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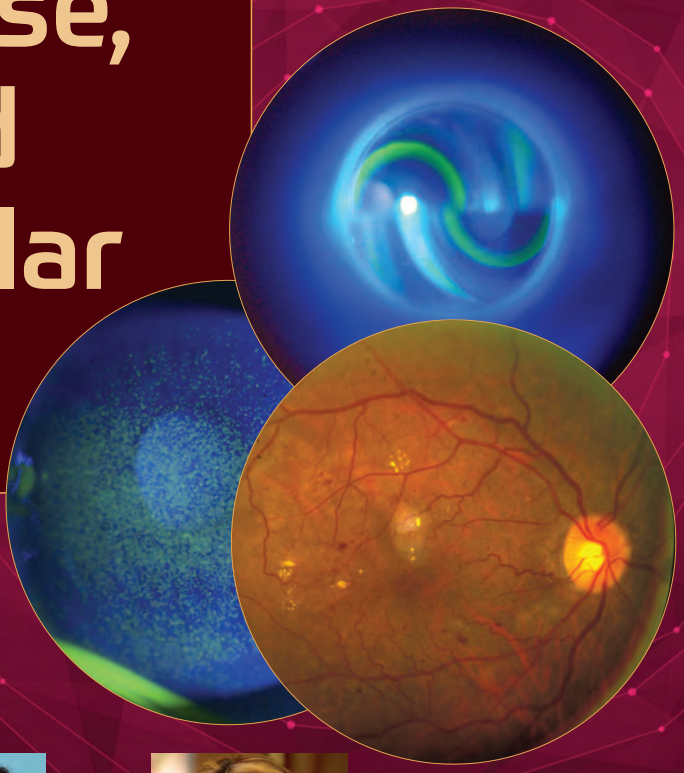
Case Studies in Dry Eye Disease, Glaucoma, and Diabetic Macular Edema



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The prevalence of ocular disease is increasing as the population ages and as the incidence of metabolic disturbances such as diabetes increases. The number of patients who present with more than 1 ocular condition necessitating treatment is also on the rise. As the demand for specialty care increases, the burden of treating patients with complex needs is expected to shift onto the general ophthalmologist. The treatment landscape for dry eye disease (DED) is expanding, and accumulating evidence supports the use of new treatment modalities that optimize the ocular surface while minimizing drop burden. New evidence is also available regarding treatment individualization for patients with hard-to-treat glaucoma that might be complicated by DED. An evolving evidence base also informs strategies for managing diabetic macular edema, which should be individualized depending on response to treatment and coexisting ocular disease. The desired results of this activity are for ophthalmologists to improve their ability to apply current evidence-based treatments to their practices for better patient outcomes.

TARGET AUDIENCE

This educational activity is intended for ophthalmologists.

LEARNING OBJECTIVES

Upon completion of this activity, participants will be better able to:

- Use the latest evidence-based data to guide treatment plans for patients with DED
- Develop individualized long-term treatment plans to optimize vision outcomes for patients with glaucoma
- Design treatment strategies for patients with persistent DME after anti-VEGF treatment

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Case Studies in Dry Eye Disease, Glaucoma, and Diabetic Macular Edema

Introduction

As the population increases, a growing number of patients with eye diseases threatening their sight will seek treatment. Ocular conditions that are increasing in prevalence, and which often overlap, include diabetic eye disease, open-angle glaucoma (OAG), dry eye disease (DED), and cataract. It has been estimated that 50% to 60% of people with diabetes[1] or glaucoma/ocular hypertension[2,3] will develop DED, and virtually anyone who lives long enough develops cataract. These conditions affect not just visual function but also quality of life. In recent years, treatment options have expanded. The availability of novel treatments provides the opportunity to individualize patient care as never before. However, the introduction of new treatments can also generate questions regarding the optimal integration of new therapies into existing clinical practice patterns. In this educational activity, a panel of experts will present cases that highlight considerations guiding the treatment of DED, OAG, and diabetic macular edema (DME) in current clinical practice.

