

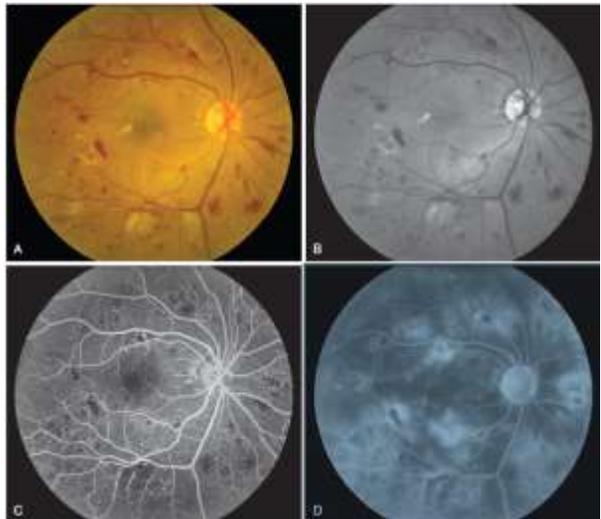
OZURDEX IN DME

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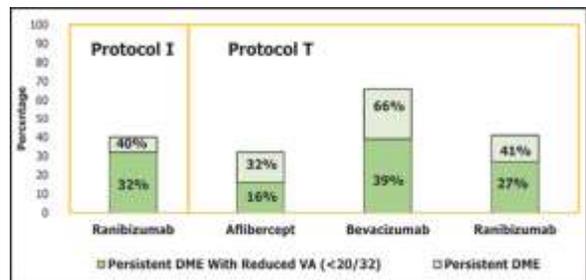
INTRODUCTION

- Diabetic retinopathy (DR) is a leading cause of vision loss and blindness in adults ≥ 40 years of age.
- The vision loss associated with DR most commonly results from diabetic macular edema (DME), which is estimated to affect **20%** of patients with DR.
- Diabetic macular edema is characterized by capillary leakage, fluid accumulation, and macular thickening following breakdown of the blood-retinal barrier (BRB).



INTRODUCTION

- Inhibitors of VEGF have become first-line treatment in DME management after multiple clinical trials demonstrated significant clinical efficacy compared to prior standard therapies.
- However, these clinical trials revealed that only 31–46% of patients receiving anti-VEGF therapy gained 3 or more lines of vision.
- Significant proportions of patients have an incomplete response to anti-VEGF therapy anatomically, functionally or both.

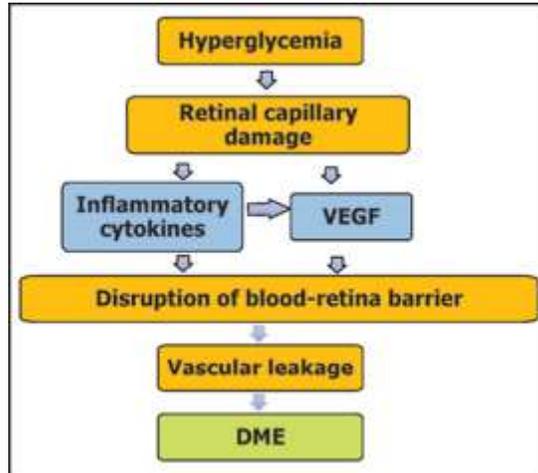


TAKE HOME POINTS

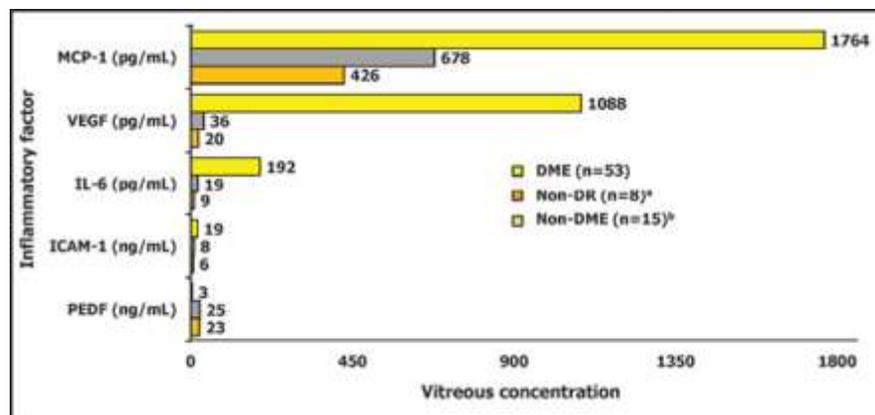
- **CHRONIC INFLAMMATION IS CENTRAL TO PATHOPHYSIOLOGY OF DME.**
- Inflammatory cytokines better reflect disease severity than VEGF.
- OCT biomarkers could identify poor anti-VEGF responders.
- DEX implant is effective for the treatment of DME.
- DEX implant effects last for less than 6 months.
- Cataract develops in **2/3** of patients, most cases develop in the **2nd** year of treatment.
- Significant IOP elevations occur in **1/3** of patients, peak **1-3** months after injection, and return to baseline by **6th** month.
- DEX implant is a good option for the right patient.

