Real-World Visual Outcomes of Treatment-Naive Patients with Diabetic Macular Oedema

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ABSTRACT

Aim: The aim of this audit was to determine whether patients with diabetic macular oedema attending a routine clinical practice were able to achieve and maintain the visual outcomes reported by clinical trials.

Methods: A retrospective observational study of 131 treatment-naive eyes of patients attending one suburban and one semi-rural ophthalmology clinic, in or close to Melbourne, Australia. Data were extracted from the Diabetic Macular Oedema module of the Fight Retinal Blindness! Registry[1] from 2014 to 2020. Main outcome measures included diabetic retinopathy characteristics at baseline, pre-existing ocular conditions, previous treatments, current treatment given, visual acuity, and central subfield thickness.

Results: The average number of treatment injections was 5.58 in the first 12 months, compared with 5.51 beyond 36 months ($p>0.05$). Eighty percent of patients had a baseline visual acuity of better than 6/12 and there was a statistically significant improvement in acuity from baseline to Year 1, Year 2 and Year 3 ($p<0.05$). Baseline central serous thickness was 340.58µm and improved significantly at each time point ($p<0.05$).

Conclusion: Patients attending this routine clinical practice in the real world were not able to achieve and maintain the visual outcomes reported by the phase 3 clinical trials. This is most likely due to under-treatment and suggests that the dosing schedule for patients with diabetic macular oedema should be re-evaluated.

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Accepted for publication: 17th March 2021

Keywords: diabetic macular oedema, anti-VEGF, real-world outcomes, treatment naive eyes

INTRODUCTION

It is estimated that 1.7 million Australians have diabetes and associated eye disease, namely diabetic retinopathy (DR) which is the most commonly reported complication. All individuals with type 1 and type 2 diabetes are at risk of developing DR with the duration of diabetes being the most significant factor. Sight-threatening complications of retinopathy occur due to diabetic macular oedema (DMO) which causes swelling of the retina and accumulation of extracellular fluid in the macula.[2-6]

Both intravitreal injections of corticosteroids and/or vascular endothelial growth factor (VEGF) inhibitors are the current treatment options for DMO. Triamcinolone acetonide and intravitreal dexamethasone implant (Ozurdex) corticosteroids have been reported to reduce DMO and improve visual outcomes. Whilst corticosteroids require reduced injection frequency compared with VEGF inhibitors, they are associated with side effects such as cataract development and increased intraocular pressure.[7-10] VEGF inhibitors include ranibizumab, aflibercept and bevacizumab. Phase 3 randomised control trials for DMO indicate that patients demonstrate significant improvement in visual acuity (VA). Better visual gains are reported in patients whose starting VA is poor, that is 6/24 or less.[7,9,11-14]

Despite the improvements in visual gains reported in clinical trials, real-world data from patients in the clinical setting, evaluating the use of VEGF inhibitors indicates that patients with DMO receive significantly fewer injections and smaller visual gains, suggesting that these patients may not be receiving optimum care.[15,16] Diabetic patients are more likely to miss an appointment compared to patients with neovascular age-related macular degeneration (nAMD) who undertake a similar treatment regime.[17-19] The risk of sub-optimal treatment is progressive retinal damage, reduced vision and ultimately blindness.[20,21] The difference in reported visual gains may be

due to the strict treatment schedule of clinical trials, exclusion of patients with comorbidities and VA cut-offs at 6/9 to 6/12.[16,22] A recently published guideline for the treatment of DMO suggests the necessity of a significantly increased number of treatment injections compared to an initial loading dose followed by injections every 4-8 weeks until the oedema is resolved.[22] Cheung et al[22] indicate that further clarification of the treatment regime is needed, particularly given the 'common perception is that, because anti-VEGF therapies have now been used for nAMD, the principles of treatment applied to AMD may be extrapolated to DME. However, nAMD and DME differ vastly in their pathophysiology, clinical presentation, natural history, treatment goals and outcomes'.

The aim of this audit was to determine whether patients with DMO attending a routine clinical practice were able to achieve and maintain the visual outcomes reported by the phase 3 clinical trials which compared the use of anti-VEGF therapies.

METHODS

This was a retrospective observational study of patients attending one suburban and one semi-rural ophthalmology clinic, in or close to Melbourne, Australia. Patients were undertaking treatment for DMO with one ophthalmology consultant. The treatment protocol for DMO generally used at this clinic involved three loading doses of anti-VEGF and if DMO persists after the third injection, monthly injections are given until the retina is free of fluid. Patients are then monitored at regular intervals; initially monthly for the first three months and then, based on fluid dynamics and VA, the interval is extended on an individual-needs basis. Other necessary treatment, such as peripheral retinal laser or corticosteroids, is given as required.

