretinal surgery, central corneal scar, dense cataract, infectious conjunctivitis, vitreous haemorrhage, asteroid hyalosis, macular ischaemia, hole, schisis or scar. A washout of 2 months was adopted for previously treated eyes with other anti-VEGF agents due to inadequate response or financial issue.

Ziv-aflibercept 0.05 mL (1.25 mg aflibercept) was prepared according to standard compounding protocols with storage at 4°C for 4 weeks. The same operator performed the vision exam, optical coherence tomography (OCT) test and intravitreal injection. Best-corrected visual acuity (BCVA) was assessed by ETDRS R chart (Precision Vision, La Salle, Illinois, USA). Central macular thickness (CMT) or mean thickness in central 1000 µm diameter area was done using spectral domain OCT 3D-2000 Topcon FA plus (Topcon, Tokyo, Japan).

The injection regimen followed the protocol for DMO set by initial 5 monthly injections, then TAE by 2 weeks based on OCT. For eyes with nAMD, three initial monthly injections were done, then monthly until absence of activity by OCT, then TAE by 2 weeks. Eyes with incomplete clinical response received monthly injections. When the interval between injections reached beyond 4 months, injections were stopped, and OCT was repeated every 4 months thereafter.

SPSS V.22 was used for statistical analysis. To assess the change from baseline in CMT and BCVA, paired comparison was carried using Wilcoxon signed-rank test calculator with significance set at $p \leq 0.05$.



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Table 1 Response to treat and extend intravitreal ziv-aflibercept therapy

	Disease	BCVA mean±SD (p values) in logMAR	CMT mean±SD (p values) in microns	Number of IVT ziv-aflibercept injections±SD	Number of eyes
Baseline	AMD	1.22±0.60	361.0±125.8		35
	DMO	0.82±0.32	477.1.0±101.6		18
12 months	AMD	0.71±0.43 (p<0.001)	255.4±89.2 (p<0.001)	9.7±2.6	35
	DMO	0.48±0.24 (p<0.001)	294.1±86.2 (p<0.001)	8.4±2.8	17
18 months	AMD	0.79±0.49 (p<0.001)	250.3±61.4 (p<0.001)	2.6±1.8	32
	DMO	0.55±0.31 (p=0.001)	265.0±68.0 (p=0.001)	2.5±1.0	15
24 months	AMD	0.75±0.46 (p=0.001)	243.7±51.0 (p<0.001)	1.7±1.5	22
	DMO	0.51±0.14 (p=0.011)	344.6±112.9 (p=0.011)	1.4±1.2	9
30 months	AMD	0.77±0.51 (p=0.001)	261.5±66.8 (p=0.007)	1.0±1.2	19
	DMO	0.47±0.17 (p=0.042)	282.0±54.6 (p=0.027)	1.2±1.0	5

P values are in comparison with baseline values.

BCVA, best-corrected visual acuity; CMT, central macular thickness; DMO, diabetic macular oedema; IVT, intravitreal; logMAR, logarithm of the minimum angle of resolution; nAMD, neovascular age-related macular degeneration; NS, not significant.

RESULTS

A total of 127 eyes were prospectively enrolled at the time of study analysis: 53 eyes met the inclusion criteria and 57 eyes did not reach the 12-month follow-up. Seventeen eyes were excluded because of irregular visits (nine eyes with follow-up 16–30 months all with good response), 1 eye received aflibercept during travel, 1 eye developed lamellar macular hole after sixth injection and 4 eyes were lost to follow-up after a good response to two or three injections.