CHRONIC INFLAMMATION IS CENTRAL TO PATHOPHYSIOLOGY OF DME

- Inflammation has an important role in the pathogenesis of DME.
- The inflammatory cascade associated with DME pathogenesis begins with the chronic hyperglycemia of diabetes.



- Levels of several aqueous and vitreous inflammatory cytokines are higher in eyes with DME than in healthy eyes or in eyes of diabetic patients without DR.
- These factors often have shared functions, including promoting leukocyte adhesion to endothelial cells and breaking down the BRB.



Funatsu, *et al.* Association of vitreous inflammatory factors with diabetic macular edema. *Ophthalmology*. 2009 Jan;116(1):73-9.

TAKE HOME POINTS

- Chronic inflammation is central to pathophysiology of DME.
- INFLAMMATORY CYTOKINES BETTER REFLECT DISEASE SEVERITY THAN VEGF.**
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INFLAMMATORY CYTOKINES BETTER REFLECT DISEASE SEVERITY THAN VEGF

- Inflammatory cytokines other than VEGF may be more correlated with or drivers of disease severity.

ETDRS retinopathy severity	N	Cytokine concentration (pg/mL)					
		VEGF	IL-1 β	IL-6	IL-8	MCP-1	IP-10
10	28	967.0	10.0	32.1	22.8	252.2	2.1
20	23	952.8	11.0	33.5	20.6	303.6	2.5
35	26	956.4	9.2	33.1	22.7	339.5	5.6
43	18	1084.7	10.7	33.2	24.4	468.8	5.5
47	13	1172.6	18.8	56.6	29.2	645.2	9.5
53	8	1177.3	22.7	106.7	49.4	921.2	22.3
65	7	1142.7	23.7	116.8	51.0	1215.1	31.3
75	8	1051.4	27.6	147.0	75.7	1286.6	34.3
81	5	1165.4	45.8	188.6	74.4	1630.8	29.2
P value		.733	.003	<.001	.001	<.001	<.001

Dong, et al. Study of 27 Aqueous Humor Cytokines in Type 2 Diabetic Patients with or without Macular Edema. PLoS One. 2015 Apr 29;10(4):e0125329.

- Intravitreal corticosteroids block production of VEGF and other inflammatory mediators, inhibit leukostasis, and enhance the barrier function of vascular endothelial cell tight junctions.
- Off-label treatment with intravitreal triamcinolone acetonide (TA) has been shown to be more effective than placebo in improving vision in patients with refractory DME in **Protocol B**.
- The **Protocol I** study evaluating intravitreal TA or ranibizumab in combination with laser treatment reported similar efficacy of TA and ranibizumab in pseudophakic eyes, in which there is no confounding of cataract development associated with corticosteroid treatment.

TABLE 3. Changes in Aqueous Concentrations (pg/mL) of Inflammatory and Angiogenic Cytokines After Intravitreal Injection (Triamcinolone vs Bevacizumab) in Diabetic Macular Edema Group

Variable	IVTA Group (n=11)			IVBe Group (n=11)		
	Preinjection	Postinjection	P Value ^a	Preinjection	Postinjection	P Value ^a
IL-6	29.9 (10.1-82.5)	13.8 (2.8-36.3)	<.01	26.7 (13.8-107.0)	24.0 (6.5-147.0)	.477
IL-8	28.2 (6.23-77.5)	25.3 (12.4-95.8)	.597	23.9 (11.1-39.7)	23.6 (11.0-74.2)	.374
IP-10	366.0 (171.0-1380)	249.0 (26.7-717.0)	.013	401.0 (126.0-1990)	433.0 (268.0-4570)	.110
MCP-1	3850 (2060-4380)	1090 (351-4150)	.010	3770 (2660-4490)	3840 (1790-4490)	.594
PDGF-AA	68.7 (31.4-141.0)	37.1 (10.9-89.7)	.016	81.0 (14.3-140.0)	72.7 (23.8-117.0)	.722
VEGF	55.0 (36.0-262.0)	10.5 (0.1-372.0)	.050	61.5 (31.8-200.1)	0.1 (0.1-28.3)	<.01

