

Contralateral eye-to-eye comparison of intravitreal ranibizumab and a sustained-release dexamethasone intravitreal implant in recalcitrant diabetic macular edema

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Objective: To compare the effects of intravitreal ranibizumab (RZB) or dexamethasone (DEX) intravitreal implant in cases of recalcitrant diabetic macular edema (DME).

Methods: Retrospective, interventional study examining patients with symmetric bilateral, center-involved DME recalcitrant to treatment with RZB, who received DEX in one eye while the contralateral eye continued to receive RZB every 4–5 weeks for a study period of 3 months.

Results: Eleven patients (22 eyes) were included: mean logarithm of the minimal angle of resolution (logMAR) visual acuity (VA) for the DEX arm improved from 0.415 (standard deviation [SD] ± 0.16) to 0.261 (SD ± 0.18) at final evaluation, and mean central macular thickness (CMT) improved from 461 μm (SD ± 156) to 356 μm (SD ± 110 ; net decrease: 105 μm , $P=0.01$). Mean logMAR VA for the RZB arm improved from 0.394 (SD ± 0.31) to 0.269 (SD ± 0.19) at final evaluation. Mean CMT improved from 421 μm (SD ± 147) to 373 μm (SD ± 129 ; net decrease: 48 μm , $P=0.26$).

Conclusion: A subset of recalcitrant DME patients demonstrated significant CMT reduction and VA improvement after a single DEX injection.

Keywords: aflibercept, bevacizumab, central macular thickness, macular edema, dexamethasone implant, diabetic macular edema, diabetic retinopathy, ranibizumab

Introduction

Diabetic macular edema (DME) is the main cause of visual impairment among working-age adults in the developed world.¹ It affects an estimated 21 million people² and is a significant contributor to overall vision loss in the diabetic retinopathy (DR) population. As the prevalence of DR continues to increase,³ so too will the need for effective therapies for DME.

Treatment of DME has shifted from the use of focal laser according to the Early Treatment of Diabetic Retinopathy Study parameters to widespread use of intravitreal pharmacologic agents.⁴ The most commonly used medications target elevated levels of vascular endothelial growth factor (VEGF), including bevacizumab, ranibizumab (RZB), and aflibercept, all of which have demonstrated efficacy in large studies.⁴

However, the pathologic microenvironment of DME contains elevated levels of other biomarkers besides VEGF.⁵ Numerous cytokines, transcription factors, and inflammatory stimulants are involved to varying degrees,⁵ and agents that target this broader inflammatory process – namely corticosteroids formulated for intraocular use – have

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Table 1 Previous studies examining the use of sustained-release DEX implant in “persistent,” “resistant,” or “recalcitrant” DME

Study	N	Number of prior anti-VEGF injections	logMAR VA criteria	CMT criteria	Description
Totan et al ¹¹	30 eyes	3	N/A	>275 μ m	“Resistant”
Bansal et al ¹⁰	67 eyes	3	N/A	>300 μ m (\times 90 days)	“Recalcitrant”
Lazic et al ⁹	16 eyes	3	N/A	>225 μ m	“Resistant”
Dutra Medeiros et al ⁸	58 eyes	N/A	N/A	>250 μ m (\times 90 days)	“Persistent”
Pacella et al ^{7*}	20 eyes	N/A	0.3–1.0	\geq 275 μ m	“Persistent”
Rishi et al ¹²	18 eyes	1 [#]	\geq 0.3	N/A	“Recalcitrant”
Zucchiatti et al ⁶	9 eyes	N/A	N/A	\geq 300 μ m (\times 90 days)	“Persistent”

Notes: *Study used the nontreated contralateral eye as “control.” [#]Inclusion criteria required at least one prior treatment with anti-VEGF agent or one focal laser treatment, with at least 3 months of follow-up. Data from previous studies.^{6–12}

Abbreviations: CMT, central macular thickness; DEX, dexamethasone; DME, diabetic macular edema; logMAR, logarithm of the minimum angle of resolution; N/A, not applicable; VEGF, vascular endothelial growth factor; VA, visual acuity.

shown significant efficacy in treating DME, as well.⁴ The widespread use of intravitreal steroids has been limited by concerns over the elevated risks of increased intraocular pressure (IOP) and accelerated cataract formation,⁴ but is still utilized in certain treatment “niches” – pseudophakic patients with DME, for example.⁴