A total of 53 eyes (five bilateral) of 48 Caucasian subjects (31 male and 16 female) were followed for a mean of 25.2 months (SD=7.3 months; range 12–36 months). Eyes were treated for nAMD (35 eyes) and DMO (18 eyes). The mean age was 71.9 years (range 40–92). There were 33 treatment naïve eyes and 20 treatment non-naïve eyes. There were significant visual gain and significant decrease in macular thickness at the 2 year assessment (table 1). In this longitudinal study, 21 patients (24 eyes) reached the 30-month follow-up. At 30 months, significant visual gain and reduction in macular thickness were again noted in both groups of nAMD and DMO (table 1 and figure 1). In eyes with nAMD, CMT decreased by 107.8 µm at the 30-month follow-up (p=0.012) with BCVA gain of 0.52 (p<0.001). In eyes with DMO, CMT decreased by 224.3 µm at the 30-month follow-up (p=0.027) with BCVA gain of 0.46 (p=0.042). Combining all disease categories, the mean number of injections was 9.2 at 12 months, 2.5 between 12 months and 18 months, 1.6 between 18 months and 24 months and 1.0 between 24 months and 30 months. Combining all disease categories, the mean number of injections was 9.2 at 12 months, 2.5 between 12 months and 18 months, 1.6 between 18 months and 24 months and 1.0 between 24 months and 30 months. Naïve eyes tended to need more injections and to have more visual gain and more macular flattening. At the 24-month follow-up, 18 naïve eyes had a mean flattening of 135.7 microns and a visual gain of 0.51 logarithm of the minimum angle of resolution (logMAR), while 13 non-naïve eyes had a mean flattening of 75.4 microns (60.3 microns difference, p=0.31) and a visual gain of 0.27 logMAR (0.24 difference, p=0.16). The mean number of injections for naïve versus non-naïve eyes was 9.7 versus 8.4 from 0 months to 12 months, 2.6 versus 2.4 from 12 months to 18 months and 1.9 versus 1.1 between 18 months and 24 months.

Initiation of TAE in nAMD occurred after a mean of 8.0 injections (range 4–16) at 9.9 months (range 5–18 months). No eye with nAMD had initiation of TAE after three injections. Initiation of TAE in DMO occurred after a mean of 7.7 injections (range 4–17) or 11.4 months (range 6–17 months). Only five

eyes had good response after 5 monthly injections and TAE regimen initiated after the fifth injection. One eye developed a single episode of transient iritis, which recovered well to topical treatment. No systemic complications were noted.

DISCUSSION

Ziv-aflibercept intravitreal injections achieved long-term visual gain and anatomic stability over 30-month of follow-up in this prospective small series. We used a similar regimen to several prospective TAE protocols (table 2)^{8–12} such as used with ranibizumab in the Treat-and-Extend Protocol in patients with naïve wAMD (TRES-AMD) study.⁸ In TRES-AMD study visual and anatomic gains at 2 years were comparable between TAE group (23 eyes) and monthly dosing group (18 eyes): 8.7 letters gain versus 10.5 (p=0.64), 199 µm versus 170 µm (p=0.54) and 18.6 injections versus 25.5 injections. Similarly, we achieved quite similar anatomic gains but superior visual gains (due to initial selection bias of a majority of eyes with very poor vision from submacular haemorrhage such as in figure 1) (table 2) to that reported with monthly aflibercept⁹ or TAE aflibercept regimens for nAMD.¹⁰ In another comparative prospective randomised multicentre protocol for nAMD, the Lucentis Compared to Avastin Study (LUCAS) researchers found that TAE with bevacizumab or ranibizumab gained mean increases in BCVA of 7.9 and 8.2 letters, respectively, after 1 year of treatment in nAMD.¹² This was comparable with the BCVA gains in the Comparison of Age-Related Macular Degeneration Treatments Trials (CATT) study, which employed monthly injections of these drugs; CATT gains were 8.0 and 8.5 letters, respectively, at 1 year.¹³ Furthermore, the LUCAS researchers analysed the 2-year outcome in a total of 339 patients: bevacizumab was equivalent to ranibizumab, with 7.4 and 6.6 letters gained, respectively. The bevacizumab group received 18.2 injections versus 16.0 injections for the ranibizumab group through 2 years. Finally, DeCroos and colleagues⁹ completed the Aflibercept Treatment with Less-frequent Administration Study, a 2-year, multicentre, prospective, open-label study evaluating aflibercept as TAE regimen in naïve nAMD eyes of 40 patients. The mean letter gain was 7.2 and 2.4 letters at 1 and 2 years, respectively. The mean number of injections was 8.0 and 6.5 during the first and second years, respectively.