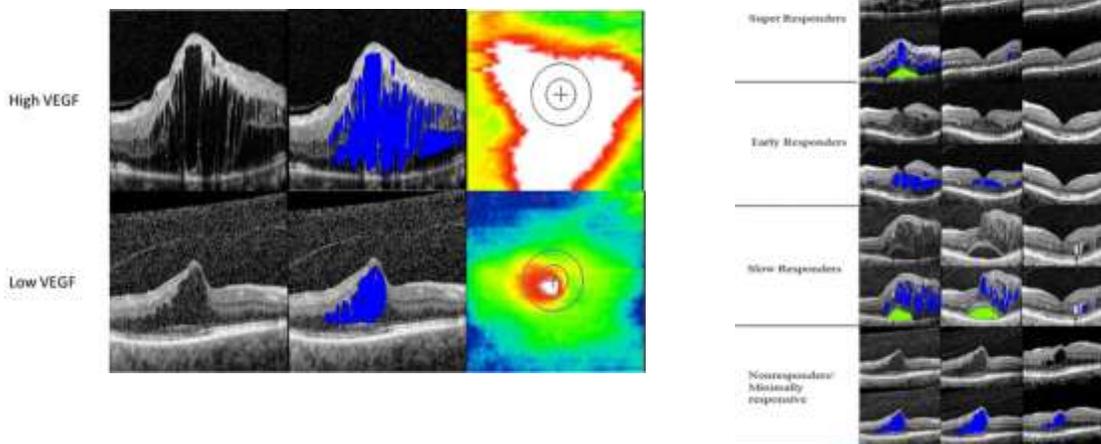
Sohn HJ, Han DH, Kim IT, Oh JK, Kim KH, Lee DY, Nam DH. Changes in aqueous concentrations of various cytokines after intravitreal triamcinolone versus bevacizumab for diabetic macular edema. Am J Ophthalmol. 2011 Oct;152(4):686-94.

TAKE HOME POINTS

- Chronic inflammation is central to pathophysiology of dme.
- Inflammatory cytokines better reflect disease severity and chronicity than VEGF.
- OCT BIOMARKERS COULD IDENTIFY POOR ANTI-VEGF RESPONDERS.**
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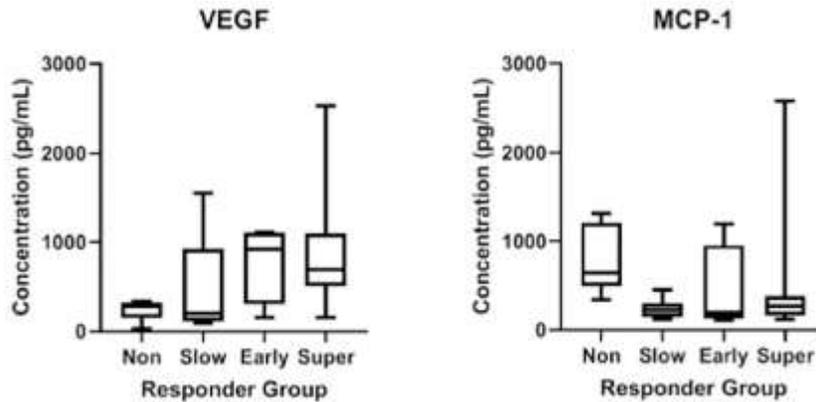
OCT BIOMARKERS COULD IDENTIFY POOR ANTI-VEGF RESPONDERS

- IMAGINE study assessed aqueous humor cytokine expression as predictive biomarkers for anatomic treatment response to intravitreal ranibizumab in DME.

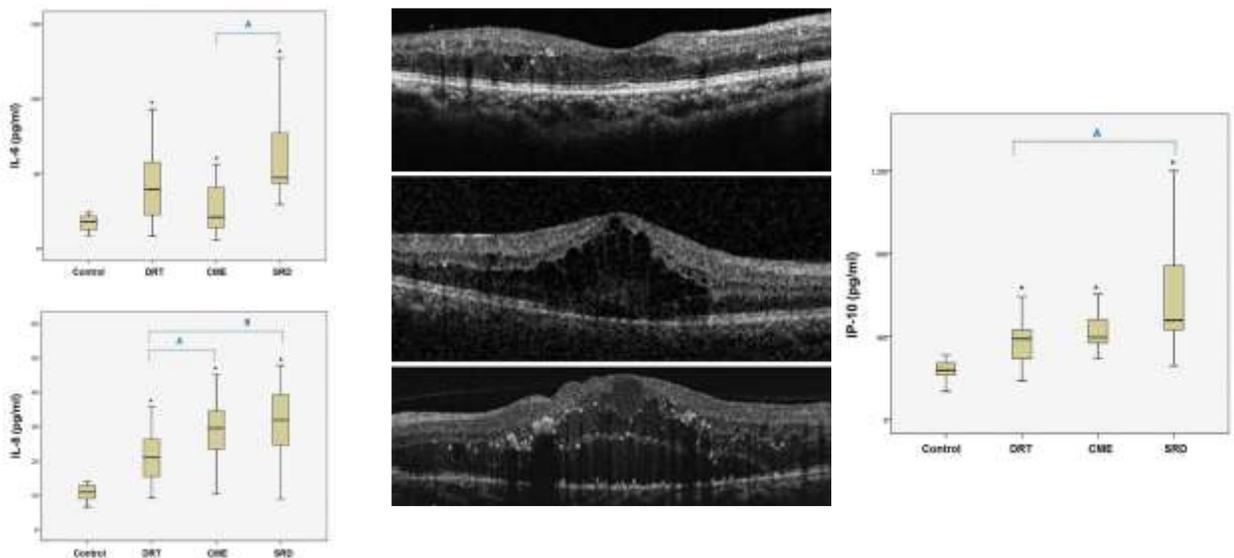


Abraham, et al. Aqueous Cytokine Expression and Higher Order OCT Biomarkers: Assessment of the Anatomic Biologic Bridge in the IMAGINE DME Study. Am J Ophthalmol. 2021 Feb;222:328-339.