–Thomas Samuelson, MD

Case 1. Man With Diabetes Who Has Glaucoma, Cataracts, and Newly Diagnosed Dry Eye Disease

From the Files of Elizabeth Yeu, MD

- 83-year-old white man was referred by a community optometrist for evaluation of coexisting cataract and OAG
- He reported eyes were gritty and red, and vision was blurred, particularly in the morning; these symptoms seemed to improve throughout the day
- Glaucoma therapy consisted of once-daily latanoprost and twice-daily timolol
- Medical history is significant for systemic hypertension, diabetes mellitus, and benign prostatic hypertrophy, all of which have been managed with systemic medications
- On examination, best-corrected visual acuity (BCVA) was 20/100 OU, with a significant astigmatic correction of approximately 6D OD and 4D OS
- Slit-lamp examination revealed 1+ telangiectasia and 2+ meibum requiring moderate pressure to express; mild lissamine green staining of the inferior conjunctiva in both eyes; 1+ punctate epithelial erosions of both corneas inferiorly; and a mixed cataract with 3+ nuclear sclerosis, cortical spoking, and posterior subcapsular opacities in each eye
- Tear break-up time was 5 seconds OU
- Tear osmolarity was modestly elevated and asymmetric at 302 mOsm/L OD and 313 mOsm/L OS

The Standard Patient Evaluation of Eye Dryness (SPEED) questionnaire (available at https://dryeyeandmgd.com/wp-content/uploads/2017/04/Official-SPEED-Questionnaire.pdf), which is one of several questionnaires designed to assess dry eye symptoms, was administered, and the patient's score was 13 out of a possible 28 points. The SPEED instrument is a validated tool for assessing symptoms of ocular dryness, is highly reproducible, has high diagnostic yield, and correlates with clinical signs.[4] Higher SPEED scores correlate with more profound symptoms. Corneal topography **(Figure 1)** showed signs of mild pellucid marginal degeneration in both eyes. His intraocular pressure (IOP) was 15 mm Hg OD and 14 mm Hg OS, with very low central corneal thickness (456 µm OD and 452 µm OS). His iridocorneal angles were open. On dilated fundus examination, his cup-to-disc ratio was 0.85 in both eyes, with temporal sloping and inferior thinning. Optical coherence tomography (OCT) of the retinal nerve fiber layer revealed both superior and inferior thinning OD and inferior thinning OS **(Figure 2)**. Visual field testing revealed a superior arcuate defect OD and nonspecific defects OS **(Figure 3)**.

Commentary

Dr Yeu: There are many issues to consider in this patient, and some of his ocular issues are related: he has moderate DED, with a meibomian gland disease (MGD) component; he has OAG and visually significant cataracts; and he has diabetes. We know that 50% to 60% of patients with glaucoma have some symptoms of ocular surface disease,[2,3] and that MGD in particular is present in 58% of patients with glaucoma overall and in 96% of patients with glaucoma using topical prostaglandin therapy.[5] This might be related to the known toxic effects of preservatives such as benzalkonium chloride on the ocular surface.[6] The proinflammatory nature of prostaglandins might also play a role.[5] Topical glaucoma medications can contribute to both symptoms and signs of ocular dryness.[6] The prevalence of MGD is also common in people with diabetes—close to 60%.[7] In patients with diabetes, ocular surface abnormalities occur in parallel with diabetic peripheral neuropathy, possibly because of loss of corneal innervation coupled with reduced tear secretion.[8] Also, up to