Eyes considered to have “recalcitrant,” “persistent,” or “resistant” DME despite adequate and continuous anti-VEGF therapy have been proposed as an additional niche for intravitreal steroid use.^{6–12} Although variable criteria for determining this state have been employed in the published literature (Table 1), the accumulated data suggest that there is a subset of patients for whom anti-VEGF therapy exerts a suboptimal effect, yet who show significant improvement when treated with a sustained-release intraocular steroid because of its inhibitory effects on the inflammatory components of the DME microenvironment.⁵

A sustained-release dexamethasone (DEX; Ozurdex®; Allergan Inc., Irvine, CA, USA) implant has been shown to be effective in treating DME in Phase II and III studies, including in trials that specifically examined its effects in vitrectomized DME patients with suboptimal responses to anti-VEGF therapy.^{13–18} More recently, smaller noncomparative series have shown the efficacy of the DEX implant in anti-VEGF-resistant DME;^{6–12} however, the variability of entry criteria and the elusiveness of an anti-VEGF control arm has made interpretation of these results somewhat difficult.

A cohort of consecutively treated patients, who 1) demonstrated a minimal response to sequential anti-VEGF therapy that could be classified as “recalcitrant”, 2) demonstrated symmetric manifestations of DME in both eyes in terms of visual acuity (VA) and central macular thickness (CMT), and 3) underwent a therapeutic trial of the DEX implant in only one eye, were identified. The paired contralateral eye – which continued to receive regular anti-VEGF therapy – as a matched control to eliminate diet, genetics, blood sugar

control, systemic health status, and environmental factors as variables, was evaluated. Thus, this study compared the therapeutic responses of matched contralateral eyes of recalcitrant DME patients: a single intravitreal DEX implant in one eye versus ongoing intravitreal anti-VEGF therapy in the other eye over a 3-month period.

Methods

This study is a retrospective, consecutive case series. Included patients were diagnosed with bilateral DME and had previously undergone consistent monthly bilateral intravitreal injections with an anti-VEGF agent (ranibizumab). Patients were considered “recalcitrant” if regular (ie, monthly) anti-VEGF therapy was maintained for at least 3 months, and, there was persistent central macular edema (>300 μ m) and/or a minimal response to therapy (<25% reduction in CMT). Importantly, all patients had near-equivalence of CMT (ie, within 50 μ m) between the two eyes.

Finally, all patients then underwent a unilateral therapeutic trial with the DEX implant (Ozurdex®) while being maintained on anti-VEGF therapy at regular intervals in the contralateral eye. Patients were followed every 4–6 weeks for the subsequent 3 months, and VA, CMT, and IOP were evaluated at every visit. Snellen best corrected visual acuity (BCVA) was measured at each visit. CMT was evaluated by optical coherence tomography (OCT) (Heidelberg Engineering, Heidelberg, Germany), and IOP was measured using a portable tonometer (Tonopen, Reichert Technologies, Depew, NY, USA).

Demographic data gathered at the time of patient intake included age, sex, diabetes type (1 or 2), and the most recent hemoglobin A1c. Clinical data were gathered from the initial patient encounter (“Diagnosis”), the date of initial therapy with the DEX implant (“Treatment Baseline”), and from each follow-up visit during the ensuing 3-month period (“Month 1,” “Month 2,” and “Month 3”).

Patients were excluded from the study if follow-up had not been maintained for 3 months after baseline treatment with the DEX implant, if there were potential confounding etiologies for the macular edema (eg, retinal vein occlusion, epiretinal membrane, or vitreomacular traction), or if the patient had uncontrolled systemic diabetes. Patients were also excluded if they had any contraindication to therapy as outlined in the prescribing information for the DEX implant.¹⁹ All patients provided appropriate informed consent to undergo the therapy described above.

Data analysis

Data were entered into an Excel spreadsheet (Microsoft Corporation, Redford, WA, USA), and statistical analysis was performed using Stata version 9.0 (StataCorp, LP, College Station, TX, USA). Snellen BCVA was converted to logarithm of the minimal angle of resolution (logMAR) units for statistical analyses. The Mann–Whitney *U*-test and Wilcoxon signed rank test were employed, and statistical significance was set at $P < 0.05$. This study received approval from the William Beaumont Hospital Institutional Review Board and was conducted in compliance with the Health Insurance Portability and Accountability Act of 1996, and it adhered to the tenets of the Declaration of Helsinki.