- The anatomical responders represent eyes with a more VEGF driven phenotype.
- Nonresponders and slow responders represent a more inflammation-driven phenotype that would benefit from alternate therapy.



Abraham, *et al.* Aqueous Cytokine Expression and Higher Order OCT Biomarkers: Assessment of the Anatomic Biologic Bridge in the IMAGINE DME Study. *Am J Ophthalmol.* 2021 Feb;222:328-339.



Kim, *et al.* Comparison of aqueous concentrations of angiogenic and inflammatory cytokines based on optical coherence tomography patterns of diabetic macular edema. *Indian J Ophthalmol.* 2015 Apr;63(4):312-7.

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DEX IMPLANT IS EFFECTIVE FOR THE TREATMENT OF DME

- The DEX implant releases the potent corticosteroid dexamethasone into the vitreous over a period of ≤ 6 months.
- Dexamethasone differs from TA in pharmacologic activity and lipid solubility, as well as delivery requirements.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use OZURDEX[®] safely and effectively. See full prescribing information for OZURDEX[®].

OZURDEX[®] (dexamethasone intravitreal implant)

For Intravitreal Injection
Initial U.S. Approval: 1998

RECENT MAJOR CHANGES

- Indications and Usage (1.3) 9/2014
- Contraindications (4.2, 4.3, 4.4) 9/2014
- Warnings and Precautions (3.2) 9/2014

INDICATIONS AND USAGE

- OZURDEX[®] is a corticosteroid implant for:
- The treatment of macular edema following branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO) (1.3)
 - The treatment of non-infectious uveitis affecting the posterior segment of the eye (1.4)
 - The treatment of diabetic macular edema (1)

DOSAGE AND ADMINISTRATION

- For ophthalmic intravitreal injection. (2.1)
- The intravitreal injection procedure should be carried out under controlled aseptic conditions. (2.2)
- Following the intravitreal injection, patients should be monitored for elevation in intraocular pressure and for endophthalmitis. (2.2)

DOSAGE FORMS AND STRENGTHS

Intravitreal implant containing dexamethasone 0.7 mg in the NOVADUR[®] solid polymer drug delivery system. (3)

CONTRAINDICATIONS

- Ocular or periocular infections (4.1)
- Glaucoma (4.2)
- Torn or ruptured posterior lens capsule (4.3)
- Hypersensitivity (4.4)

WARNINGS AND PRECAUTIONS

- Intravitreal injections have been associated with endophthalmitis, eye inflammation, increased intraocular pressure, and retinal detachments. Patients should be monitored following the injection. (5.1)
- Use of corticosteroids may produce posterior subcapsular cataracts, increased intraocular pressure, glaucoma, and may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses. (5.2)

ADVERSE REACTIONS

In controlled studies, the most common adverse reactions reported by 20–70% of patients were cataract, increased intraocular pressure and conjunctival hemorrhage. (6.1)

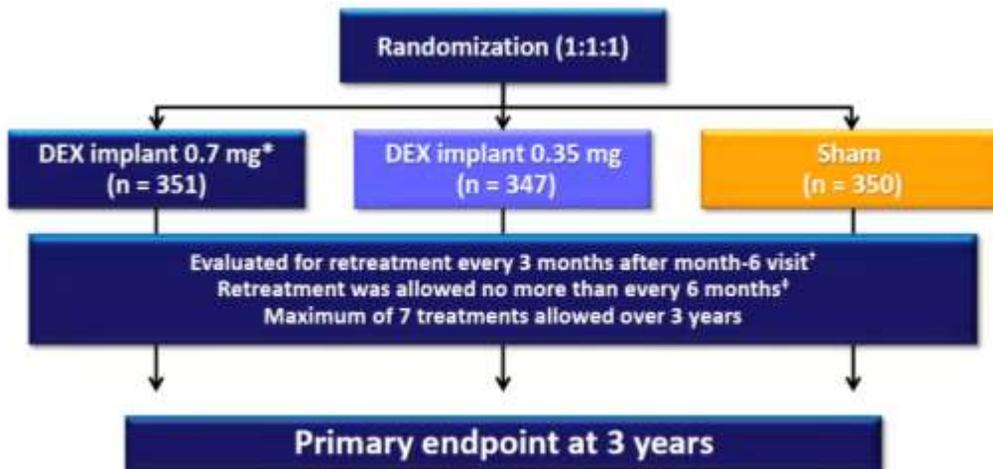
To report SUSPECTED ADVERSE REACTIONS, contact Allergan at 1-800-435-8571 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Kanellopoulos, MD