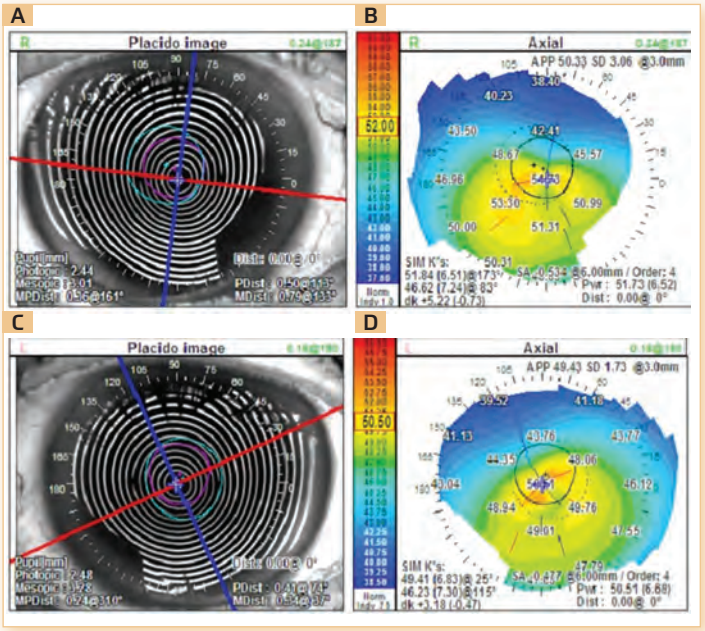


Figure 1. Right (A and B) and left (C and D) corneal topographic analyses of the eyes of the patient presented in Case 1. Note the irregular steepening inferiorly in both eyes.

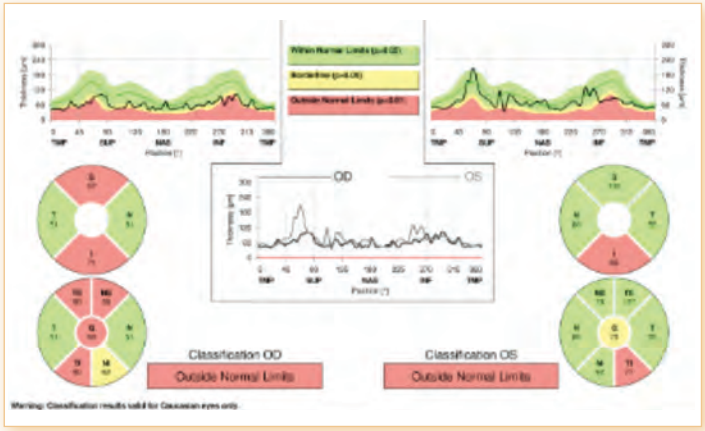


Figure 2. Retinal nerve fiber layer optical coherence tomography images of the patient presented in Case 1. Both eyes have abnormal thinning of the retinal nerve fiber layer in a glaucomatous pattern.

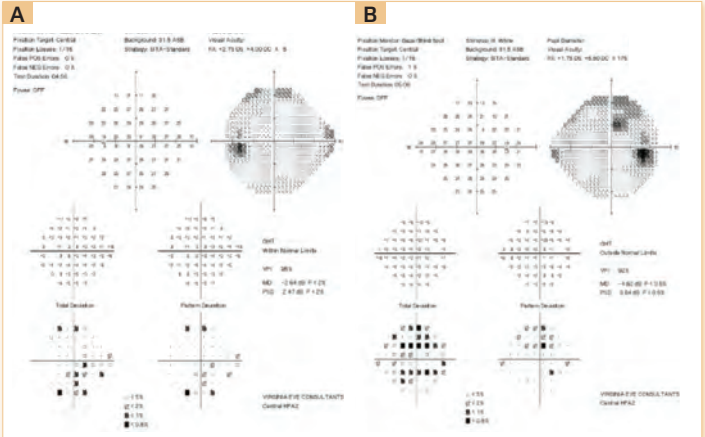


Figure 3. Left (A) and right (B) visual fields of the patient presented in Case 1. A superior arcuate defect is visible in the right field

77% of patients undergoing cataract surgery have some degree of corneal staining, although most are asymptomatic **(Figure 4)**.[9]

With this in mind, what are our treatment options to improve this patient's quality of life?

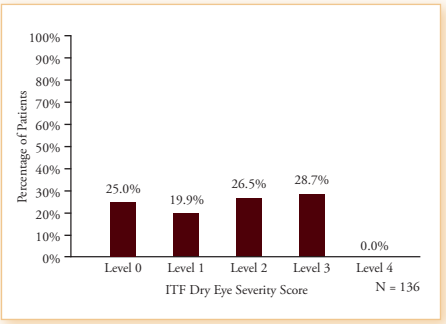


Figure 4. Prevalence of corneal staining among eyes undergoing cataract surgery.[9] Levels indicate extent of staining: 0 = lowest (none); 4 = highest.

