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Five-year outcomes of eyes initially enrolled in the 2-year BEVORDEX trial of bevacizumab or dexamethasone implants for diabetic macular oedema

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ABSTRACT

Background The BEVORDEX trial compared outcomes of eyes with diabetic macular oedema (DMO) randomised to receive either intravitreal dexamethasone (DEX-) implant or bevacizumab over 2 years. We assessed long-term efficacy and safety outcomes 5 years from enrolment.

Methods Patients received standard clinical care after they finished the study. Their files were reviewed for visual and anatomical outcomes, post-trial treatments and complications.

Results Three-year and five-year data were available for 82% and 59% of eyes enrolled in the BEVORDEX study, respectively. Visual acuity gains at end of trial were generally lost by both treatment groups at 5 years but the macular thickness did not change from end of trial to 5 years. A similar proportion of eyes from each treatment group gained ≥ 10 letters at 5 years from enrolment in the BEVORDEX trial.

Eyes that were initially randomised to the DEX-implant group had significantly fewer treatments but were more likely to develop proliferative diabetic retinopathy (PDR) over the 5-year period compared with eyes initially randomised to bevacizumab. The proportion of eyes that had cataract surgery by 5 years was similar between initial treatment groups.

Conclusions Eyes in the BEVORDEX trial had similar 5-year rates of cataract surgery, however, more eyes converted to PDR in the group initially treated with DEX-implant. Eyes that were initially treated for 2 years with either intravitreal DEX-implant or bevacizumab followed by standard of care had similar visual and anatomical outcomes at 5 years.

7.4 letters better than mean baseline BCVA at 5 years, it was a decrease of 4.7 letters from the end of original Protocol T study.²

The BEVORDEX study compared outcomes of eyes with DMO which were randomised to receive dexamethasone (DEX-) implant or intravitreal bevacizumab.³ Patients received DEX-implants up to every 16 weeks or bevacizumab up to every 4 weeks for 2 years. No significant difference was found in the primary endpoint of proportion of eyes with a 10-letter gain in best corrected VA (BCVA). Secondary outcomes found the bevacizumab group had more injections over the first year (9.1 vs 2.8), the reduction in DMO was similar for each treatment group and the DEX-implant group eyes had a greater risk of loss of vision, mainly due to cataract progression. Patients received standard care in the Australian healthcare system on completion of the study. Here, we have analysed the 5-year outcomes of patients from enrolment in the 2-year BEVORDEX clinical trial.

METHODS

Patient files were reviewed for visual and anatomical outcomes, post-trial treatments and complication rates. Visual outcome at 5 years was determined by last observation carried forward (LOCF) for those that did not complete follow-up. VA was measured on LogMAR or Snellen charts and expressed as LogMAR letters. The best of uncorrected, corrected or pinhole vision was used. The original BEVORDEX study was 2 years in length. 'End of study' is defined as the end of the BEVORDEX study throughout this analysis. Enrolment of patients in the BEVORDEX trial is the time point that baseline data is defined for each eye for the present study. Five-year outcomes, determined by LOCF, are taken from enrolment of the original BEVORDEX study. A separate sensitivity analysis was carried out in a subset of patients from Sydney Eye Hospital, that were invited to return for a BCVA measurement 5 years from their initial baseline study visit.

RESULTS

Data were available for 82% (n=72) of eyes 3 years after enrolment in the BEVORDEX study, 72% at 4 years (n=63) and 59% with 5 or more years follow-up (n=52). Of the 16 eyes without

INTRODUCTION

Clinical studies play an integral role in developing our understanding of the best treatment regimen for our patients but are limited in duration. It is important to know what happens to these participants after the trial ends and they revert back to real-world clinical practice.

The DRCR Network recently published the 5-year outcomes of patients enrolled in the Protocol T study¹ which compared three different anti-vascular endothelial growth factor (VEGF) agents for treatment of diabetic macular oedema (DMO). Data were available from 68% of the patients 3 years following the end of their 2-year study. Although mean visual acuity (VA) was still



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Table 1 Baseline characteristics of BEVORDEX treatment groups that were followed

	DEX-implant (46 eyes)	Bevacizumab (42 eyes)	P value
Mean follow-up, days (CI)	1366 (1215 to 1516)	1488 (1364 to 1611)	0.2
Baseline BCVA, letters (SD)	55.5 (12.5)	56.3 (11.9)	0.75
Baseline CMT, μm (SD)	474.3 (95.9)	503 (140.9)	0.38
Number of eyes that had 5-year follow-up	26	26	0.61
Baseline phakic eyes	30	32	0.81
Baseline NPDR	31	32	0.58

BCVA, best corrected visual acuity; CMT, central macular thickness; DEX, dexamethasone; NPDR, non-proliferative diabetic retinopathy.

follow-up data, 10 were of patients who had passed away. Seven patients (17.9%) of the original trial and three (11.5%) of the trial completers died by 5 years. The characteristics of the eyes from the two study arms were similar at baseline, including the number of eyes at baseline with non-proliferative diabetic retinopathy (NPDR) and the number of phakic eyes (table 1).