Single-user non-identifiable data pertaining to these patients were extracted from the DMO module of the Fight Retinal Blindness! (FRB!) Registry.[1] Extracted data used for this analysis included DR characteristics at baseline, pre-existing ocular conditions, previous treatments, current treatment given, number of letters read on a logarithm of the minimum angle of resolution (logMAR) vision chart, and central subfield thickness (CST) using spectral-domain optical coherence tomography (SD-OCT) (Zeiss, Germany). Data from 284 eyes treated for DMO was extracted from the FRB! database from 11 June 2014 to 3 July 2020. A total of 131 treatment-naive eyes (RE = 66; LE = 65) of 131 patients were included for data analysis. One hundred and fifty-three eyes were excluded on the basis of previous treatment for DMO.

All patient outcomes were included in the analysis, irrespective of whether they had been lost to follow-up. Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY. Comparison of means testing was performed using dependent and independent t-tests or a non-parametric equivalent in the event that data assumptions were violated and not normally distributed. The level of significance was set at α=0.05.

The procedures used for this audit adhered to the ethical responsibility requirements of the FRB! Project and followed the tenets of the Declaration of Helsinki. Patients provide consent at their first visit to the practice that their de-identified data may be used for the purposes of clinic audits. With respect to the FRB! database, the design of the FRB! Project ensures maximum data security and anonymity[1] and has received ethical approval from the Royal Australian and New Zealand College of Ophthalmologists' Human Research Ethics Committee.

RESULTS

Disease characteristics and treatments

Over half of the eyes in this study (53.8%) were classified with mild (36.9%) or moderate DR (16.9%). 28.5% of eyes had severe non-proliferative DR and 18% of eyes had either low-risk proliferative DR (15.4%) or high-risk proliferative DR (2.3%). Overall, 3,165 visits were recorded for this audit and treatment was administered on 1,457 occasions (46%) with monitoring occurring on 1,708 occasions (54%). Aflibercept was administered more frequently compared with any other treatment option (Table 1). Referral to the patient support program associated with aflibercept is actively encouraged as part of normal clinic protocol and patient uptake of this support program appeared to be high. An internal clinical audit of referrals to the aflibercept 'Smart Sight' program indicated that 88% of patients accepted the referral.

Table 1. Treatment visits by type

Treatment administered	Number of occasions	%
Aflibercept	1,019	69.9
Ranibizumab	95	6.5
Bevacizumab	67	4.6
Ozurdex	46	3.2
Triamcinolone	3	0.2
Peripheral retinal laser	227	15.6
Total	**1,457**	**100**

Thirty-nine eyes received treatment for up to 52 weeks before discontinuing and the number of treatment occasions was 797, with a mean of 20.4 treatments per eye. The number of eyes receiving treatment for 104, 156 and 208 weeks was 24, 37 and 19 respectively and only 10 eyes received treatment for 260 weeks. When corrected for loss to follow-up, the average number of treatments per eye was stable, 5.58 in the first 12 months, compared with 5.51 beyond 36 months (Wilcoxon Signed Rank Test: p>0.05). The reason for discontinuation of treatment was related to a variety of factors including that they were deceased, relocated a significant distance from the clinic or were unable to be contacted after missing an appointment.

Visual acuity and central subfield thickness

The time range used to analyse time periods for both VA and CST were baseline (0-30 days), 1 year (10-14 months), 2 years (22-26 months), 3 years (34-38 months), 4 years (56-50 months), and 5 years (58-60 months). VA and CST over time is shown in Table 2. Mean baseline VA was 69.94 letters (6/12). Eighty percent of patients had a baseline VA of better than 70 letters (6/12); 11.2% had baseline VA of 56 to 69 letters (6/12-6/19) and 5.6% and 3.2% had baseline VA of 25 to 55 letters (6/24-6/60) and 0 to 35 letters (<6/60), respectively. A means comparison was conducted to determine whether there was a significant change in VA and the change in letters is shown in Figure 1. There was a statistically significant improvement in VA score from baseline to Year 1 (p=0.000), baseline to Year 2 (p=0.000) and baseline to Year 3 (p=0.009). At Year 4, VA improved by 5.34 letters and the improvement from baseline to Year 5 was almost 10 letters, however despite this apparent improvement, it did not reach statistical significance, likely due to the very small proportion of treatment-naive eyes that were still continuing treatment at this time, thereby affecting analysis.

The proportion of eyes that gained or lost either ≥10 letters or ≥15 letters by 52 weeks, 104 weeks and 156 weeks is shown in Table 3.

Baseline CST was 340.58µm and improved significantly to 295.72µm at Year 1 (p=0.003) and eyes demonstrated statistically significant improvement of -41.99µm from baseline to Year 2 (p=0.001). Significant change in CST was also found from baseline to Year 3 (p=0.000), Year 4 (p=0.009) and Year 5 (p=0.037). The change in CST from baseline to all time points for these treatment-naive eyes is shown in Figure 2.