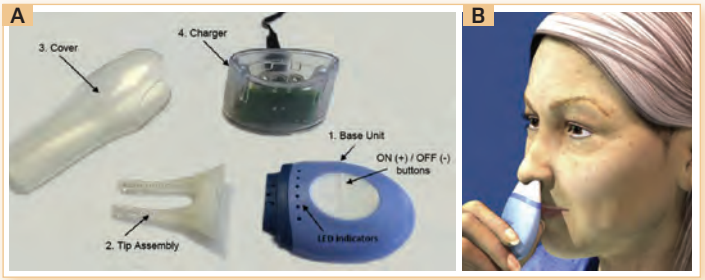
Abbreviation: ITF, International Task Force.

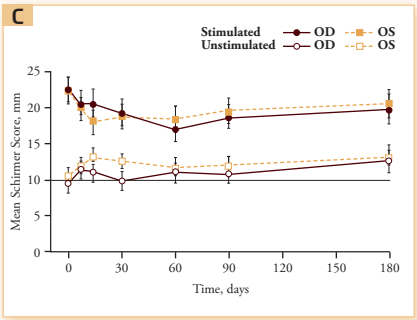
Dr Samuelson: From the glaucoma perspective, the first question is, Is his IOP adequately controlled? His IOP is in the mid-teens in both eyes, but given his very thin corneas, this is likely a significant underestimation of his true IOP. An optimal regimen for this patient would minimize topical medications because they have been associated with ocular surface inflammation in DED.[6] Options for this patient might include selective laser trabeculoplasty (SLT) to reduce his glaucoma medication burden or, if he undergoes cataract surgery, a minimally invasive glaucoma surgery (MIGS) procedure can accomplish the same goal. In your preoperative planning, you would want to try to reduce his ocular surface inflammation, which will likely necessitate a multifaceted approach. One way to accomplish this is with a short-term drug holiday. So long as he does not have a central fixation-threatening visual field defect, he should be able to tolerate a 1- to 2-week drug hiatus. If there is concern about elevated IOP during this washout period, an oral carbonic anhydrase inhibitor can be used for short-term coverage in patients without contraindications.

Dr Yeu: Because he had not yet received any treatment for his DED, I had some additional options to quell his inflamed eyes before surgery. Topical corticosteroids are not recommended for long-term use, but a brief course before surgery can help suppress inflammation and quiet the eye[10]; these should be used with caution in glaucomatous eyes, given the risk of a steroid response with elevated IOP, although that occurrence is uncommon with a short treatment period. We could also try a short course of cyclosporine or lifitegrast, both of which suppress inflammation in order to improve Schirmer score and corneal staining.[10,11] He might also benefit from dietary omega-3 fatty acid supplementation, which has been shown to improve tear break-up time and Schirmer scores in patients with DED.[12] The role of omega-3 fatty acids is unclear, however, because a recent randomized clinical trial failed to demonstrate a benefit in patients with moderate-to-severe DED.[13] In this study, no patients discontinued any of their prior DED therapies during the study, so the benefits of omega-3 supplementation could not be assessed singularly. In my own experience, and as demonstrated by Pflugfelder and others,[14] I have seen clinical improvement with certain omega-3 supplementation. Neurostimulation might also be helpful for this patient. This new treatment stimulates the nasolacrimal reflex to increase tear production.[15] The small, handheld device has 2 prongs that are inserted into the nostrils and deliver electrical pulses to the trigeminal nerve to produce tears **(Figures 5A and 5B)**.[16] In a randomized, double-masked, placebo-controlled, crossover trial, neurostimulation promoted mucin release from conjunctival goblet cells, as assessed by degranulation (n = 15; $P = .001$ for the ratio of degranulated to nondegranulated goblet cells vs sham in the temporal bulbar and inferior bulbar regions). In a prospective, single-arm pilot study, neurostimulation improved mean Schirmer scores and reduced corneal and conjunctival staining **(Figures 5C and 5D)**.[15,16] Two device-related adverse events were reported: migraine in 1 patient and mild nasal discomfort that resolved spontaneously after 2 days in 1 patient.

