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Article

Five years outcome of Antivegef Injection for management of Diabetic Macular Edema

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Abstract

Background: Intravitreal injections (IVI) of anti-vascular endothelial growth factor (anti-VEGF) are used to treat diabetic macular edema (DME). *Material & Method*: Retrospective electronic data review for four years after starting treatment and prospective recording for an additional 1 year were conducted to assess the five years visual outcome of anti-VEGEF injections in the treatment of DME. Main outcome was visual acuity 5 years after starting the treatment. *Results*: One hundred eyes were evaluated, the median of vision all over the five years had improved compared to the Baseline; this difference was statistically significant all over the five years in total (P 0.001), but by comparing each year to the baseline vision, the statistically significant difference was noted for the first four years only, while the 5th year vision difference from Baseline was not statically significance P0 (0.484). *Conclusion*: Anti-VEGFs produce a significant improvement in best-corrected visual acuity (BCVA) in patients with DME but this improvement is lost after 5 years of follow-up.

Keywords: Diabetic macular edema, Aflibercept, Ranibizumab, Bevacizumab

Introduction

A leading cause of visual impairment among diabetics is diabetic macular edema (DME) affecting about 21 million all over the world.(1) Different treatment options, including macular laser, intravitreal anti-VEGF injections, intravitreal steroids have been shown to be effective for DME.(1)

Diabetic macular edema (DME) is characterized by damage to the inner blood-retina barrier caused by metabolic changes and inflammation.(2) The inflammation is caused by inflammatory cells, cytokines, growth factors, and enzymes.(2) previously, laser treatment and vitrectomy were commonly used to treat DME.(2, 3). Currently, the standard treatment has become intravitreal injections of anti-VEGF.(2, 4)

Different types of anti-VEGF are used to treat DME like bevacizumab (Avastin) which is used as off-label, in addition to the approved drugs; ranibizumab (Lucentis,), and more recently aflibercept (Eylea).(5) Although many injections are needed during the first few years of treatment. A Single-dose of injection is not enough to evaluate the efficacy of treatment, and most patients required repeated injections. The original management protocol mandates frequent follow-up visits which is costly and inconvenient.(6) Other treatment protocol includes pro re nata (PRN) protocol and treats and extend protocol.(7, 8)

In Treatment as-needed or (PRN) regimen repeating injection depends on recurrence of ME which reduce the number of injections. PRN protocol reduces the stress and financial cost of the hospital eye service.(7)

The treat and extend (TAE) protocol was used originally in age-related macular degeneration (AMD) management. TAE differs from the PRN protocol in that we rely on clinical examinations and macular thickness on OCT to determine the duration between injections. Thus, an individualized follow-up regimen is set for each eye.(7)

In Diabetic Retinopathy Clinical Research Network (DRCR.net) Protocol T, residual macular edema was still present in at least half of the injected eyes and up to 73% of them twelve weeks after initiating the treatment according to the anti-VEGF used. While 32% to 66% had residual macular edema by the end of the 24th week of initiating the treatment. Two years following the treatment, these eyes final average vision was 20/32 regardless of the used anti-VEGF. Moreover, good visual outcomes were obtained in eyes with persistent DME following 6 monthly injections in the second and third year using either Protocol T or Protocol I.(9, 10)

The aim of our study is to assess the long-term visual outcome of DME treatment with anti-VEGEF.

Methods

Patients who started intravitreal anti-VEGF injections for DME 4 years ago in Royal Victoria infirmary in Newcastle (eyes with previous steroid injections were excluded) were followed up until the completion of 5 years.

Inclusion criteria:

1) Had a diagnosis of DME.
2) Started treatment with intravitreal anti-VEGF (bevacizumab, ranibizumab, or aflibercept) 4 years ago.
3) Had continuous enrolment within royal Victoria infirmary for five years after starting the treatment.

Exclusion criteria:

1) Eyes had a concomitant diagnosis of underlying macular pathology (e.g., macular degeneration or retinal vascular occlusions.
2) Previous therapy with an intraocular or periocular steroid (e.g., triamcinolone, dexamethasone).

All data were recorded using an electronic medical record (EMR) system (Medisoft Ophthalmology; Medisoft Limited, Leeds, UK), which mandated the collection of a standardized data set throughout the DME care pathway. The lead clinician and Caldicott Guardian (nominee responsible for data protection) at the hospital gave written approval for anonymized data extraction.