Results

Eleven consecutive patients were identified with bilateral, symmetric DME that had proven to be recalcitrant to anti-VEGF therapy, as defined above – this cohort encompassed eleven eyes treated with the DEX implant and the eleven paired contralateral eyes that continued treatment with RZB for the same 3-month period. Demographic data for these patients are found in Table 2, including the most recent hemoglobin A1c at treatment baseline (mean: 6.51, range: 5.9–7.0).

Baseline ophthalmic features of paired contralateral eyes, including VA, CMT, and IOP, are shown in Table 3. No significant difference was noted between DEX eyes and RZB eyes in regard to mean logMAR VA (0.415 and 0.394,

respectively; $P = 0.294$, Mann–Whitney *U*-test), mean CMT (461.3 and 421.1 μm , respectively; $P = 0.795$), and mean IOP (17.1 and 16.0 mmHg, respectively; $P = 0.535$).

Furthermore, there was no significant difference between paired eyes in terms of prior anti-VEGF therapy: eyes in the DEX arm had received a mean of 8.91 prior anti-VEGF injections, as compared to a mean of 9.10 injections for the RZB arm ($P = 0.944$, Mann–Whitney *U*-test). Yet, in spite of previous therapy from the “Diagnosis” time point to the “Treatment Baseline” time point in this current study, an incomplete treatment response had been noted for DEX and RZB eyes in terms of mean logMAR VA (DEX: 0.505–0.415, $P = 0.976$; RZB: 0.573–0.394, $P = 0.555$) and mean CMT (DEX: 434.1–461.3 μm , $P = 0.968$; RZB: 428.1–421.1 μm , $P = 0.810$).

Treatment outcomes in each arm were compared to study baseline from visits at Month 1, Month 2, and Month 3 and are presented in Table 4. In terms of VA, both the DEX and RZB arms improved during the study period, with gains in mean logMAR VA of 0.153 and 0.125, respectively, but only improvement in the DEX arm achieved statistical significance ($P = 0.004$, compared to $P = 0.058$ for RZB arm, Wilcoxon signed rank test).

CMT decreased during the study period in both the DEX arm and the RZB arm (net decrease of 105.8 versus 47.9 μm , respectively), although these differences did not differ significantly ($P = 0.332$, Mann–Whitney *U*-test). However, only the improvement in mean CMT in the DEX arm achieved statistical significance from baseline to Month 3 ($P = 0.01$, Wilcoxon signed rank test), whereas the improvement in mean CMT for the RZB arm did not ($P = 0.26$). The greatest difference in mean CMT between the two study arms was seen at Month 2, when the mean CMT for the DEX arm improved to 314.6 μm (from 461.3 μm ; $P = 0.02$) while the mean CMT for the RZB arm had only improved to 406.9 μm (from 421.1 μm ; $P = 0.61$).

No patients were lost to follow-up during the study period. No significant complications, including infectious endophthalmitis, vitreous hemorrhage, retinal detachment, or lens disruption/subluxation, were noted for either treatment arm during the study period. In eyes that received the DEX implant, only two eyes demonstrated IOP > 30 mmHg at any time point, and both normalized by the end of the study period (neither eye required IOP-lowering therapy at the end of the study period). No eyes in the RZB arm demonstrated elevations of IOP > 30 mmHg.

Discussion

Our understanding of the optimal treatment patterns for DME has evolved commensurate with our understanding

Table 2 Demographic and clinical characteristics of patients

Feature	Number (%)
N=11 patients	
Age, years	
Mean (range)	62 (51–84)
Sex	
Male	4 (36.4)
Female	7 (63.6)
Diabetes mellitus, type 1 or 2	
Type 2	11 (100)
Most recent hemoglobin A1c, mean (range)	6.51 (5.9–7.0)