Once his ocular surface is quiet, which MIGS approach would you favor in this patient? Would you consider a toric intraocular lens (IOL), given his high astigmatism?

Dr Samuelson: In general, the canal-based MIGS procedures provide modest IOP and medication reductions in early and moderate OAG,[17,18] whereas subconjunctival filtering MIGS might produce greater IOP reductions, which might be needed if this patient needs to achieve complete freedom from IOP-lowering medications.[19,20] Filtering surgery such as trabeculectomy can contribute to postsurgical astigmatism,[21] and toric IOLs should be used cautiously in combined surgery using a transscleral glaucoma surgical approach. MIGS procedures, however, tend to be more astigmatically neutral,[21] making toric IOLs a possibility for this patient. Although the use of premium IOLs, especially multifocal, is controversial, there is generally little or no downside to using toric IOLs in patients with glaucoma.





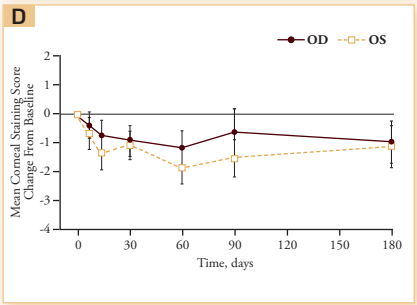


Figure 5. Intranasal tear neurostimulation. (A and B) A handheld device features 2 prongs that are inserted into the nostrils to deliver electrical stimulation to the trigeminal nerve to promote tear secretion.[16] (C) Stimulated and unstimulated mean Schirmer scores.[15] Differences were significant at $P < .0001$ at all timepoints (n = 40). (D) Corneal staining scores in the same study as in Figure 5C.[15]

Figures 5A and 5B reprinted from *American Journal of Ophthalmology*, 177, Gumus K, Schuetzle KL, Pflugfelder SC, Randomized controlled crossover trial comparing the impact of sham or intranasal tear neurostimulation on conjunctival goblet cell degranulation, 159-168, Copyright 2017, with permission from Elsevier. Figures 5C and 5D reproduced from Friedman NJ, Butron K, Robledo N, Loudin J, Baba SN, Chayet A. A nonrandomized, open-label study to evaluate the effect of nasal stimulation on tear production in subjects with dry eye disease. *Clin Ophthalmol.* 2016;10:795-804. Copyright 2016 by Dove Medical Press Limited. Reprinted with permission.

Dr Yeu: The patient also has diabetes, although he has had no history of DME. Would you expect a higher risk of macular edema after cataract surgery? Would you alter your routine perioperative prophylactic regimen in this patient?

Dr Kuppermann: His risk might be slightly higher than that in a patient without diabetes, but there is no evidence to support an alternate macular edema prophylaxis regimen in this patient with no history of DME.

Case Conclusion

The patient initiated oral omega-3 fatty acid supplementation and preservative-free artificial tears. Given that the magnitude and steep meridian of his astigmatism was consistent among different devices and that his refractive astigmatism was fairly regular within the central 2 mm, the patient underwent bilateral cataract surgery with toric IOLs combined with a MIGS procedure. Although the Hydrus Schlemm canal–based microstent or iStent inject trabecular microbypass stent or a goniotomy procedure would also have been viable options, the patient received XEN subconjunctival gel stents. The postoperative course was uncomplicated. A toric IOL placement is indicated only for the surgical correction of regular corneal astigmatism in patients with cataracts. Using a toric IOL in a patient with irregular astigmatism should be performed with caution and only in the setting in which there is regularly irregular corneal astigmatism, as seen in this patient example. The central cornea should demonstrate fairly regular bowties. The keratometry values among the topographies, biometry, and manifest refraction should be consistent in the measurements of astigmatism magnitude and steep meridian.