Despite the retrospective nature of part of the current study, prospective defining of the EMR mandated data set was done before initial data entry. So, the study methodology is more like an electronic case report form used in clinical trials and should not be considered as a conventional retrospective review of data.

Retrospective electronic data review for four years after starting treatment and prospective recording until completion of 5 years follow-up was conducted.

Outcome measure:

Primary outcome was the Best-corrected visual acuity ETDRS letters (before starting treatment,1year, two years, three years, four years, five years of starting treatment).

Secondary outcomes include correlation between the age and visual outcome, Number of letters as visual gain or loss between the baseline vision and at 5th year of follow-up, Number of injections over the first, 2nd, 3rd, 4th, and 5th years, the relation between previous PRP laser treatment and visual acuity outcome The number of patients who lost follow-up and causes of incomplete 5 years follow up period including death.

Ethics: Ethical permission is not a prerequisite for anonymized database analyses like this current study as they are considered as audits or treated as service improving project (see http://www.hra.nhs.uk/research-community/beforeyou-apply/determine-whether-your-study-is-research/). This study was conducted in accordance with the Declaration of Helsinki and the United Kingdom's Data Protection Act.

Registration number: Ethical permission is not a prerequisite for anonymized database analyses in this current study as they are considered as audits or treated as a service-improving project (see http://www.hra.nhs.uk/research-community/beforeyou-apply/determine-whether-your-study-is-research/).

Statistical analysis: Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp). The Kolmogorov-Smirnov test was used to verify the normality of distribution. Significance of the obtained results was interpreted at the 5% level.

The used tests were
1 - Chi-square test
For categorical variables, to compare between different groups.
2 - Monte Carlo correction
Correction for chi-square when more than 20% of the cells have expected count less than 5.
3 - Student t-test
For normally distributed quantitative variables, to compare between two studied groups.
4 - Mann Whitney test
For abnormally distributed quantitative variables, to compare between two studied groups.
5 - Friedman test
For abnormally distributed quantitative variables, to compare between more than two periods or stages and Post Hoc Test (Dunn's) for pairwise comparisons.
6 - Spearman coefficient
To correlate between two distributed abnormally quantitative variables.

Results

On reviewing the EMR database DME was found in 288 eyes (246 patients) for which treatment with anti-VEGEF started between 2013 and 2015, of whom 147 eyes (118 patients) had met the inclusion criteria.
Forty patients out of 118 (34%) didn't complete the five years of follow-up, in which 26 patients (22%) died, nine failed to attend, two had been referred back to diabetic screening program because of stable retinopathy, two had their care transferred to the different eye hospital and one traveling abroad. Data on VA at Baseline and five years of follow-up were available for 100 eyes from 78 persons. **Table (1)** shows the patients' demography and clinical features.

Table 1. Patients' demography and clinical features.

Characteristic	N=100 eyes (78patients)
Age, years	
Mean (SD)	67.87(11.61)
Range	42 - 95
Sex, N (%)	
Female	36(46)
Male	42(54)
Type of diabetes, N (%)	
Type 1 diabetes	14(19.5)
Type 2 diabetes	58(80.5)
Baseline vision, median (range)	65(hand motion-86)
Baseline CMT, median (IQR)	453.0(409.5_526.5)
Previous focal laser, N (%)	43(43)
Previous PRP, N (%)	35(35)
Previous vitrectomy, N (%)	2(2)

The median of vision all over the five years had improved compared to the Baseline; this difference was statistically significant all over the five years in total (P0.001), but by comparing each year to the baseline vision using Friedman test and Post Hoc Test (Dunn's), the statistically significant difference was noted for the first four years only, while the 5th year vision difference from Baseline was not statically significance P0 was (0.01, 0.001, 0.005, 0.007, 0.484) for the 1st,2nd,3rd,4th,5th year respectively (**Figure 1**).