MEAD STUDY

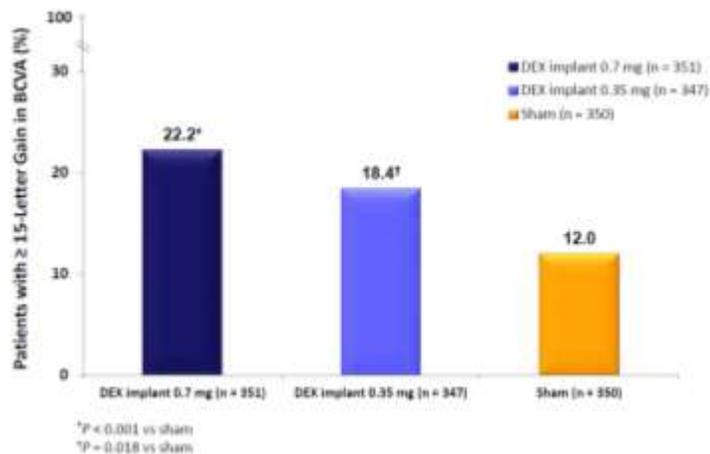


Boyer, et al. Three-year, randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with diabetic macular edema. *Ophthalmology*. 2014 Oct;121(10):1904-14.

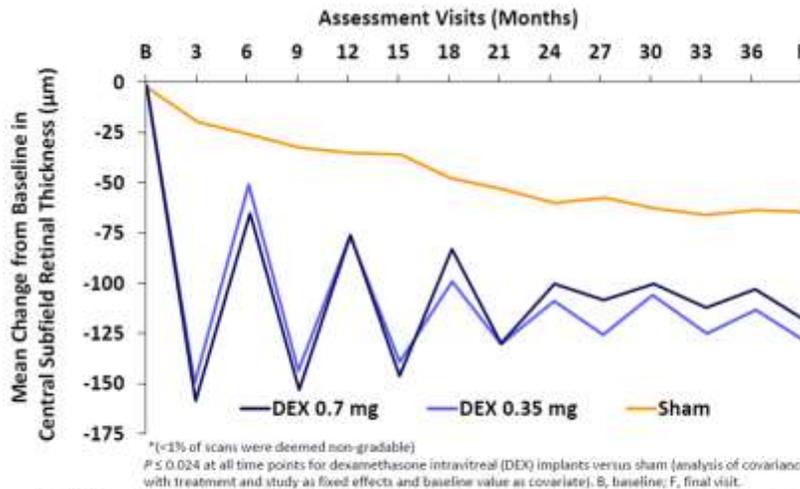
Key Inclusion Criteria	Key Exclusion Criteria
<ul style="list-style-type: none"> • Adults with diabetes • DME in the study eye <ul style="list-style-type: none"> – Best-corrected visual acuity (BCVA) 34 to 68 letters (20/200–20/50) – CRT \geq 300 μm • Previous treatment with medical or laser therapy for DME <ul style="list-style-type: none"> – Treatment-naïve patients who refused or would not benefit from laser therapy were allowed 	<ul style="list-style-type: none"> • HbA1C > 10% • Prior treatment without adequate washout period, including <ul style="list-style-type: none"> – Intravitreal anti-VEGF within 3 months – Intravitreal triamcinolone within 6 months • History of marked intraocular pressure (IOP) elevation in response to steroid treatment • Inadequately controlled ocular hypertension in study eye

Boyer, et al. Three-year, randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with diabetic macular edema. Ophthalmology. 2014 Oct;121(10):1904-14.

- With an average of 4-5 injections over 3 years, patients statistically significant and clinically meaningful visual improvements.



Boyer, et al. Three-year, randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with diabetic macular edema. Ophthalmology. 2014 Oct;121(10):1904-14.



- ➔ At all study time points DEX implant-treated eyes displayed greater reductions from baseline in CSRT than sham-treated eyes
- ➔ The efficacy of DEX implant on CSRT peaked at 1-3 months before gradually declining (saw-tooth pattern)

Danis, *et al.* Anatomical effects of dexamethasone intravitreal implant in diabetic macular oedema: a pooled analysis of 3-year phase III trials. *Br J Ophthalmol.* 2016 Jun;100(6):796-801.