Table 3 Features of matched contralateral eyes at treatment outset

Feature	Number (%)		P-value
	Eye receiving intravitreal dexamethasone implant (N=11)	Eye receiving intravitreal ranibizumab (N=11)	
Duration of prior treatment, months			
Mean (range)	19.4 (5–50)		
Laterality			
Right eye (OD)	5 (45.5)	6 (54.5)	
Left eye (OS)	6 (54.5)	5 (45.5)	
Lens status			
Phakic	3 (27.3)	4 (36.4)	
Pseudophakic	8 (72.7)	7 (63.6)	
Prior anti-VEGF injections			
Mean (median)	8.91 (8.0)	9.10 (8.5)	0.944
Visual acuity, logMAR			
Mean (SD)	0.415 (0.165)	0.394 (0.313)	0.294
CMT, μm			
Mean (SD)	461.3 (156.8)	421.1 (146.8)	0.795
IOP, mmHg			
Mean (SD)	17.1 (4.18)	16.0 (3.87)	0.535

Abbreviations: CMT, central macular thickness; IOP, intraocular pressure; logMAR, logarithm of the minimum angle of resolution; SD, standard deviation; VEGF, vascular endothelial growth factor.

of the pathological mechanisms underlying the disease, as well as with the availability of additional therapeutic agents. Focal laser therapy has been supplanted as the most common therapy for DME by the use of intravitreal injections of anti-VEGF medication, and the DEX implant has demonstrated comparable (or superior) efficacy to such agents in numerous studies.^{5–17}

Studies of the pathological microenvironment of DR and DME have revealed a highly complex picture of the signals that drive vascular permeability and lead to macular edema.⁵

Thus, it is not surprising that clinicians encounter significant variability in patient response to drugs that target only one biochemical signal in the intravitreal microenvironment (ie, VEGF). Since there are no widely available tests to directly determine the relative contribution of such signals in individual patients, clinicians instead select between various therapeutic agents on the basis of empirical responses to particular agents.

As expected, the sustained-release DEX implant was effective in treating DME. However, this study is unique in

Table 4 Treatment outcomes – baseline, Months 1–3

	Value (SD)		P-value (DEX vs RZB)
	Eye receiving intravitreal DEX implant (N=11)	Eye receiving intravitreal RZB (N=11)	
Mean VA, logMAR			
Baseline	0.415 (0.165)	0.394 (0.313)	0.294
Month 1	0.334 (0.172)	0.378 (0.282)	0.873
Month 2	0.366 (0.171)	0.338 (0.183)	0.818
Month 3	0.261 (0.182)	0.269 (0.186)	0.976
Net gain	0.153	0.125	0.624
P-value (baseline to Month 3)	0.004	0.058	
Mean CMT (μm)			
Baseline	461.3 (156.8)	421.1 (146.8)	0.795
Month 1	353.3 (99.8)	413.1 (117.1)	0.490
Month 2	314.6 (86.4)	406.9 (128.9)	0.509
Month 3	355.6 (110.2)	373.2 (142.6)	1.0
Net decrease	105.8	47.9	0.332
P-value (baseline to Month 3)	0.01	0.26	

Note: Bold values are delta values (change from one time point to another) or significant P-values.

Abbreviations: CMT, central macular thickness; DEX, dexamethasone; logMAR, logarithm of the minimum angle of resolution; RZB, ranibizumab; SD, standard deviation; VA, visual acuity.

such a way that it confirmed the efficacy of the DEX implant in reducing recalcitrant, persistent, or anti-VEGF-resistant DME when compared to continued anti-VEGF therapy in an extremely controlled manner: in contralateral eyes of the same patients matched for VA, CMT, and prior treatment history. Moreover, the use of contralateral eyes as the primary control group accounted for some of the complex pathobiologic influences that drive DME, such as patient compliance, testing conditions, treatment procedures, and – of course – the effects of systemic diabetic control.

In this series, a cohort of patients was identified whose response to the DEX implant in terms of improved VA and CMT reduction was significantly greater than that seen with continued anti-VEGF use in the contralateral eye – at least, in the short term. The overall difference in CMT reduction between the two arms did not achieve statistical significance at any time point, but the greatest absolute difference was noted at Month 2, consistent with prior studies that have demonstrated a peak effect for the DEX implant at around 2–3 months posttreatment.¹⁸ Overall, the improved clinical response of this cohort supports the use of a single injection of the DEX implant to treat a subset of DME patients who can empirically be considered “recalcitrant” to more frequent anti-VEGF injections.