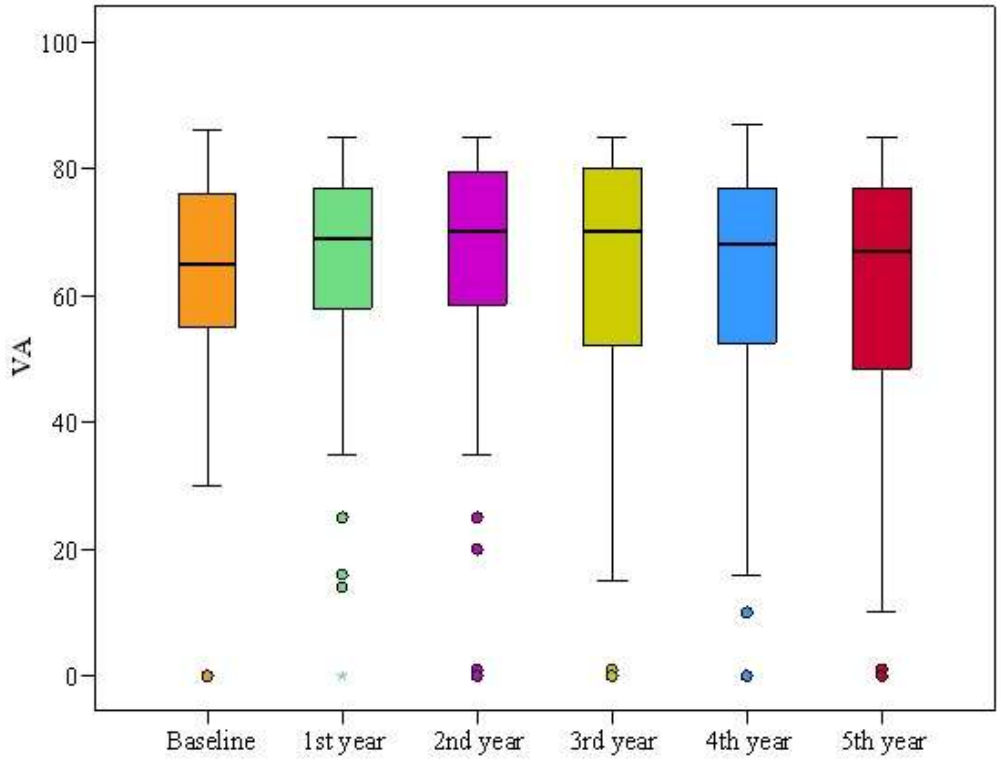

Figure (1): Compare VA in total cases all over the 5 years of follow-up

Figure (2) shows the percentage of 3 groups of eyes with improved vision (gaining >=15 letters), stable vision (within +/- 15 letters), or getting worse (lost >=15 letters) for each year compared to the baseline vision.

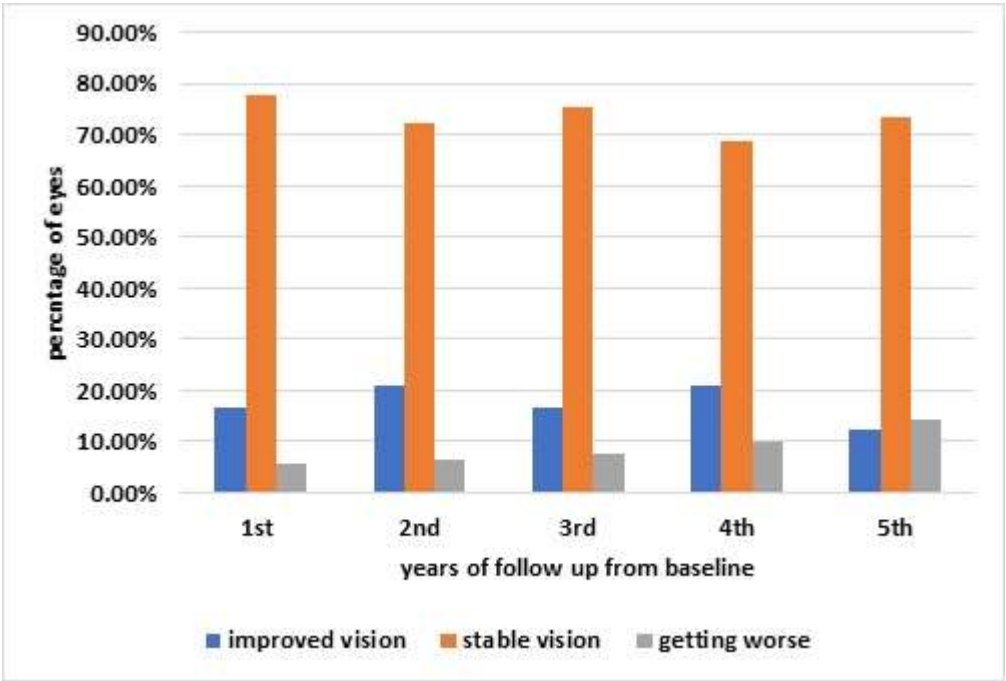

Figure (2): Percentage of eyes groups with improved, stable, and deteriorated vision all over the five years.