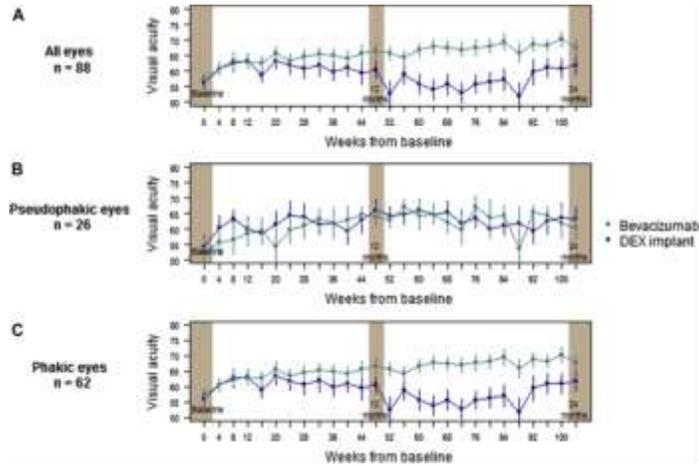
TAKE HOME POINTS

- Chronic inflammation is central to pathophysiology of DME.
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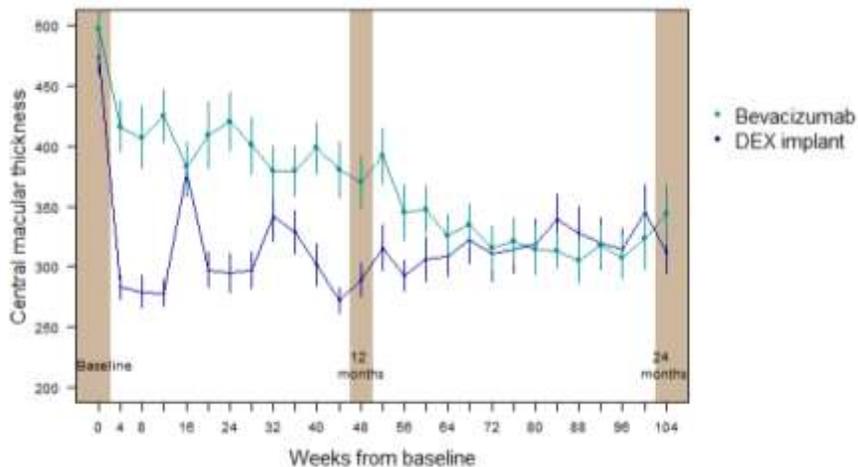
- Re-treatment was considered every 4 weeks for BEV and 16 weeks for DEX.
- Worse VA in DEX group, especially in phakic eyes.

BEVORDEX



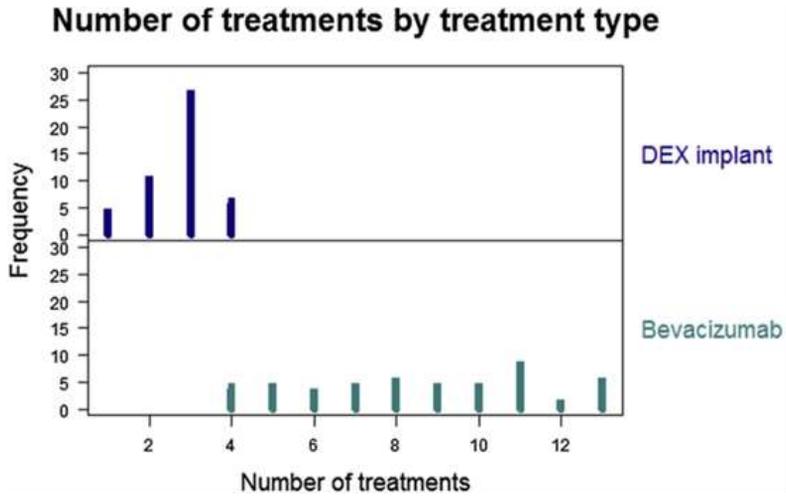
Fraser-Bell, et al. Bevacizumab or Dexamethasone Implants for DME: 2-year Results (The BEVORDEX Study). Ophthalmology. 2016 Jun;123(6):1399-401.

- Greater reduction in CMT in DEX group at 1 year, but BEV group caught up by the end of 2nd year.



Fraser-Bell, et al. Bevacizumab or Dexamethasone Implants for DME: 2-year Results (The BEVORDEX Study). Ophthalmology. 2016 Jun;123(6):1399-401.

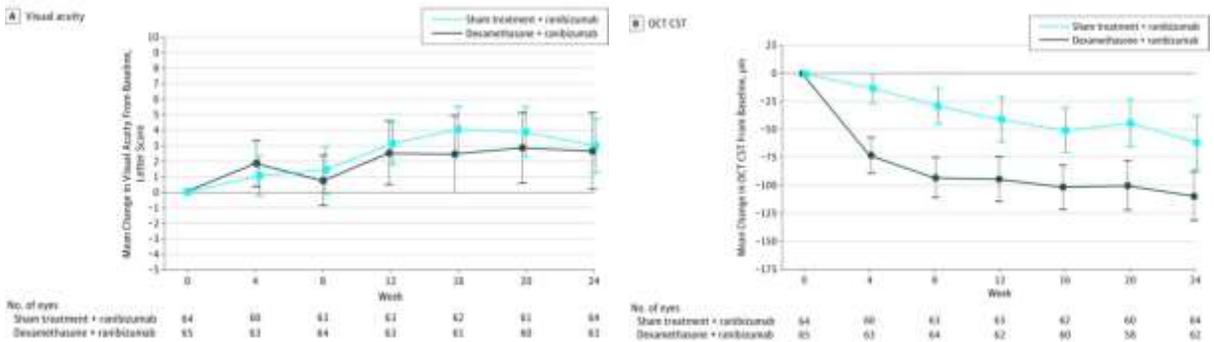
- Less difference in number of injections in 2nd year.