VA outcomes

The proportion of eyes that gained ≥ 10 letters at 5 years from enrolment in the original study was the same for each initial treatment group (14 eyes for each, 30% DEX-implant and 33% bevacizumab). The mean (SD) VA at start of study was 56.3 (11.9) and 55.5 (12.5) with 62.4 (14.6) and 65.9 (13) letters at end of trial (Becavizumab, DEX-implant). This vision gain was not maintained to 5 years and final mean VA (95% CI) fell to 58.5 (55.1 to 61.9) and 59.5 (57.4 to 63.6) letters in our LOCF analysis. There was no significant difference in final VA between the two treatment groups at 5 years, as with the original trial (table 2, figure 1A).

We performed a separate sensitivity analysis to assess BCVA rather than VA obtained in patient file, of 44% of the 54 eyes enrolled in the SEH cohort that returned for a 5-year visit. We found no difference, between initial study treatment groups, in final mean (SD) VA (55.6 (14.6) letters in the bevacizumab group versus 66.8 (9.2) letters in the DEX-implant group, $p=0.09$) or change in vision from baseline (4.4 letters bevacizumab vs 4.3 letters DEX-implant, $p=0.78$) (table 3).

Anatomical outcomes

The reduction in central macular thickness (CMT) found at end of trial was maintained from end of trial to 5 years for both

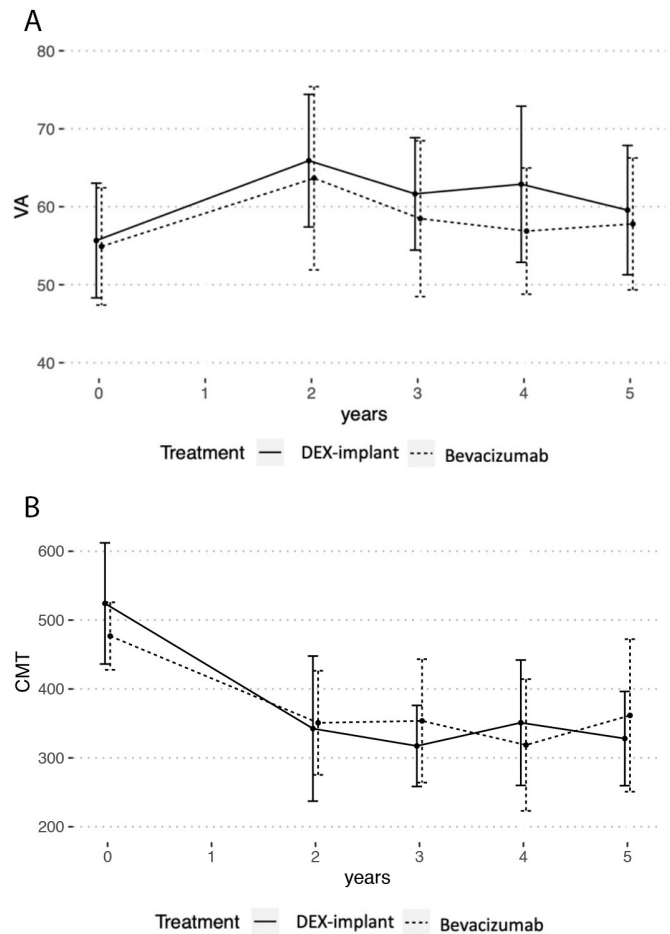


Figure 1 Visual acuity (VA) and central macular thickness (CMT) of each treatment group of the BEVORDEX trial followed to 5 years from enrolment. (A) Mean VA logMAR letters; (B) mean CMT μm . Error bars denote CI. DEX-implant, dexamethasone implant.

treatment groups with no significant difference between them (table 2, figure 1B).