As regards the age as baseline factor Spearman correlation shows a negative correlation between age and vision all over the five years, but this correlation was only statistically significant for the first and 2nd year (P=0.039, P =0.019).

The median number of injections was highest in the 1st year six injections with interquartile range (3-8), there was a statistically significant difference in the number of injections all over the subsequent four years (P =0.001) and also for each year compared to the 1st year (P 0=0.001 for 2nd,3rd,4th and 5th year) using Friedman test and Post Hoc Test (Dunn's). (**Figure 3**)

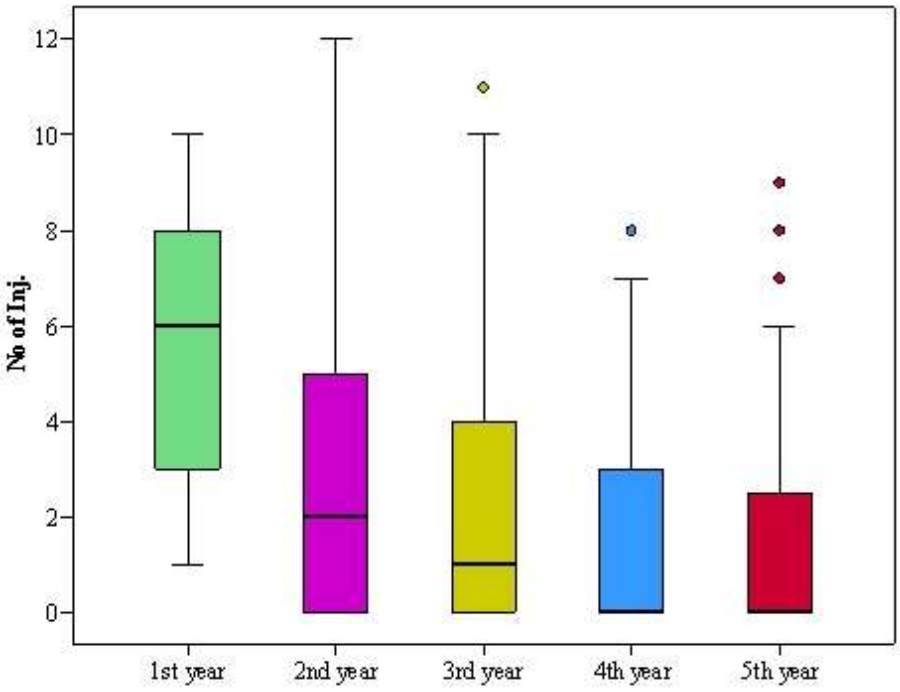

Figure (3): Compare the number of Injections all over the 5 years of follow-up.

The relation between previous PRP laser treatment and vision all over the five years of follow-up were analyzed using Mann Whitney test Eyes with no prior PRP had statistically significant better vision than eyes with previous PRP at the baseline (P =0.024), after one year of follow-up (P =0.018), by the end of the 3rd year (P =0.039), and by the 4th year (P = 0.031). At the 2nd and 5th year, the median vision was 70 letters for eyes with no previous PRP and was 67 letters, 65 letters for eyes previously treated with PRP, but This difference was not statistically significant. (**Table 2**)

Table (2): Relation between previous PRP laser treatment and VA all over the five years (n = 100)