Fraser-Bell, et al. Bevacizumab or Dexamethasone Implants for DME: 2-year Results (The BEVORDEX Study). Ophthalmology. 2016 Jun;123(6):1399-401.

Protocol U

- Addition of DEX did not result in superior visual acuity at 6 months.
- Combination group had a greater reduction in CMT.



Maturi, et al. Effect of Adding Dexamethasone to Continued Ranibizumab Treatment in Patients With Persistent Diabetic Macular Edema: A DRCR Network Phase 2 Randomized Clinical Trial. JAMA Ophthalmol. 2018 Jan 1;136(1):29-38.

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CATARACT DEVELOPS IN 2/3 OF PATIENTS, MOST CASES DEVELOP IN THE 2ND YEAR OF TREATMENT

Patients with a Phakic Study Eye at Baseline	Incidence During the Study (%)
Cataract-related AE	
DEX implant 0.7 mg	67.9
DEX implant 0.35 mg	64.1
Sham	20.4
Cataract surgery	
DEX implant 0.7 mg	59.2
DEX implant 0.35 mg	52.3
Sham	7.2

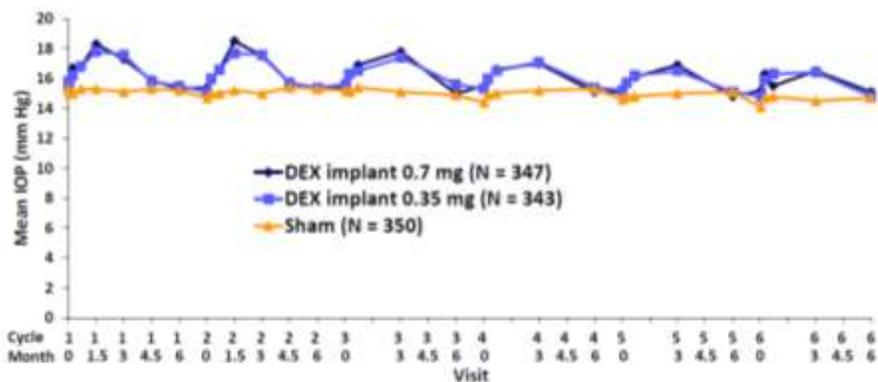
- The incidence of cataract-related AEs increased after the first study year
- Most cataract surgeries were performed between 18 and 30 months

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SIGNIFICANT IOP ELEVATIONS OCCUR IN 1/3 OF PATIENTS, PEAK 1-3 MONTHS AFTER INJECTION, AND RETURN TO BASELINE BY 6TH MONTH

- No cumulative effect of repeated injections on IOP was observed.



Analysis based on safety data from all patients who received treatment in indicated treatment cycles.

Maturi, et al. Intraocular pressure in patients with diabetic macular edema treated with dexamethasone intravitreal implant in the 3-year mead study. Retina. 2016 Jun;36(6):1143-52.

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DEX IMPLANT IS A GOOD OPTION FOR THE RIGHT PATIENT

Study Participants

To be included in the analysis, patients had to fulfill the following criteria: (1) age ≥ 18 years; (2) type 1 or 2 diabetes mellitus; (3) DME (both naïve and refractory) causing visual loss, with study eye BCVA ≥ 20 to 40 letters on the minimum angle of resolution

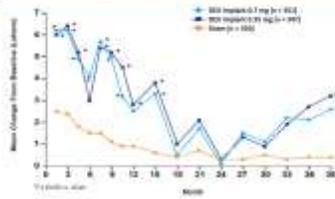
of mesh thickness subconjunctival implant, both eye timing of lines or 1 measure given at implants (1) also edema 1 choroida occlusion post surg common previous months 1 Pain AIC (H postifera DEX im

CST: $477 \pm 124 \mu\text{m}$). Eyes had to be treatment naïve on presentation and initially treated with 3 monthly anti-VEGF injections (aflibercept, ranibizumab or bevacizumab) (i.e., loading phase) leading to a suboptimal response: defined as ≤ 5 letter gain in VA (including vision loss), or reduction of less than 20% of CST on SD-OCT 1 month after the third anti-VEGF injection (M3) [7, 12] and received further treatment as follows: either (a) continued on anti-VEGF injections without switching agents for at least 12 months ($n = 72$ eyes) or (b) switched to DEX implant after ≤ 1 further anti-VEGF injection ($n = 38$ eyes).

