Bevacizumab or Dexamethasone Implants for DME: 2-year Results (The BEVORDEX Study)

Both vascular endothelial growth factor inhibitors and steroids given intravitreally have demonstrated superior visual acuity (VA) benefits to laser and/or sham for center-involving diabetic macular edema (DME).1

The BEVORDEX study was the first head-to-head randomized clinical trial of bevacizumab versus a slow-release intravitreal dexamethasone implant (DEX-implant; Ozurdex; Allergan Inc., Irvine, CA) for DME. This study was conducted in accordance with the Declaration of Helsinki and was approved by local Human Research Ethics Committees. We previously reported the methodology and the primary and 12-month secondary outcomes.2 At 12 months, we reported no difference between the groups in proportion of eyes achieving the primary endpoint of a 10-letter gain in VA. There was significantly greater decrease in central macular thickness with fewer intravitreal injections in the DEX-implant group compared with the bevacizumab group at 12 months. However, a greater number of eyes in the DEX-implant group lost vision, mainly owing to cataract.

Eyes continued in the trial for another year on the same treatment allocation (i.e., bevacizumab every 4 weeks or DEX-implant every 16 weeks, both as required). Sixty-eight of the 88 enrolled eyes (77%) completed the 24-month trial. The CONSORT flow-sheet (Supplementary Fig 1, available at www.aaojournal.org) shows that of the 20 eyes (from 13 patients) that exited the study early, 10 had been assigned to DEX-implant and 10 to bevacizumab.

The VA improvement seen at 12 months in both groups was maintained at 24 months, with 20 of 46 DEX-implant–treated eyes (43%) and 19 of 42 bevacizumab-treated eyes (45%) achieving ≥10 letter VA gain (P = 0.99). The proportion of bevacizumab-treated eyes with ≥10 letter VA gain was comparable with other trials of discontinuous anti-vascular endothelial growth factor therapy in DME (e.g., Prospective Randomized Trial of Intravitreal Bevacizumab or Laser Therapy in the Management of Diabetic Macular Edema [BOLT] at 49% and Diabetes Retinopathy Clinical Research Network Protocol I at 49%), although baseline VA, inclusion criteria, and retreatment strategies were different.3,4

The mean improvement in VA was 6.9 letters in DEX-implant–treated eyes (95% CI, 2.7–11.1) and 9.6 letters (95% CI, 6.9–12.3) in bevacizumab-treated eyes (P = 0.30; Fig 1A). At baseline, 26 of 88 study eyes (29.5%) were pseudophakic; 10 randomized to bevacizumab and 16 to DEX-implant. In pseudophakic eyes, the improvement in VA in DEX-implant–treated eyes was similar to bevacizumab-treated eyes (Fig 1B). In phakic eyes, there was a difference in mean VA change between the 2 treatment groups between the 12- and 24-month time-points (Fig 1C), with the DEX-implant group experiencing worse VA. This likely represented development of cataract in the DEX-implant group with subsequent improvement in vision by 24 months after cataract surgery, with 11 of 30 DEX-implant–treated eyes (37%) and 2 of 32 bevacizumab-treated eyes (6%) undergoing cataract surgery during the study. It is possible a larger study may have identified a statistically significant greater mean improvement in VA in favor of bevacizumab in phakic eyes.

Although there was a significantly greater reduction in central macular thickness in the DEX-implant group at 12 months, the graph of central macular thickness over time (Supplementary Fig 2, available at www.aaojournal.org) shows that the bevacizumab group gradually caught up so that there was no difference between the groups at 24 months. This pattern was also reflected in regression of hard exudates from the foveal center.5

Eyes randomized to receive bevacizumab received more injections (mean; 9.1; median, 9.0; SD, 3.1) than those randomized to the DEX-implant (mean, 2.8; median, 3.0; SD, 0.9) during the first 12 months of treatment. However, the difference was less pronounced in the second year of treatment, with the mean number bevacizumab injections being 4.8 (median, 2.0; SD, 5.1) compared with 2.2 (median, 2.0; SD, 1.2) DEX-implant injections. Over 2 years, the number of bevacizumab intravitreal injections was comparable with the number of ranibizumab injections in the deferred laser cohort of Diabetes Retinopathy Clinical Research Network Protocol I.6 The 5-year results from the Diabetes Retinopathy Clinical Research Network Protocol I trial reported a significant decrease in the number of ranibizumab injections required for DME in years 3 through 5, so the difference in treatment load may be less significant after 2 years of intensive anti-vascular endothelial growth factor therapy.1

One bevacizumab-treated eye lost ≥10 letters, whereas 5 of 46 DEX-implant–treated eyes had this degree of vision loss. In 2 eyes in the DEX-implant group and 1 eye in the bevacizumab group with a history of laser-treated proliferative diabetic retinopathy, neovascularization developed after cataract surgery. There was 1 patient with undiagnosed syphilis who developed acute posterior placoid chorioretinopathy after receiving a DEX-implant to that eye.7 There were no cases of endophthalmitis or retinal detachment. There was no new systemic safety signal.

As expected, DEX-implant–treated eyes had higher rates of increased intraocular pressure. An increase in intraocular pressure by ≥5 mmHg from baseline at any visit, occurred in 34 of 46 DEX-implant–treated eyes (74%) and 20 of 42 bevacizumab-treated eyes (48%), with 10 of 46 DEX-implant–treated eyes (22%) requiring the addition of topical ocular hypotensives, whereas no bevacizumab-treated eyes required this. Remem-bering eyes with advanced or uncontrolled glaucoma were excluded from entry, no study eye underwent incisional glaucoma drainage surgery similar to the low rates seen in other trials of Ozurdex in DME (0.6% in the MEAD trial and 0% in the PLACID trial).3

A strength of this study was the opportunity to use the DEX-implant every 16 weeks. Previous industry-sponsored studies have failed to reach predefined primary endpoints because of the mistaken belief that the DEX-implant usually has a therapeutic effect lasting 6 months.1
In conclusion, the 24-month results of the BEVORDEX study identified no significant difference in the primary endpoint of proportion of eyes with a 10-letter gain in VA between bevacizumab and DEX-implant treatment, with both agents providing good improvements. The burden of injections was significantly greater with bevacizumab. However, the DEX-implant group had more cases of visual loss, mainly in eyes that were phakic at baseline. Elevated intraocular pressure in the DEX-implant group could largely be managed with topical therapy. Therefore, the DEX-implant could be considered a second-line treatment option in phakic patients with DME, whereas potentially a first-line treatment option in pseudophakic patients.

Figure 1. Mean visual acuity (VA) according to treatment type from baseline to 24 months. Mean VA was recorded every 4 weeks and standard error bars are included for (A) all eyes entering the trial, (B) eyes that were pseudophakic on entering the study (the mean improvement in VA was 8.9 letters [95% CI, 2.0–13.4] for those treated with the dexamethasone implant and 7.7 letters [95% CI, 3.03–14.8] for those treated with bevacizumab; \( P = 0.77 \)), (C) eyes that were phakic on entering the study (the mean improvement in VA was 5.8 letters [95% CI, 0.07–11.5] for those treated with the dexamethasone implant and 10.2 letters [95% CI, 7.17–13.3] for those treated with bevacizumab; \( P = 0.19 \)).

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References