	VA	Previously, laser treatment		U	P
		No (n = 65)	Yes (n = 35)		
Baseline	Min. – Max.	0.0 – 86.0	30.0 – 85.0	826.0*	0.024*
	Mean ± SD.	64.34 ± 17.83	58.97 ± 15.63		
	Median (IQR)	70.0 (61.0 – 77.0)	61.0 (47.0 – 70.0)		
1st year	Min. – Max.	0.0 – 85.0	0.0 – 85.0	810.50*	0.018*
	Mean ± SD.	67.83 ± 16.02	59.20 ± 19.96		
	Median (IQR)	70.0 (63.0 – 78.0)	61.0 (49..0 – 73.50)		
2nd year	Min. – Max.	0.0 – 85.0	0.0 – 85.0	911.50	0.101
	Mean ± SD.	68.25 ± 16.55	60.46 ± 22.66		
	Median (IQR)	70.0 (61.0 – 81.0)	67.0 (47.50 – 77.0)		
3rd year	Min. – Max.	0.0 – 85.0	0.0 – 85.0	852.50*	0.039*
	Mean ± SD.	67.12 ± 18.41	57.26 ± 24.54		
	Median (IQR)	73.0 (61.0 – 81.0)	65.0 (47.0 – 77.0)		
4th year	Min. – Max.	0.0 – 87.0	0.0 – 85.0	840.50*	0.031*
	Mean ± SD.	67.34 ± 17.89	55.80 ± 25.25		
	Median (IQR)	70.0 (61.0 – 79.0)	65.0 (47.0 – 77.0)		
5th year	Min. – Max.	0.0 – 84.0	0.0 – 85.0	907.0	0.095
	Mean ± SD.	61.85 ±21.68	53.31 ±25.78		
	Median (IQR)	70.0 (59.0 – 77.0)	65.0 (35.50 – 73.50)		

IQR: Interquartile range SD: Standard deviation U: Mann Whitney test

p: p value for comparing between No and Yes Previously, laser treatment

*: Statistically significant at $p \leq 0.05$

Discussion

Intravitreal anti-vascular endothelial growth factor (anti-VEGF) medications have become the standard treatment for DME. Ranibizumab (Lucentis®, Genentech), bevacizumab (Avastin®, Genentech), and aflibercept (Eylea®, Regeneron Pharmaceuticals) are three different agents proved to be effective in DME treatment. The choice between the three different anti-VEGF agents is partially based on availability and cost. Despite its effectiveness and high safety profile still associated with possible ocular or systemic adverse effects, around 40% of cases show suboptimal response. Switching to different anti-VEGF is a common approach adopted by ophthalmologists for patients with incomplete responses to the first used agent after several monthly injections. Several studies revealed improved response after switching to another anti-VEGF. It is still unclear whether this improvement results from switching. Those cases are late responders, which

are improved by sustained treatment and higher number of injections injection currently, no clear guidelines for switching between different anti-VEGF.(3, 11) This study will assess the long-term anatomical and functional outcome of DME treatment with anti-VEGF.

Of those who met the inclusion criteria, 34% Did not remain under follow-up over five years. The main reason was the patient's death, which might be expected due to their underlying diabetic condition. Only two patients did not have further follow-up because of stability. They were referred back to the diabetic screening program for a yearly follow-up, reflecting that most patients diagnosed with DME treated with anti-VEGF require regular follow-up visits with intervals shorter than 12 months.

We found a modest mean vision improvement of 3 letters at two years which was statistically significant (P =0.001). Vision was dropped by a mean of -3.6 letters compared to baseline by five years, but this was not statistically significant (P =0.484). We could not conclude from our study if the higher injection numbers in the first two years accounted for the highest visual gain with the visual decline due to fewer injections over the subsequent years or whether this was due to DME's natural history. The OCT macular thickness had gone down from 483 μm to 328 μm suggesting the main problem was not residual fluid. The high rate of additional treatment (intravitreal steroid and focal laser) during the follow-up period (32%of eyes) reflects that the sample represents those who may be harder to treat.

Bressler et al assessed factors associated with visual acuity on DME treatment with anti-VEGF in the Exploratory analysis of protocol T and showed that younger age is associated with statistically significant better vision at two years (P =0.001), median age (interquartile range) in the trial was 61(54-67) years. In our study, the median age(interquartile range) was 67(59-75) years; results similarly show a negative correlation between the age and visual acuity outcome, and this was statistically significant at the first two years (P =0.039 at one year, p=0.019 at two years). There was a weak negative correlation between the age and vision over 3rd, 4th and 5th years but wasn't statistically significant (P =0.116, p=0.261, P =0.221).(5)

Bressler et al assessed another baseline factor in the exploratory analysis of protocol T which was prior PRP. Results revealed that eyes with no prior PRP had more vision improvement at two years than eyes with prior PRP, which was statistically significant (P <0.001).in our study, eyes with no previous PRP show statistically significant better vision than eyes with PRP over the first,3rd, and 4th year (P =0.018, P =0.039, P =0.031), but this difference was not statistically significant at the 2nd and 5th year of follow up (P =0.101, P =0.095).(5)

In the current study mean two-year vision improvement was lower than the two-year data result from FONG ET AL study of bevacizumab in DME in which 309 patients were included. All over the 2 years period, about 3.1 injections were administrated. Number of letters gained at 24 months was 5.3 letters compared to 3 letters gain in the current study; this could be explained by a significant difference in a sample size of 309 eyes compared to 100 in our study.(12)

A similar vision improvement to our study of 3.8 letters at the two years was reported by Curry et al using aflibercept for DME using a treat and extend protocol.(13)

In protocol T the mean V.A. letter score improvement at two years was 12.8 with aflibercept, 10.0 with bevacizumab, and 12.3 with ranibizumab, which is nearly 3 to 4 times higher than our result.