We achieved good anatomical and visual outcome with ziv-aflibercept TAE regimen in DMO as well. Previous studies have demonstrated short-term efficacy of ziv-aflibercept in DMO.^{14–17} TAE regimens in DMO have been successful using ranibizumab.¹⁸

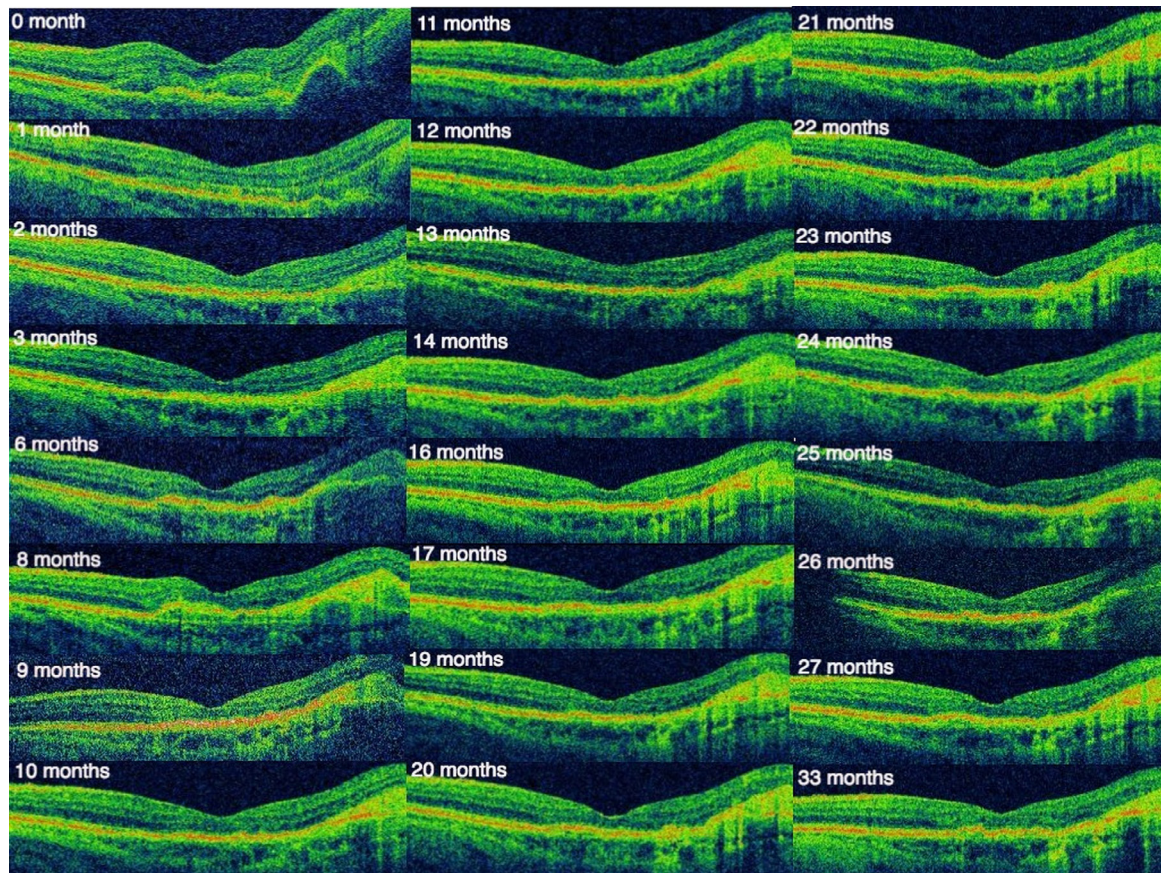


Figure 1 This 88-year-old Caucasian man had naïve neovascular age-related macular degeneration in the left eye with presenting vision of finger counting 6 m from fresh submacular bleed and ended with 20/20 over 36 months of follow-up after 15 intravitreal injections of ziv-aflibercept. Initially, 6 monthly injections caused resolution of subretinal haemorrhage, then the patient was informed to extend the interval treatment to 6 weeks. Indocyanine green angiography failed to detect polypoidal lesions under the RPE detachment. The patient showed up for OCT testing but resumed his injections 4 months later because he was very happy with his improved vision. He again received 4 monthly injections as RPE detachment had extended further into the fovea. After 3 months of no show for treatment, he received three additional injections every 2 months. Then he refused further treatment but accepted OCT monitoring for the next 15 months for potential drug toxicity. Vision stabilised at the 20/20 level. OCT, optical coherence tomography; RPE, retinal pigment epithelium.