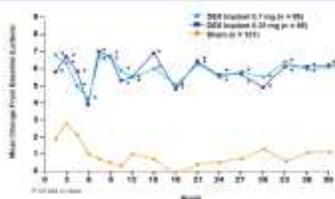
had 1 or both eyes with a best-n equivalent, 20/32 to central subfield thickness (CST) had received treatment with at ranibizumab) within the pre-ible for the study. However, be- February 2014 to July 2015, es.

➤ Pseudophakic patients have a better visual outcome.

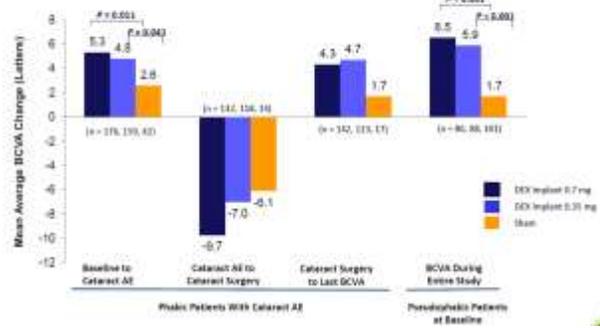
Mean Change in BCVA Total Population Through Month 36



DEX implant in Eyes that were Pseudophakic at Baseline Through Month 36

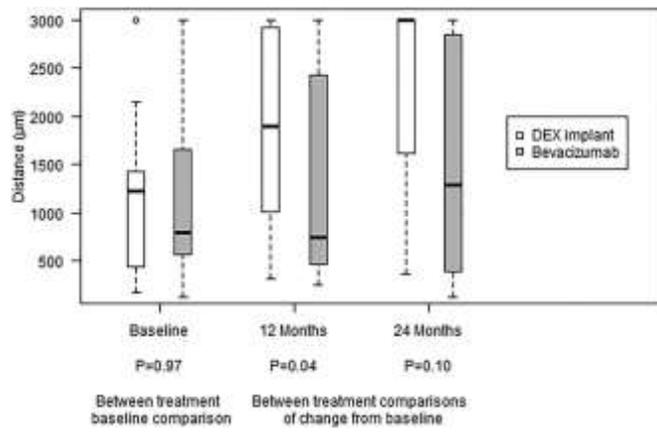
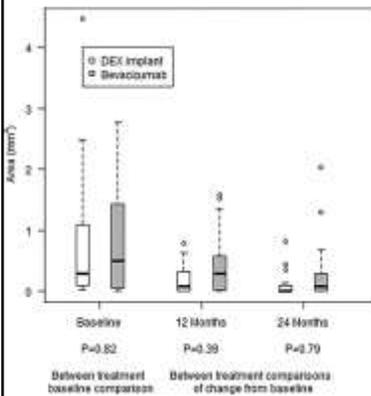


Effect of Lens Status on BCVA Outcome



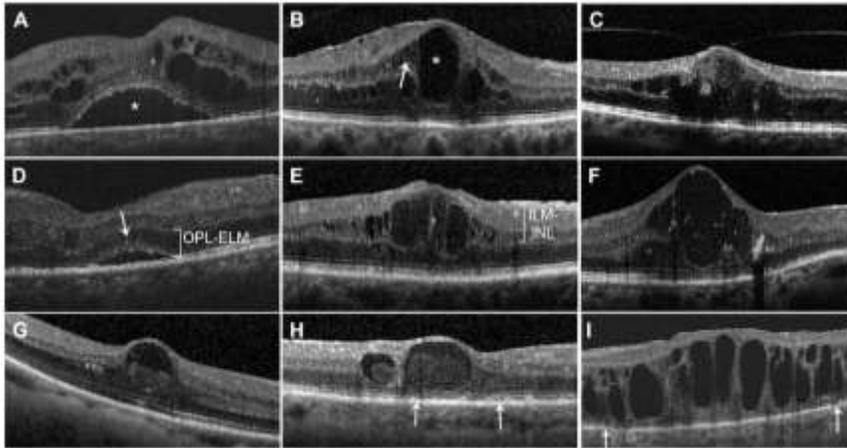
Boyer, et al. Three-year, randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with diabetic macular edema. *Ophthalmology*. 2014 Oct;121(10):1904-14.

➤ Patients with hard exudates threatening/involving the fovea could benefit more from DEX implant.



Mehta, et al. Efficacy of dexamethasone versus bevacizumab on regression of hard exudates in diabetic maculopathy: data from the BEVORDEX randomised clinical trial. *Br J Ophthalmol*. 2016 Jul;100(7):1000-1004.

- SRF, IS/OS continuity, absent HRF, and an attached vitreoretinal interface were identified as biomarkers for better visual outcome after DEX implant.



Zur, et al. OCT Biomarkers as Functional Outcome Predictors in Diabetic Macular Edema Treated with Dexamethasone Implant. *Ophthalmology*. 2018 Feb;125(2):267-275.

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THANK YOU