The patient was able to discontinue all IOP medications, and his SPEED score improved from 13 to 6 with a multimodal approach of long-term omega-3 supplementation, cyclosporine, and neurostimulation. Postoperatively, his quality of life is much improved. His uncorrected distance visual acuity at postoperative month 4 was 20/40 OD and 20/25 OS. His BCVA was 20/25 OU. His postoperative IOP was 10 mm Hg OD and 8 mm Hg OS.

Case 2. Woman With Medically Uncontrolled Glaucoma and Blepharitis

From the Files of Arsham Sheybani, MD

- 61-year-old white woman with advanced pigmentary glaucoma presents for care
- Poorly controlled IOP on 2 medications
- Previously underwent bilateral gonioscopy-assisted transluminal trabeculotomy
- BCVA is 20/20 OU
- Slit-lamp examination is significant for moderate blepharitis OU, Krukenberg spindles on the corneal endothelial surfaces, radial slit-like transillumination defects of the iris, moderate-angle pigmentation on gonioscopy, and early nuclear sclerosis of both lenses
- Intraocular pressure is 14 mm Hg OD and 24 mm Hg OS; historically, maximum IOP was 43 mm Hg
- Central corneal thickness is normal: 534 µm OD and 541 µm OS
- **Figure 6** shows her left eye's visual field and retinal nerve fiber layer OCT images
- Currently using once-daily prostaglandin and twice-daily topical carbonic anhydrase inhibitor for both eyes

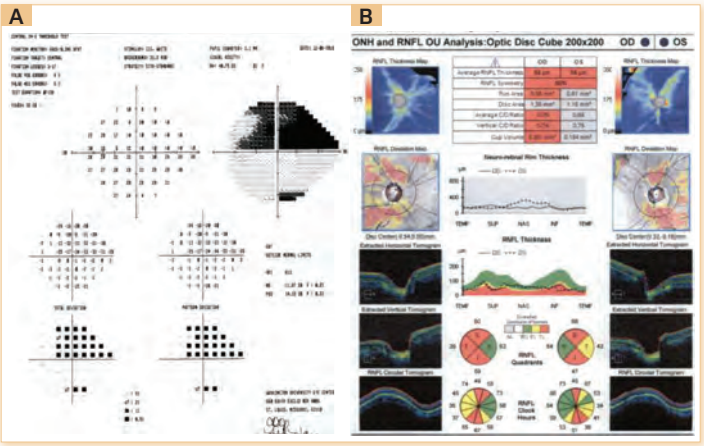


Figure 6. The left eye visual field (A) and bilateral retinal nerve fiber layer optical coherence tomography image (B) of the patient presented in Case 2. The left visual field has a dense superior arcuate defect corresponding to significant loss of the retinal nerve fiber layer. The visual field and optical coherence tomography image in the right eye were normal.

Commentary

Dr Sheybani: This patient has advanced pigmentary glaucoma in both eyes, and her disease is uncontrolled in the left eye. What are our treatment options for the left eye?

Dr Samuelson: The most conservative option would be to add a third medication, which could be easily achieved by replacing the carbonic anhydrase inhibitor with a fixed-combination product. SLT can also be effective in eyes with pigmentary glaucoma,[22] although there is an increased risk of marked IOP spikes and, possibly, corneal decompensation in eyes with heavily pigmented angles and/or corneal endothelial pigment.[23,24] I tend to stage the procedure in these eyes, treating 180° or 360° in each eye at least 2 weeks apart, to minimize this risk. Ultimately, this patient might require surgery.

Dr Sheybani: We chose the most conservative option. I added brimonidine to her regimen, which lowered her IOP to the 19- to 22-mm Hg range over several visits, but she developed follicular conjunctivitis, necessitating its discontinuation. We performed SLT over 2 sessions as you described, with minimal effect on IOP.

What would you do next?