Treatment patterns

As with the initial BEVORDEX trial, eyes that were initially randomised to the DEX-implant group had significantly fewer treatments over the 5-year period than the bevacizumab treated eyes ($n=9.0$ versus $n=19.2$, $p<0.05$ table 4). Six eyes allocated to the DEX-implant arm of the original 2-year study and 10 from

Table 2 Five-year results from entry into the BEVORDEX trial

	DEX-implant (46 eyes)	Becavizumab (42 eyes)	P value
BCVA at the end of trial (2 years)	62.4 (14.6)	65.9 (13)	0.38
VA at 5 years, letters (CI)*	58.5 (55.1 to 61.9)	59.5 (57.4 to 63.6)	0.51
Proportion of eyes who gained ≥ 10 letters from baseline to 5 years, n (%)*	14 (30.4)	14 (33.3)	0.78
Mean change in vision from baseline, letters (CI)*	1.8 (-1.6 to 5.3)	2.7 (0.62 to 6.94)	0.40
Mean CMT at end of study, μm (CI)*	329 (265 to 452)	358 (286 to 415)	0.36
Mean CMT at 5 years, μm (CI)*	327 (289 to 367)	332 (293 to 371)	0.87
Mean change in CMT (from baseline to 5 years), μm (CI)*	-150 (-199 to -100)	-173 (-232 to -121)	0.23
Paired t-test (end of study to 5 years)	0.87	0.81	

*Last observation carried forward.

BCVA, best corrected visual acuity; CMT, central macular thickness; DEX, dexamethasone; VA, visual acuity (obtain from patient file).

Table 3 Sydney Eye Hospital Cohort 5-year follow-up

	DEX-implant (27 eyes)	Bevacizumab (27 eyes)	P value
Baseline mean BCVA (SD)	51.3 (15.3)	62.4 (10.1)	0.064
Mean BCVA 2-year (SD)	60.7 (17.5)	71.1 (13.1)	0.113
Mean BCVA 5-year (SD)	55.6 (14.6)	66.8 (9.2)	0.091
Mean change in BCVA (5 years) (SD)	4.3 (11.3)	4.4 (9.2)	0.788

Of the 54 eyes that enrolled in the BEVORDEX trial, 27 eyes from each treatment group attended clinic visit for BCVA at 5 years. Baseline refers to BEVORDEX trial enrolment.
BCVA, best corrected visual acuity; DEX, dexamethasone.

the bevacizumab arm required no further intravitreal treatment poststudy completion ($p=0.32$). The remainder of the eyes (20 DEX-implant and 16 bevacizumab) had a mixture of treatments post-trial according to physician preference: bevacizumab (10, 20), aflibercept (2, 1), ranibizumab (1, 0), triamcinolone (19, 16) and DEX-implant (17, 12) (DEX-implant vs bevacizumab arm). The proportion of eyes that had cataract surgery by 5 years was similar between the original treatment group (84% vs 68%, $p=0.13$) as was the number of eyes that needed glaucoma surgery (table 4).

Diabetic retinopathy sequelae

Eyes initially randomised to DEX-implant treatment were more likely to develop PDR compared with those randomised to bevacizumab (6 compared with 1, $p<0.05$). Five of these eyes developed PDR on trial. Of the two that developed PDR post-trial (both initially treated with DEX-implant), one received triamcinolone and the other received three bevacizumab injections. Time to PDR was 207 days from last bevacizumab and 1407 days from triamcinolone. All the eyes that progressed to PDR were graded as having severe NPDR at enrolment. The average haemoglobin A1c of the seven patients who developed PDR was 8.4% at enrolment and 8.8% at trial completion. Their average duration of diabetes treatment was 15.6 years and five patients were treated with both insulin and oral antihyperglycaemic medications. All but one patient had uncontrolled hypertension (defined as an average systolic pressure ≥ 140 and diastolic pressure of ≥ 90) despite being on antihypertensive treatment. Only two patients were ex-smokers and none were current.

DISCUSSION

Post-trial observational follow-up studies are unable strictly to compare treatment groups as treatment after the study ends is no longer standardised. Patients in the BEVORDEX study were treated per protocol for 2 years, then they received other treatments as per standard of care in the subsequent 3 years. Understanding what happens when patients return to standard of care after clinical trials may reveal ways in which their long-term

outcomes can be improved and provide long-term safety and efficacy data of the drugs investigated.

