MODULE 10.9
Clinical Studies and Treatment Data - MEAD

MEAD[1]

Study Name	Three-Year, Randomized, Sham-Controlled Trial of Dexamethasone Intravitreal Implant in Patients with Diabetic Macular Edema
Purpose of study	To evaluate the safety and efficacy of dexamethasone intravitreal implant (Ozurdex) 0.7 and 0.35 mg in the treatment of patients with DME.
Study authors	Boyer DS, Yoon YH, Belfort Jr. R, Bandello F, Maturi RJ, Augustin AJ, Li X-Y, Cui H, Hashad Y, Whitcup SM for the Ozurdex MEAD Study Group
Published in	*Ophthalmology.* 2014;121:1904-1914.
Study also known as	MEAD
Subsequent studies	N/A

Study Overview

Ozurdex is a biodegradable, sustained-release implant previously approved to treat macular edema related to retinal vein occlusion and to treat noninfectious posterior segment uveitis.[2] MEAD comprised 2 large, multicenter 3-year clinical trials designed to evaluate dexamethasone 0.7 mg and 0.35 mg to support the regulatory filing. The study started enrolling patients in 2005 and ended in 2012; there were 131 sites in 22 countries included (n = 1048). Regardless of when a patient was enrolled, he or she was followed for 36 months before exiting the study. Patients were randomized in a 1:1:1 fashion to dexamethasone 0.7 mg (n = 351), dexamethasone 0.35 mg (n = 347) or sham (n = 350).

Previous studies found the implant to be efficacious in treating persistent diabetic macular edema (DME),[3,4] DME resistant to anti–vascular endothelial growth factor (anti-VEGF) treatment,[5] and DME in difficult-to-treat vitrectomized eyes.[6]

In this study, patients with type 1 or type 2 diabetes and fovea-involved DME that was associated with diabetic retinopathy (DR) and had been treated previously with medical or laser therapy were included. Treatment-naïve patients were also enrolled. Baseline best-corrected visual acuity (VA) was required to be between 34 and 68 Early Treatment Diabetic Retinopathy Study (ETDRS) letters (about 20/50 to 20/200). Central retinal thickness (CRT) in the 1-mm central macular subfield was required to be at least 300 µm as determined by time-domain optical coherence tomography (OCT). Key exclusion criteria included aphakia or anterior chamber lens implantation in the study eye, a history of pars plana vitrectomy, and glaucoma or optic nerve head or visual-field damage consistent with glaucoma or a history of steroid-induced intraocular pressure (IOP) increase. A retreatment criterion was established in 2010 (after numerous patients had already exited the study) that allowed for retreatment with the implant if there was evidence of residual edema and it had been more than 6 months since the most recent study treatment. The study design required patients to exit before receiving escape treatment; study authors pointed to that detail as a reason for the high rate of discontinuation.

Study visits were scheduled every 1.5 months (about every 6 weeks) during the first year and then every 3 months during years 2 and 3. About two-thirds of patients completed the study in the dexamethasone arms, and around 43% completed the study in the sham arm (see Figure 1). The main outcome was the percentage of patients with BCVA improvement of at least 15 ETDRS letters at the end of the study (with missing values imputed using last observation carried forward); secondary outcomes included average

change in best-corrected visual acuity (BCVA) from baseline, mean change in BCVA from baseline, time to 15-letter gain from baseline, and average change in CRT from baseline.

Study Implications

Anti-VEGF injections create a treatment burden not only for the patient but the clinician as well. Not all patients are able to maintain a monthly visit schedule, and some do not respond adequately to intravitreal treatments. Intravitreal corticosteroids block production of VEGF, inhibit leukostasis, and enhance the barrier function of vascular endothelial cell tight junctions.[1] When MEAD was first designed, it was initially thought that dexamethasone was a 6-month drug; thus, the studies were enrolled and patients followed accordingly. The results of the MEAD study led the FDA to approve Ozurdex 0.7 mg initially in pseudophakic patients only, but the agency quickly amended its approval to include all patients with DME regardless of lens status.

Study authors also noted an increase in CRT in the sham group post-cataract surgery that did not exist in the dexamethasone group, "suggesting a protective effect of