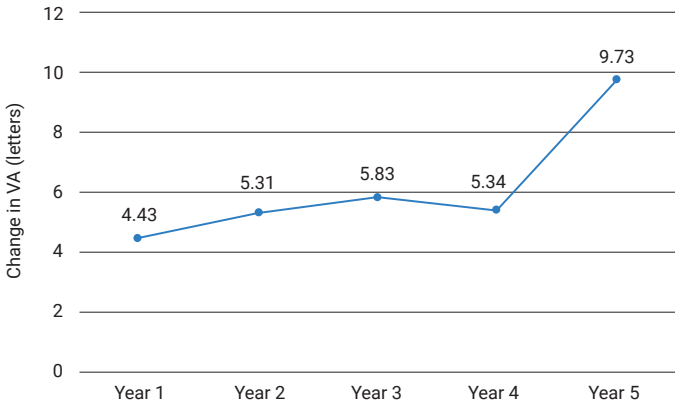

Figure 1. Change in VA letters over time.

Table 3. Proportion of eyes with gain or loss of ≥10 letters or ≥15 letters

	52 weeks	104 weeks	156 weeks
Vision gain, n (%)			
≥15 letters	13 (10.3)	11 (13.1)	5 (11.1)
≥10 letters	22 (17.4)	19 (22.6)	11 (24.4)
Vision loss, n (%)			
≥10 letters	11 (8.7)	9 (10.7)	2 (4.41)
≥15 letters	5 (3.9)	4 (4.7)	4 (8.8)

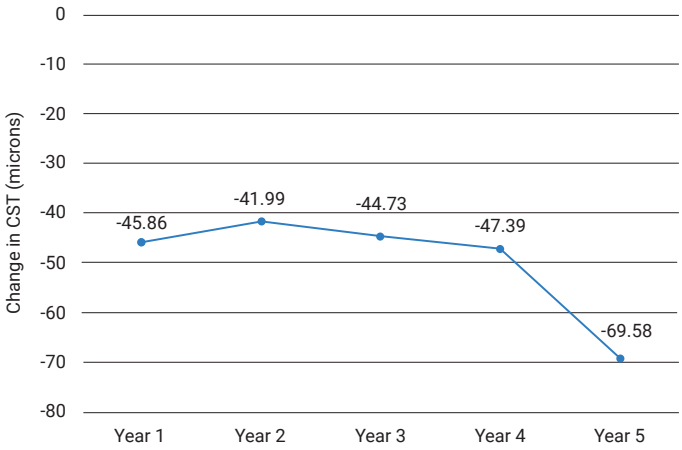

Figure 2: Change in CST over time.

DISCUSSION

The aim of this retrospective audit of 131 treatment-naive eyes was to determine whether patients with DMO attending a routine clinical practice were able to achieve and maintain the visual outcomes reported by the phase 3 clinical trials.

Over half of the patients in this study had mild or moderate DR and their baseline VA was 69.94 letters (6/12), with the majority of eyes having a baseline VA of 70 letters or better. Baseline VA

Table 2. Visual acuity and central subfield thickness, over time

		Baseline	Year 1	Year 2	Year 3	Year 4	Year 5
VA	Mean	69.94	74.37	75.25	75.77	75.28	79.67
	(SD)	(17.08)	(14.06)	(10.93)	(10.65)	(9.11)	(5.17)
	Change from baseline		*+4.43*	*+5.31*	*+5.83*	*+5.34*	*+9.73*
CST	Mean	340.58	294.72	298.59	295.85	293.19	271.0
	(SD)	(103.63)	(79.98)	(97.71)	(60.98)	(51.02)	(30.53)
	Change from baseline		*-45.86*	*-41.99*	*-44.73*	*-47.39*	*-69.58*

in this study was better than that reported by other studies.[16,23,24] Visual gains achieved by patients in this study ranged from 4 to almost 6 letters over time and was better than that reported in a similar real-world retrospective audit where vision improved by a mean of 2.9 letters.[16] When comparing outcomes stratified by baseline VA reported by Biechl,[16] eyes with a starting VA of ≥70 letters lost an average of 3.2 letters at 5 years. Despite better visual gains in this study compared to the real-world audit, when compared with the VIVID, VISTA and DRCR.net Protocol T studies,[12,14,23,24] patients in our study were not able to approach the reported visual acuity gains which were double in these trials. It is possible that eyes with worse acuity yield better visual gains[22] although this was not the case in the DRCR.net Protocol T study, which reported the visual gains were similar irrespective of baseline acuity.[24] The reason for a lower improvement in vision in this study may be related to better baseline acuity, particularly as visual gains reported in the real-world audit by Biechl[16] were also not as great as the clinical trials.