Eyes in the DEX arm received one-third the number of intravitreal injections as their paired, contralateral eyes, and patients found the potential reduced treatment burden to be an advantage. With the very low incidence of post-injection endophthalmitis seen in large trials with the DEX implant,^{18,20–22} fewer injections may offer a safer, less morbid alternative in appropriate patients, and result in equal or greater efficacy in reducing CMT.

No significant complications associated with the intravitreal injections given in either arm of the trial were encountered. A modest, transient elevated IOP was seen in two eyes that received injection of the DEX implant, each of which was treated with IOP-lowering medication for 1–2 months followed by a return to normal IOP and discontinuation of topical therapy.

It is interesting to note that the eyes in the RZB arm trended toward improvement of both VA and CMT over the 3-month study period, in spite of having a minimal or suboptimal prior response during the treatment period from initial presentation to the beginning of this therapeutic trial. A mild improvement in the control arm in macular edema treatment trials is commonly seen, likely due to a variety of factors, including potential overall better systemic control of blood sugar, blood pressure, and other variables that

may impact the clearing of the edema, as in this series. It is seemingly quite unlikely that there would be any crossover effect of the intravitreal DEX from one eye to the other given the pharmacokinetics of clearing and mechanism of action of this steroid, and there has yet to be any published data to support such a hypothesis.

The current study is limited by its small size (which likely factors into the unexpected improvement in the RZB arm, described earlier), use of Snellen VAs, short follow-up, lack of comparison of the DEX implant to shorter-acting steroids, other anti-VEGF agents, or to a switch to other such agents, and no combination therapy arm that examined treatment with both the DEX implant and ranibizumab. Large prospective, randomized studies, with larger sample sizes and correlations with intravitreal cytokine profiles, will be better able to identify the population of DME patients who may best respond to short- or long-acting steroid formulations, anti-VEGF agents, or both as clinicians seek to optimize their treatment regimens.

In the current clinical environment, there is increasing support from the published literature for a transition from intravitreal anti-VEGF therapy to the use of intravitreal sustained-release steroids – alone or in combination with continued anti-VEGF therapy – when confronted with suboptimal visual and/or anatomic responses to first-line DME treatment. The current study supports the idea that other inflammatory pathobiologic pathways contribute to persistent DME, even in the setting of consistent anti-VEGF therapy, and that these may be responsive targets for intravitreal steroid treatment. Importantly, the study does so with a consecutive head-to-head comparison of contralateral eyes that controls for any variability in patient glycemic and blood pressure control, genetics, idiosyncratic responses to therapy, and compliance with follow-up and treatment – factors known to potentially contribute to the considerable variability seen in the outcomes of intravitreal therapy for retinal vascular disease. Within the complex pathological milieu of DME, there is a subset of patients (or, further, variable time points within the treatment course of an individual patient) wherein the use of the DEX implant should be considered strongly as an alternate or potentially adjunctive therapeutic agent.

Summary

In select cases of chronic DME recalcitrant to first-line intravitreal anti-VEGF therapy, sustained-release steroids may be a superior alternative or adjunctive treatment. Compared to contralateral eyes with similar disease, DEX intravitreal

implants led to greater vision improvement and net reduction of CMT, with fewer injections.