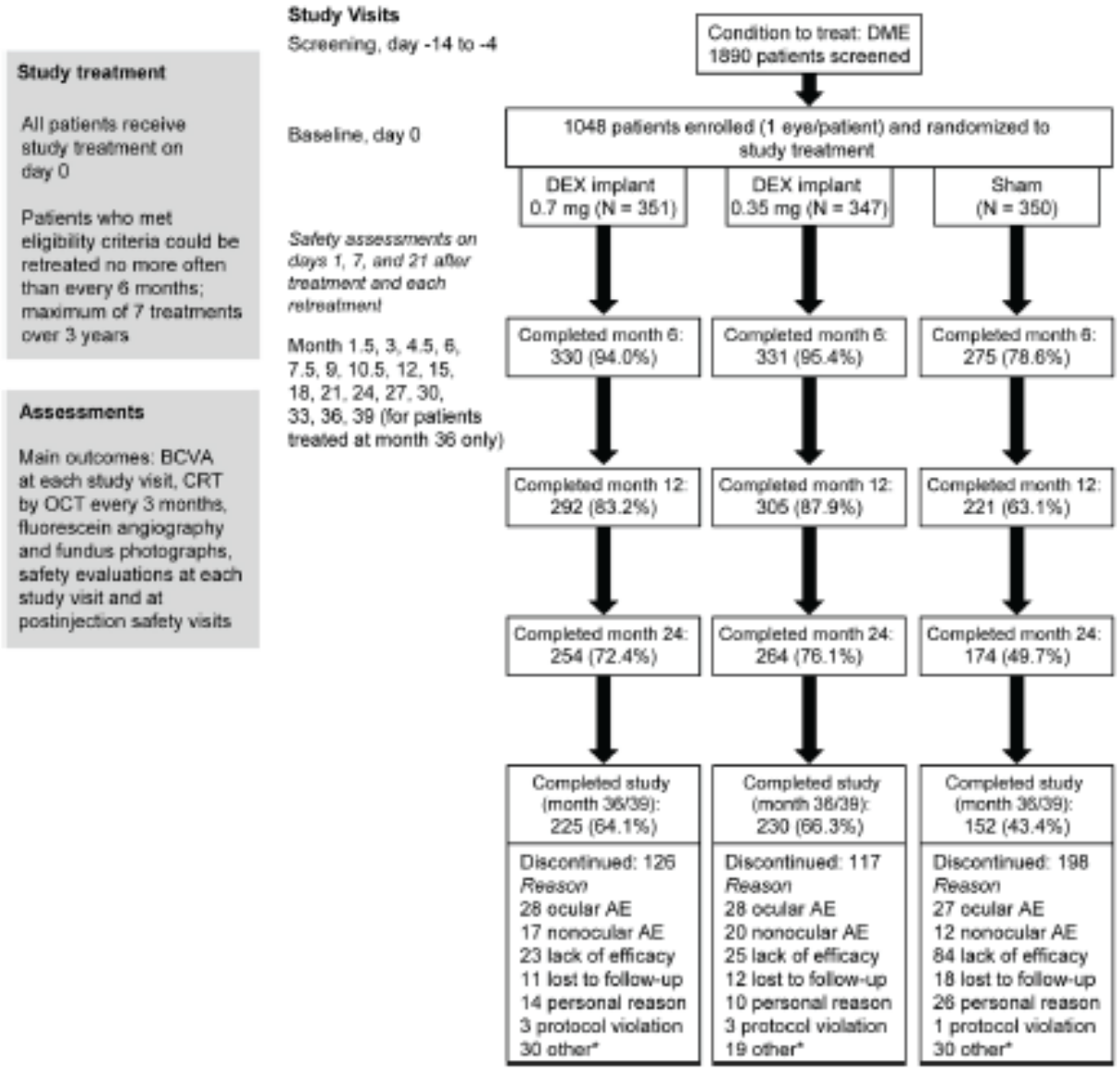

Figure 1: Study design and patient flow.

dexamethasone following cataract surgery."[1] Compared to other sustained-release corticosteroids, dexamethasone has a much lower rate of incisional surgery (< 1% in both arms) for the treatment of elevated IOP, and has a lower rate of cataract development than the other corticosteroids. Study authors attribute this to the fact that dexamethasone is less lipophilic than either triamcinolone acetonide or fluocinolone acetonide.[1]

MEAD was the largest of the studies of dexamethasone for DME and had been designed as a monotherapy trial. In comparison to the anti-VEGF studies, MEAD did not allow for rescue therapy (ie, photocoagulation), so if a patient did require additional treatment, he or she was exited from MEAD. Data on that patient until the point of exit was included in the final data analysis.[1]