(This more significant visual acuity improvement could be related to several points. First, the mean baseline vision was slightly better in protocol T 65 letters than 62.1 letters in the current study. Second, the higher median number of injections all over the two years (15 for aflibercept group, 15 for ranibizumab,16 for bevacizumab) compared to 8 injections in ours. Third, the previous PRP (only 16.6% of eyes received previous PRP in protocol T before starting anti-VEGF compared to 36% in our study). Previous PRP had a negative association with the degree of visual improvement in protocol T.(5, 14)

Our result showed that 71% percent of eyes retain vision over five years. 8% of eyes lost >15 letters by the end of the first year, which increased to 17% in year 5. In comparison with Wecker T, et al assessed the five-year outcome of anti-VEGF in DME and showed a slightly lower percentage of eyes retaining vision after five years (62.3%). Percentage of eyes lost > 15 letters by the end of the first year and the fifth year was similar to our study (9 % in the first year, 19% in the 5th year.) After five years, the mean V.A. remained close to ±0 letters from baseline.(15)

Our result showed that only 12 % of eyes gaining >15 letters in the fifth year which is lower than the comparable figure in Protocol I (at 5 years) in which27% of eyes gained ≥15 letters in the 5th year for the subgroup of ranibizumab with prompt laser, and 38% of eyes had ≥ 15 letter vision improvement in the 5th year in subgroup treated with ranibizumab and deferred laser. Superior protocol I 5 years result could be related to the additive beneficial effect of focal laser either prompt or deferred as part of treatment protocol.(16)

Most of the injections were administrated in the first two years, with 5.86 injections in the first year declining to 2.9 injections in the 2nd year. A statistically significant drop in the number of injections was noticed in the subsequent three years compared to the first 24 months, FONG ET AL showed less injection during the 2nd year of bevacizumab in DME with a mean of 1.7 injections.(12) Curry et al assessed two years of data of aflibercept in DME and showed almost more significant injections with a mean of 11.2 and 6.9 over the first and second year respectively; those figures are literally twice the means of injections in our study)this could be related to the compliance of attending the follow-up visits. However, both results show that injections number decreased by half during the second year compared to the first year.(13)

Sugimoto et al. A mean of 8.8 bevacizumab injections were administrated over two years using a treat and extend protocol, which is double the number in our study (mean of 4.38 injections all over the first two years); however, the number of treated eyes in this study was only eight eyes (compared to 100 eyes in our study).(7)

In the current study, the median number of anti-VEGF injections all over the five years was 12.5, which was similar for ranibizumab with prompt laser subgroup in protocol I, slightly more injections were a median of 17 in the ranibizumab with deferred laser subgroup. In our study, 49% and 44% of eyes received at least one additional ranibizumab injections in the fourth and fifth years, respectively, in protocol I for ranibizumab, and deferred laser percentage was 55% and 48% for the 4th and 5th years, while for ranibizumab and prompt laser was 46% and 38% for the 4th and 5th year. Those figures demonstrated that only half of the treated eyes or even less still require injections in the 4th year, and this figure decline more by the 5th year.(16)

In our study a median of six injections were administrated all over the first year, similar to the first-year result by Wecker T, et al of anti-VEGF in DME.(15) However, both studies show a drop in the number of injections in the subsequent four years, with median injection numbers between

zero and two. In contrast, the other study result shows a new peak in the 5th year with a median of six; whether the decrease in years 2–4 is and high rise in the 5th year due to diminished disease activity with new reactivation or reduced adherence to therapy cannot be deduced from this data. However, the number of eyes that continued the follow-up to the 5th year (13 eyes) is minimal compared to those who started the treatment (479 eyes).(15)