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Disclosure

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References

- Klein R, Klein BE, Moss SE, et al. The Wisconsin epidemiologic study of diabetic retinopathy. IV. Diabetic macular edema. *Ophthalmology*. 1984;91(12):1464–1474.
- Yau JW, Rogers SL, Kawasaki R, et al; Meta-Analysis for Eye Disease (META-EYE) Study Group. Global prevalence and major risk factors of diabetic retinopathy. *Diabetes Care*. 2012;35(3):556–564.
- Kempner JH, O'Colmain BJ, Leske MC, et al; Eye Diseases Prevalence Research Group. The prevalence of diabetic retinopathy among adults in the United States. *Arch Ophthalmol*. 2004;122(4):552–563.
- Thomas BJ, Shienbaum G, Boyer DS, Flynn HW Jr. Evolving strategies in the management of diabetic macular edema: clinical trials and current management. *Can J Ophthalmol*. 2013;48(1):22–30.
- Dugel PU, Bandello F, Loewenstein A. Dexamethasone intravitreal implant in the treatment of diabetic macular edema. *Clin Ophthalmol*. 2015;9:1321–1335. eCollection 2015. Review.
- Zucchiatti I, Lattanzio R, Querques G, et al. Intravitreal dexamethasone implant in patients with persistent diabetic macular edema. *Ophthalmologica*. 2012;228(2):117–122.
- Pacella E, Vestri AR, Muscella R, et al. Preliminary results of an intravitreal dexamethasone implant (Ozurdex®) in patients with persistent diabetic macular edema. *Clin Ophthalmol*. 2013;7:1423–1428.
- Dutra Medeiros M, Postorino M, Navarro R, et al. Dexamethasone intravitreal implant for treatment of patients with persistent diabetic macular edema. *Ophthalmologica*. 2014;231(3):141–146.
- Lazic R, Lukic M, Boras I, et al. Treatment of anti-vascular endothelial growth factor-resistant diabetic macular edema with dexamethasone intravitreal implant. *Retina*. 2014;34(4):719–724.
- Bansal P, Gupta V, Gupta A, et al. Efficacy of Ozurdex implant in recalcitrant diabetic macular edema – a single-center experience. *Int Ophthalmol*. Epub 2015 Aug 2.
- Totan Y, Guler E, Guragac FB. Dexamethasone intravitreal implant for chronic diabetic macular edema resistant to intravitreal bevacizumab treatment. *Curr Eye Res*. 2016;41(1):107–113. Epub 2015 Jan 22.
- Rishi P, Rishi E, Kuniyal L, Mathur G. Short-term results of intravitreal dexamethasone implant (OZURDEX) in treatment of recalcitrant diabetic macular edema: a case series. *Oman J Ophthalmol*. 2012;5(2):79–82.
- Haller JA, Kuppermann BD, Blumenkranz MS, et al; Dexamethasone DDS Phase II Study Group. Randomized controlled trial of an intravitreal dexamethasone drug delivery system in patients with diabetic macular edema. *Arch Ophthalmol*. 2010;128(3):289–296.
- Callanan DG, Gupta S, Boyer DS, et al; Ozurdex PLACID Study Group. Dexamethasone intravitreal implant in combination with laser photocoagulation for the treatment of diffuse diabetic macular edema. *Ophthalmology*. 2013;120(9):1843–1851.
- Boyer DS, Yoon YH, Belfort R Jr, et al. Three-year, randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with diabetic macular edema. *Ophthalmology*. 2014;121(10):1904–1914.
- Danis RP, Sadda S, Cui H, et al. Anatomic outcomes with dexamethasone intravitreal implant in diabetic macular edema: a pooled analysis of two randomized phase III trials. ARVO 2014 Annual Meeting; May 4–8; 2014; Orlando, FL.
- Boyer DS, Faber D, Gupta S, et al; Ozurdex CHAMPLAIN Study Group. Dexamethasone intravitreal implant for treatment of diabetic macular edema in vitrectomized patients. *Retina*. 2011;31(5):915–923.
- Shah AR, Xi M, Abbey AM, et al. Efficacy of intravitreal dexamethasone implant in vitrectomized eyes with recalcitrant diabetic macular edema previously treated with anti-VEGF therapy. *J Ophthalmic Vis Res*. In press.
- Anon. *Ozurdex Prescribing Information*; 2014. Available from: http://www.allergan.com/assets/pdf/ozurdex_pi.pdf. Accessed October 26, 2015.
- Haller JA, Bandello F, Belfort R Jr, et al; Ozurdex GENEVA Study Group. Dexamethasone intravitreal implant in patients with macular edema related to branch or central retinal vein occlusion twelve-month study results. *Ophthalmology*. 2011;118(12):2453–2460.
- Callanan DG, Gupta S, Boyer DS, et al; Ozurdex PLACID Study Group. Dexamethasone intravitreal implant in combination with laser photocoagulation for the treatment of diffuse diabetic macular edema. *Ophthalmology*. 2013;120(9):1843–1851.
- Boyer DS, Yoon YH, Belfort R Jr, et al; Ozurdex MEAD Study Group. Three-year, randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with diabetic macular edema. *Ophthalmology*. 2014;121(10):1904–1914.

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