Significant loss of patients with DMO can be expected over 5 years. Here, we analysed data from just 59% eyes of the original BEVORDEX cohort that were available 5 years from enrolment. This is similar to the DRICNet Protocol T extension follow-up rate (68%) and also the 5-year results of the randomised trial with open-label extension of triamcinolone acetonide for refractory diabetic macular oedema (TDMO) (66%).^{2,4} Nearly half the loss of eyes follow-up was from patient mortality, which was 17.9% in BEVORDEX at 5 years, very similar to the 18.0% of Protocol T extension (18.0%).²

Mean improvements in BCVA in the BEVORDEX trial were 6.9 letters in the DEX-implant treated group (95% CI 2.7 to 11.1) and 9.6 letters in the group treated with bevacizumab (95% CI 6.9 to 12.3). After 3 years in routine clinical care, they had lost a mean of 3.9 (DEX-implant) and 6.4 letters (bevacizumab) bringing the vision close to, but still slightly better than, baseline (1.8 and 2.7 letters, DEX-implant and bevacizumab). These results are consistent with those of the TDMO trial, which included only 'refractory' DMO, with a mean 5-year improvement of only 1.8 letters in the triamcinolone group.⁴ The DRIC Protocol T Extension study reported a drop in mean VA of around five letters 3 years after that study ended but it was still 7.4 letters better than baseline.²

The difference in final 5-year vision between Protocol T (76.4 letters all agents, 95% CI 5.9 to 9.0) and BEVORDEX (bevacizumab 59.5 letters (95% CI 57.4 to 63.6) and DEX-implant 58.5 letters (95% CI 55.1 to 61.9)) could be explained by differences in baseline characteristics. Mean CMT at baseline was greater for the BEVORDEX cohort (bevacizumab 503 μm , 141 SD and DEX-implant 474 μm , 96 SD) than the Protocol T cohort (aflibercept 385 μm (312–462), bevacizumab 377 μm (308–478 μm), ranibizumab 387 μm (306–477)), suggesting they had more chronic DMO.^{5,6} The eventual treatment patterns are also consistent with more severe disease as the mean number of injections over the extension period was higher in BEVORDEX extension than in the Protocol T extension cohort, this might also reflect better access to treatment in the Australian healthcare system. There may be anatomical features at baseline such as disorganisation of retinal inner layers (DRIL) that could predict poorer visual outcomes in some eyes.⁷ It would be interesting to conduct a post-hoc imaging bio-marker analysis to see if DRIL at baseline could predict the poorer visual outcome of some eyes in BEVORDEX but this was beyond the scope of the present study.

Despite these differences in final outcome, there has been a consistent drop in vision across all extension studies after patients exit randomised trials. This is likely due to either the vagaries of routine clinical care, which include missed appointments, financial stresses and competing health priorities, or the natural history of disease. We believe that the latter is the likely cause in our cohort as the reduction in CMT from the end of

Table 4 Treatments and complications

	DEX-implant (46 eyes)	Bevacizumab (42 eyes)	P value
Number of eyes that underwent glaucoma surgery (0–5 years)	1 (2%)	1 (2%)	0.95
Number of eyes that had cataract surgery (0–5 years) (% of phakic enrolled eyes)	26 (87)	23 (72)	0.86
Number of eyes that were NPDR at baseline who progressed to PDR (0–5 years)	6/31	1/32	<0.05
Average number of treatments for 5-year completers (26 eyes in each group), n (SD)	9.0 (6.04)	19.2 (7.04)	<0.05

DEX, dexamethasone; NPDR, non-proliferative diabetic retinopathy.

trial was maintained to 5 years as was also found in Protocol T extension. There was still an overall small improvement in mean VA from the commencement of trial, but it seems likely that patients were to a certain extent under-treated in current routine clinical care.

We conducted a separate sensitivity analysis in a cohort from one site to see if the vision loss seen at 5 years was because vision had been measured more casually rather than a protocol BCVA. This cohort did have better BCVA, 4.3 and 4.4 letters (DEX-implant and bevacizumab) than baseline, however, the overall trend was also consistent with mean vision of both groups was still worse than at the end of the clinical trial.