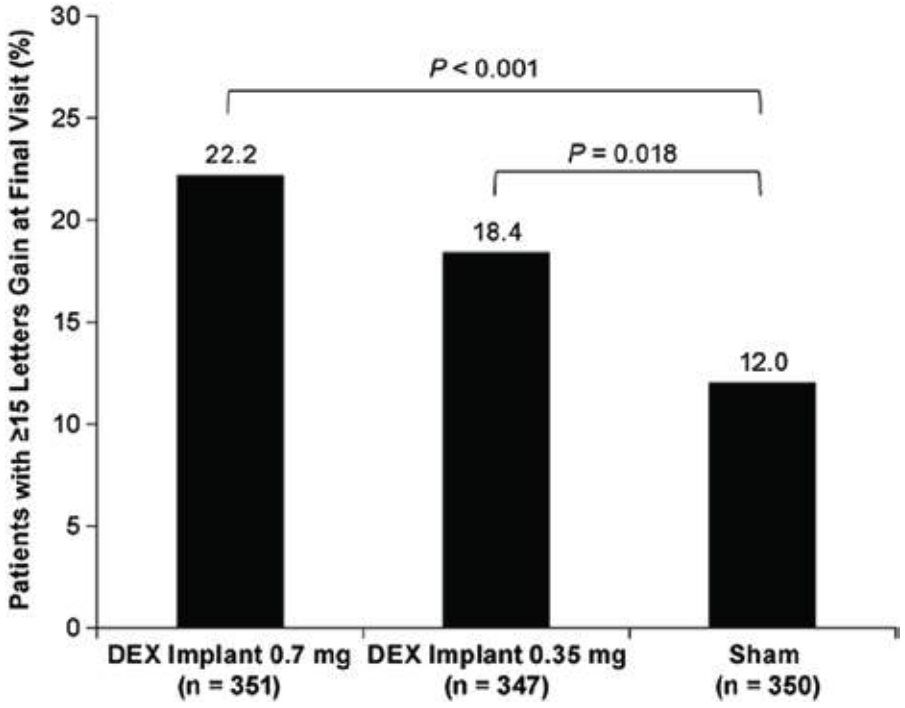

Figure 2: Primary efficacy endpoint.

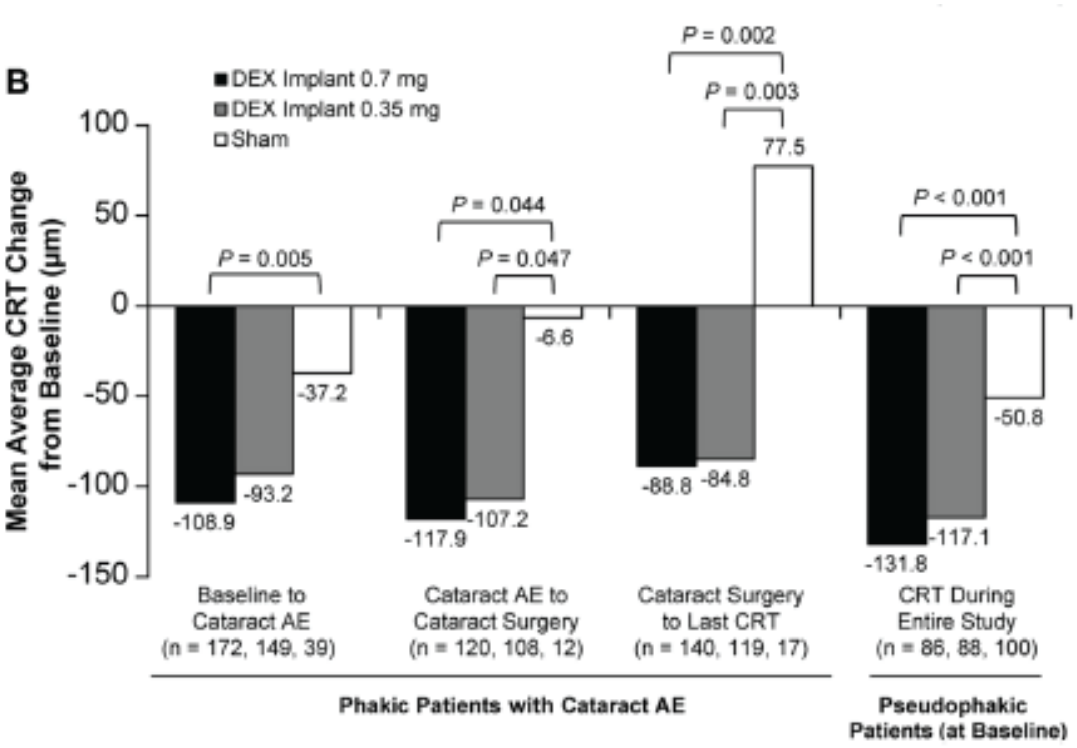

Figure 3: Mean CRT by baseline lens status.

Two points of consideration still surround the study design - mandatory exiting affects the overall results, and in this study, the high retention of sham group indicated a very healthy group of patients. Furthermore, treatments with ranibizumab in the RESTORE study yielded a mean improvement of 6.1 letters with seven injections;[7] in the MEAD study, there were a mean of 4 to 5 injections over 3 years and a gain of 6.5 letters (0.7-mg group) and 5.9 letters (0.35-mg group).[1]

In the real world, most clinicians are finding a treatment effect that starts to decline after month 4, indicating the need to inject more frequently than the on-label indication of every 6 months. Still, treatment burden is significantly less with the steroid implant than it is for the anti-VEGF injections, which tend to be injected monthly for best outcomes.[8] Clinicians also report a reduction in DME as early as 1 week after injection.[9] Most patients do not experience an IOP increase, and those that do are typically well managed with antiglaucoma medications.[9]

Take-Home Points

- Patients treated with the dexamethasone implant achieved statistically significant and clinically meaningful visual improvements over 3 years with only 4 to 5 injections.
- Cataract development is probable in phakic eyes, but removal is uneventful, and vision improvement returns to presurgical levels. (Prompt diagnosis and cataract removal within 3 months is recommended.)
- Fixed dosing every 6 months may not be as efficacious as more frequent dosing.

References

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