Prünte and colleagues¹⁸ demonstrated non-inferiority of ranibizumab TAE regimen to ranibizumab PRN regimen for BCVA in patients with DMO.

Besides the tremendous economic savings with the use of ziv-aflibercept, its additional use as TAE instead of monthly adds further economic savings with reduced number of visits and

injections.^{19 20} TAE regimen with aflibercept improved BCVA and CMT to the same extent as 2-month proactive regimen in VIEW 1 and 2,²¹ with a reduced number of injections in a prospective randomised study in Japanese with wAMD.²² In our study, TAE regimen reduced the number of injections over the bimonthly proactive for the duration of 36 months as follows: TAE (14.5

Table 2 List of prospective 2-year studies using treat and extend protocol in neovascular age-related macular degeneration (nAMD)

First author, year of publication	Number of eyes	Visual gain from baseline	CMT change from baseline (microns)	Number of injections	Anti-VEGF used	% Drop out	Name of collaborative study
De Croiset <i>et al</i> ³ 2017	40	2.4	130	14.5	Aflibercept (2mg)	22.5	ATLAS
Berget <i>et al</i> ¹² 2016	218	6.6	122	16.0	Ranibizumab (0.5mg)	21.1	LUCAS
Berget <i>et al</i> ¹² 2016	213	7.4	113	18.2	Bevacizumab (1.25mg)	21.6	LUCAS
Wykoff <i>et al</i> ⁸ 2017	40	8.7	199	18.6	Ranibizumab (0.5mg)	16.7	TREX-AMD
Abadie <i>et al</i> ¹¹ 2014	120	8.0	Not assessed	14.2	Ranibizumab (0.5mg) or Bevacizumab (1.25mg)	16.0	
Jørstad <i>et al</i> ¹⁰ 2017	50	3.5	48	17.2	Aflibercept (2mg)	10.0	
Current study at 2 years	22	24.4	120	13.8	Ziv-aflibercept (1.25mg)	0.0	
Current study at 30 months	18	26.3	108	14.7	Ziv-aflibercept (1.25mg)	0.0	

ATLAS, Aflibercept Treat and extend for Less frequent Administration Study; CMT, central macular thickness; LUCAS, Lucentis Compared to Avastin Study; TREX-AMD, Treat-and-Extend Protocol in patients with naïve wet age related macular degeneration; VEGF, vascular endothelial growth factor.

injections) (current study), bimonthly (19 injections),²² monthly (36 injections) or in other words TAE injections were 4.5 less in number than the bimonthly regimen and 21.5 less than the monthly regimen. We calculated the cost of a single dose of intravitreal ziv-aflibercept to be 40 times that of aflibercept, and with adoption of TAE over bimonthly regimen, there is further 23.6% reduction of total costs over the 36-month period.

The current study is somewhat unique in patient selection (recent onset of disease, enthusiasm for therapy and highly committed for protocols), single operator (exam, OCT and education) and no drop out (complimentary therapy and close monitoring). Drawbacks include selection bias, absence of controls, small number of patients. Also as the dose of the intravitreal ziv-aflibercept is 1.25 mg aflibercept/0.05 mL, it cannot be directly compared with Eylea (2.0 mg aflibercept/0.05 mL).

In conclusion, this is the longest follow-up of ziv-aflibercept in retinal disorders attesting to the sustained and long-term efficacy of intravitreal ziv-aflibercept used in TAE regimen. In addition, this study reaffirmed the value of ziv-aflibercept as a cost-effective VEGF antagonist with the compounded drug retaining full functional potency for at least 1 month.

Contributors AMM, MEF and JC: design; AMM: conduct of the study; AMM: collection; AMM: management; AMM, MEF, JC and AC: analysis; AC: interpretation of the data; AMM, JC and MEF: preparation; AMM, MEFA and JC: review; AMM, MEF, JC and AC: approval of the manuscript.

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Patient consent Obtained.

Ethics approval Rafic Hariri University Hospital.

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