RISE and RIDE study results of the eyes subgroup treated with 0.5 mg ranibizumab (sample size 125 rise,127 rides), which gained >= 15 letters at 24 months was superior to our study, 39.2% and 45.7% in the RISE and RIDE study, respectively compared to only 21% in our study, this could be related to closer follow up in rising and ride study which was 30 days +- 7 days started from the 3rd month, which allows earlier recognition and treatment of macular edema, while in our study cases of stable or resolved edema had the hospital visit every 3 or 4 months the exclusion of eyes with active PDR or recent PRP in last three month from study enrolment which we did not exclude in our study).(17)

In the VIVID and VISTA study, percentages of eyes with more than 15 letters visual gain at two years were (38.2% for monthly 2 mg aflibercept,31.1% for bi-monthly 2 mg aflibercept) in VIVID, and (38.3% for monthly 2 mg aflibercept,33.1% for bi-monthly 2mg aflibercept) in VISTA study (only 21% in our study). A smaller proportion of eyes with 15 letters vision improvement could be explained by the ceiling effect for our study as 33% of the eyes have baseline vision better than 73 letters while the range in the baseline vision in VIVID and VISTA study was (24 to 73 letters), other explanations could be larger sample size in VIVID and VISTA (466 VIVID,406 VISTA) and conduction of study over the wide-scale with a different racial group that could affect the treatment response.(18-20)

Egan C, Zhu H, Lee A on behalf of the UK AMD and DR EMR Users Group, *et al* Results from reviewing electronic medical records from 19 participating U.K. centres with a sample size of 3103 eyes with diabetic macular edema to assess baseline features and vision outcomes at two years for intravitreal ranibizumab injections showed mean number of letters gain after two years of 5 letters compared to 3 letters in our study, this superior visual acuity outcome could be explained by the celling effect as the mean baseline vision in our study was about 11 letters higher (62.46(sd17.11) compared to 51.1(sd19.3), and percentage of eyes with baseline vision of 72 letters or better was 34% in our study compared to 25% in this paper.(21)

Limitations

The baseline characteristic of studied eyes included type of diabetes but did not include the level of HbAIC, which affects the rate of DME development and its response to treatment. As well there was no stratification of diabetic retinopathy severity. The study was not explicitly designated for detecting subgroup associations with no matching done initially, which increases the possibility of showing associations that may have occurred by chance. This study's strengths include a large sample, a long follow-up period, partially prospective designation, and a long-term completion rate. Besides, all cases have been recruited from the same hospital, reflecting standardized treatment and outcome measurements.

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Competing interests

No competing interests exist.

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Authorship

All authors state that this manuscript has been read and approved by all the authors, the requirements for authorship as stated earlier in this document have been met and each author believes that the manuscript represents honest work.

References

1. Busch C, Fraser-Bell S, Zur D, Rodríguez-Valdés PJ, Cebeci Z, Lupidi M, et al. Real-world outcomes of observation and treatment in diabetic macular edema with very good visual acuity: the OBTAIN study. Acta Diabetol. 2019;56(7):777-84.
2. Choi MY, Jee D, Kwon JW. Characteristics of diabetic macular edema patients refractory to anti-VEGF treatments and a dexamethasone implant. PLoS One. 2019;14(9):e0222364.
3. Abu-Yaghi NE, Abed AM, Emoush LO, AlHajjaj HZ, Abojaradeh AM, Hattar MN, et al. Factors Affecting Compliance to Anti-Vascular Endothelial Growth Factor Treatment of Diabetic Macular Edema in a Cohort of Jordanian Patients. Clin Ophthalmol. 2020;14:921-9.
4. Sun X, Zhang J, Tian J, Chen S, Zeng F, Yuan G. Comparison of the Efficacy and Safety of Intravitreal Conbercept with Intravitreal Ranibizumab for Treatment of Diabetic Macular Edema: A Meta-Analysis. J Ophthalmol. 2020;2020:5809081.
5. Bressler SB, Odia I, Maguire MG, Dhoot DS, Glassman AR, Jampol LM, et al. Factors Associated With Visual Acuity and Central Subfield Thickness Changes When Treating Diabetic Macular Edema With Anti-Vascular Endothelial Growth Factor Therapy: An Exploratory Analysis of the Protocol T Randomized Clinical Trial. JAMA Ophthalmol. 2019;137(4):382-9.
6. Ehlers JP, Wang K, Singh RP, Babiuch AS, Schachat AP, Yuan A, et al. A Prospective Randomized Comparative Dosing Trial of Ranibizumab In Bevacizumab-Resistant Diabetic Macular Edema: The REACT Study. Ophthalmol Retina. 2018;2(3):217-24.