Progression of cataract in phakic eyes within the DEX-implant group was thought to be the cause of the difference in mean vision change for the phakic eyes between the two treatment groups at the 24-month primary endpoint of the BEVORDEX trial. Cataract surgical rate through the 2-year study was 37% for the DEX-implanted eyes compared with 6% in the bevacizumab treated eyes. The 5-year cataract surgical rate in the DEX-implant was 87%, similar to the TDMO study (71%).⁴ The MEAD study of DEX-implant to sham for DMO found a smaller rate of cataract surgery of 59% however the end of study was at 3 years, it is likely to have increased further by 5 years.⁷

Interestingly the cataract surgical rate at 5 years for the patients initially in the bevacizumab treatment group, was similar to those in the DEX-implant treated cohort. Anti-VEGF trials for DMO typically do not report cataract surgery rates. Neither the DRCR.net DMO study comparing three anti-VEGF agents for DMO, Protocol T, nor its 5-year extension study report the cataract surgical rate.¹² VIVID and VISTA, comparing aflibercept with macular laser over 3 years, similarly did not comment on cataract surgical rates however cataract was the most frequent ocular serious adverse event at 2%–3%.⁸ Perhaps the 5-year BEVORDEX rates are higher as the cohort, despite mostly treated through the public system, were offered cataract surgery once their DMO was controlled.

We found glaucoma surgery rates were no different between the two treatment groups at 5 years of only 2%, much less than the triamcinolone treated group in the TDMO extension study which found a rate of 9% at 5 years.⁴ Glaucoma surgery rate in the MEAD study for DEX-implant was similarly low at 0.3%–0.6%, suggesting the slow-release mechanism of the DEX-implant is safer than intravitreal triamcinolone when considering risk of incisional glaucoma surgery.⁸ However, both eyes from the DEX-implant and the bevacizumab treated arm of the trial received triamcinolone and DEX-implants post-trial. This 2% of each group is likely to represent eyes that received any number of different intravitreal treatments over the 5 years, making it difficult to predict safety data for individual agents.

PDR conversion rates, from NPDR, during the initial BEVORDEX trial were not found to be significantly different between treatment groups at 2 years.⁹ However, we found that patients who originally received bevacizumab treatment were less likely to develop PDR than those that were originally treated with DEX-implant by 5 years. The number of eyes that developed PDR was small, so a statistical analysis of systemic risk factors was not considered meaningful. We did not, however, find any notable differences in systemic risk factors for PDR such as HbA1c, length of diabetes, treatment, hypertension or smoking status between those that developed PDR and those that did not. The patients in each treatment group of the original BEVORDEX study had similar systemic complication rates and HbA1c,⁵ so, despite some evidence that steroids are angiostatic,¹⁰ our data suggest that the superior anti-angiogenic of the

VEGF-inhibitor in the present study is due to the drug rather than some imbalance of systemic risk factors. The RISE/RIDE trial also found that patients randomised to treatment with the VEGF-inhibitor (ranibizumab) were less likely to develop PDR, had lower rates of retinopathy progression and higher rates of retinopathy improvement compared with sham.¹¹ VEGF-inhibitors appear to concurrently reduce the risk of progression of retinopathy when used for the treatment of diabetic maculopathy.^{12 13}

CONCLUSION

We found similar 5-year outcomes in eyes initially treated for 2 years with either intravitreal DEX-implant or bevacizumab in the BEVORDEX trial. Vision declined from the end of the 2-year study in both groups to a level that was just above baseline while CMT stayed the same. Rates of cataract and glaucoma surgeries were similar. However, eyes initially randomised and treated for 2 years with the DEX-implant received fewer intravitreal injections and had a higher rate of progression to PDR. These findings provide evidence that more aggressive intervention in routine clinical care may improve long-term patient outcomes.

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Contributors EEC was responsible for ethics, protocol writing, collecting data, manuscript writing and coordinating; KT and VN responsible for statistics; KT, LLL and ILM responsible for data collection and reviewing manuscript. HM, ILM, SW, MCG, SF-B responsible for manuscript reviewing and involved in original BEVORDEX trial. MCG and SF-B provided supervision of the overall project.

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Competing interests MCG: grant—Allergan; personal fees—Bayer; consultant—Allergan, Novartis, Bayer; expert testimony—Bayer. SF-B: consultant—Allergan, Bayer, Novartis, LLL: consultant—Bayer, Novartis, Abbvie, Allergan; speaker fees—Bayer, Abbvie. HM: consultant—Allergan, Bayer, Novartis, Roche. KYCT: no financial disclosures. EEC: no financial disclosures. VN: no financial disclosures. ILM: Ad Board—Novartis, Bayer and Allergan. SW: Ad Board—Allergan; speaker fees—Bayer, Allergan.

Patient consent for publication Obtained.

Ethics approval Our 5-year follow-up study was conducted in accordance with the National Statement of Ethical Conduct in Human Research, and consistent with the principles that have their origin in the Declaration of Helsinki. Approval from each local health district human research ethics committees was obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Data are available upon reasonable request to the corresponding author.

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