The number of eyes achieving an increase or decrease of 10 or 15 letters in this study (Table 3) is significantly less than that reported by the VIVID, VISTA or DRCR.net Protocol T studies.[12,14,23,24] These authors report that 35 to 77% of participants in these clinical trials were able to achieve a gain in vision of 15 letters or more and only a small proportion (up to 6.5%) lost 15 letters or more. Whilst the proportion of loss of acuity was similar in this study, the visual gains of 15 letters or more were significantly less. This may be due to the higher proportion of patients (80%) with a good baseline acuity of 70 letters (6/12), although if baseline acuity is 6/12, a 15 letter increase to 6/6 (85 letters) is achievable. When compared with real-world data, the proportion of eyes achieving an improvement of ≥15 letters (10-11%) in this study is still lower than the 17% who gained ≥15 letters, as reported by Biechl.[16]

Baseline CST in this study was 340µm and the improvement at each time-point ranged from 42 to 69µm. Like the study by Biechl,[16] the improvement in CST was significant, despite the modest improvements in VA. The change in thickness however, was lower when compared with the real-world audit and the VIVID, VISTA or DRCR.net Protocol T studies and is likely due to the smaller thickness at baseline in this cohort of patients.[12,14,16,23,24]

The average number of injections administered per year as reported by the VIVID and VISTA trials was approximately ten, similar to the DRCR.net Protocol T study. In comparison, the real-world audit study by Biechl[16] reported a mean of 17 treatment injections over the full five years (approximately 3.4 per year). In our study the mean number of treatments administered per year was five, which is significantly less compared to the clinical trials and may account for the inferior visual gains in this cohort of DMO patients. Table 5 shows a summary of these outcomes and also includes the number of eyes with ≥15 letters improvement, which is also significantly more in the clinical trials.

The outcomes of this audit indicate that patients attending a routine clinical practice in the real-world are not able to achieve and maintain the visual outcomes reported by the phase 3 clinical trials. The difference may be related to the baseline VA and CST, but we suggest it is more likely due to under-treatment. Cheung et al[22] suggest that patients with DMO be treated intensively and as early as possible, with at least five to six monthly loading doses of VEGF inhibitors, with a view to administering eight to nine injections over a twelve-month period before decreasing the injecting rate in subsequent years. Whilst the guidelines proposed by Cheung et al[22] are for an Asian population, it is worth considering that a significant number of patients with DMO of varying race are being significantly under-treated in the real-world setting.

What are the reasons for under-treatment? Anecdotal clinical evidence suggests that the setting of treatment expectations to the patient at their initial presentation is not sufficiently effective. An injecting schedule of at least five to six monthly loading doses and up to nine injections per year is a 'hard sell' to a patient cohort that has issues with non-adherence due to costs, needing to take time off work, or burden on family.[17-19] In addition, some patients choose to live with slightly sub-optimal vision in exchange for a lower number of injections as a trade-off, and therefore do not return for continuing management of their disease.

The limitations of this study include that the number of patients is significantly lower than those in clinical trials[12,14,23,24] and in another retrospective real-world audit.[16] The analysis of only treatment-naive eyes may also have an influence on the

Table 4. Summary of outcomes between our study and others

	Our study	Real-world retrospective audit *(Biechl et al, 2020)*[16]	VIVID & VISTA clinical trials *(Heier et al, 2016)*[12]	DCR.net Protocol T *(Wells et al, 2016)*[14]
Visual gains (letters, n)	+4 - +6	+2.9	+10	+9.7 - +13.3
Mean number of injections	5	3.4	18 - 29	13.4 - 14.3
# eyes with ≥15 letters (%)	10 - 11	17	40 - 50	52 - 58

outcomes reported in this cohort as other studies have included eyes with previous treatment for DMO. This study has included patients that received other treatments, not just VEGF inhibitors and whist the majority of treatments were VEGF inhibitors, this may have affected the results. The outcomes may also have been affected by the treatment decisions made in the real-world clinic that rely on a different set of patient outcomes compared to clinical trials that require scheduled dosing and rely on image reading centres.

Future studies that explore real-world outcomes in patients with DMO are essential. Also, research to investigate the impact of easing the burden of repeated treatment and its cost, combined with amending the treatment protocol for diabetic patients will add to the understanding of real-world outcomes. Further research will also show whether increasing injections and amending the protocol will make a difference in terms of outcomes for these patients.

ACKNOWLEDGEMENTS

This research project was supported by a grant from Bayer Australia Ltd. The authors would like to acknowledge Shannon Brown, Lauren Moussalem and Dhanushka Galister for their assistance on this project.

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