7. Sugimoto M, Ichio A, Nunome T, Kondo M. Two year result of intravitreal bevacizumab for diabetic macular edema using treat and extend protocol. Medicine (Baltimore). 2017;96(16):e6406.
8. Wong WM, Chee C, Bhargava M, Chai C, Lin H, Zhao P, et al. Systemic Factors Associated with Treatment Response in Diabetic Macular Edema. J Ophthalmol. 2020;2020:1875860.
9. Bressler NM, Beaulieu WT, Maguire MG, Glassman AR, Blinder KJ, Bressler SB, et al. Early Response to Anti-Vascular Endothelial Growth Factor and Two-Year Outcomes Among Eyes With Diabetic Macular Edema in Protocol T. Am J Ophthalmol. 2018;195:93-100.
10. Bressler NM, Beaulieu WT, Glassman AR, Blinder KJ, Bressler SB, Jampol LM, et al. Persistent Macular Thickening Following Intravitreous Aflibercept, Bevacizumab, or Ranibizumab for Central-Involved Diabetic Macular Edema With Vision Impairment: A Secondary Analysis of a Randomized Clinical Trial. JAMA Ophthalmol. 2018;136(3):257-69.
11. Sorour OA, Liu K, Mehta N, Braun P, Gendelman I, Nassar E, et al. Visual and anatomic outcomes of sustained single agent anti-VEGF treatment versus double anti-VEGF switching in the treatment of persistent diabetic macular edema. Int J Retina Vitreous. 2020;6:17.
12. Fong DS, Luong TQ, Contreras R, Jimenez JJ, Custis PH, Patel V, et al. Treatment patterns and 2-year vision outcomes with bevacizumab in diabetic macular edema: An analysis from a large U.S. Integrated health care system. Retina. 2018;38(9):1830-8.
13. Curry BA, Sanfilippo PG, Chan S, Hewitt AW, Verma N. Clinical Outcomes of a Treat and Extend Regimen with Intravitreal Aflibercept Injections in Patients with Diabetic Macular Edema: Experience in Clinical Practice. Ophthalmol Ther. 2020;9(1):87-101.
14. 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(6):1351-9.
15. Wecker T, Ehlken C, Bühler A, Lange C, Agostini H, Böhringer D, et al. Five-year visual acuity outcomes and injection patterns in patients with pro-re-nata treatments for AMD, DME, RVO and myopic CNV. Br J Ophthalmol. 2017;101(3):353-9.
16. Elman MJ, Ayala A, Bressler NM, Browning D, Flaxel CJ, Glassman AR, et al. Intravitreal Ranibizumab for diabetic macular edema with prompt versus deferred laser treatment: 5-year randomized trial results. Ophthalmology. 2015;122(2):375-81.
17. Nguyen QD, Brown DM, Marcus DM, Boyer DS, Patel S, Feiner L, et al. Ranibizumab for diabetic macular edema: results from 2 phase III randomized trials: RISE and RIDE. Ophthalmology. 2012;119(4):789-801.
18. Ashraf M, Souka A, Adelman R, Forster SH. Aflibercept in diabetic macular edema: evaluating efficacy as a primary and secondary therapeutic option. Eye (Lond). 2016;30(12):1531-41.
19. Ziemssen F, Schlottman PG, Lim JI, Agostini H, Lang GE, Bandello F. Initiation of intravitreal aflibercept injection treatment in patients with diabetic macular edema: a review of VIVID-DME and VISTA-DME data. Int J Retina Vitreous. 2016;2:16.

20. Brown DM, Schmidt-Erfurth U, Do DV, Holz FG, Boyer DS, Midena E, et al. Intravitreal Aflibercept for Diabetic Macular Edema: 100-Week Results From the VISTA and VIVID Studies. Ophthalmology. 2015;122(10):2044-52.
21. Egan C, Zhu H, Lee A, Sim D, Mitry D, Bailey C, et al. The United Kingdom Diabetic Retinopathy Electronic Medical Record Users Group, Report 1: baseline characteristics and visual acuity outcomes in eyes treated with intravitreal injections of ranibizumab for diabetic macular oedema. Br J Ophthalmol. 2017;101(1):75-80.