Dr Samuelson: Glaucoma is now a much more surgical disease. There are many minimally invasive options to consider, many of which are available in the United States as standalone procedures **(Table 1)**.[25-29] I tend to start with canal-based surgery, but this patient has already undergone—and failed—gonioscopy-assisted transluminal trabeculotomy, which could be considered the ultimate canal-based surgery because it opens the entire 360° of the angle. There is currently no supraciliary MIGS procedure available in the United States, so the remaining options are the gel stent subconjunctival MIGS procedure or a more traditional filtering surgery, such as a trabeculectomy or tube-shunt surgery.

Dr Sheybani: We discussed the various surgical options and together elected to proceed with a gel stent implantation. In my experience, this procedure is safer and associated with a faster visual recovery postoperatively than is a full-thickness procedure. In 52 patients with refractory glaucoma, mean IOP reductions of approximately 9 mm Hg were seen at 12 months; common complications included hypotony (24.6%), IOP spikes (21.5%), and vision loss (15.4%, most of which resolved); approximately one-third of eyes required postoperative needling.[20]

Is her blepharitis an issue in surgical planning?

Table 1. Minimally Invasive Glaucoma Surgical Options

Procedure	Device	Approved in the United States	Bleb Forming
Schlemm canal	Trabectome[25]	Yes	No
	iStent[26]	Yes*	No
	Hydrus[27]	Yes*	No
	Kahook Dual Blade[28]	Yes	No
	iTrack and OMNI (for GATT and ab interno canaloplasty)[28,29]	Yes	No
	VISCO360[25]	Yes	No
Suprachoroidal	iStent Supra	No	No
	Gold shunt	No	No
Subconjunctival	EX-PRESS[25]	Yes	No
	XEN Gel Stent[25]	Yes	**Yes**
	MicroShunt	No†	**Yes**

Abbreviation: GATT, gonioscopy-assisted transluminal trabeculotomy.
* Approved in the United States only in combination with cataract surgery
† Currently in phase 3 clinical trials

Dr Yeu: It certainly is. Chronic blepharitis is a significant risk factor for bleb-related infections.[30,31] Whenever possible, blepharitis should be addressed preoperatively and then on an ongoing basis postoperatively.

Dr Sheybani: A preoperative protocol has recently been developed for the management of ocular surface and lid margin disease before bleb-based glaucoma surgery.[32] The protocol indicates that lid hygiene, oral doxycycline, topical erythromycin, and topical steroids should be considered before surgery in eyes with blepharitis. Because the patient's lid disease was relative mild, we treated her with lid scrubs, preservative-free artificial tears, and difluprednate 4 times daily for a week before surgery. We were not concerned about a steroid response given the very short time frame of use because steroid responses within 1 week are quite uncommon and she was already scheduled for a glaucoma procedure in a week.

If a patient has DME and is having cataract and/or glaucoma surgery, would you recommend injecting an intravitreal anti–vascular endothelial growth factor (VEGF) agent at the time of surgery?

Dr Kuppermann: Cataract surgery incites significant inflammation. Inflammation is a key driver of the pathophysiology of DME.[33] Therefore, cataract surgery can exacerbate DME.[34,35] In eyes with stable mild DME that is well controlled with anti-VEGF therapy, I recommend an anti-VEGF injection approximately 2 weeks before surgery; any closer to the date of surgery might impair wound healing. Eyes with DME that have persistent residual edema with anti-VEGF therapy might worsen after cataract surgery. In these cases, a dexamethasone implant (DEX) can help control both inflammation and DME in the perioperative period. I would administer the steroid 2 weeks before surgery to make sure that effective and therapeutic dexamethasone levels are present at the time of cataract surgery to both minimize cataract surgery–related inflammation and provide significant resolution of underlying DME. Careful monitoring of IOP would be important, however, in using DEX in this patient who has significant underlying glaucoma.

Dr Samuelson: Given this patient's advanced glaucoma and uncontrolled IOP, what surgical option would you consider at the time of cataract surgery?

Dr Sheybani: Because her target IOP is likely in the low teens, she will benefit most from a bleb-based procedure. We could perform a combined cataract and trabeculectomy procedure, but I would start with combined cataract and gel stent surgery. Gel stent implantation is a bleb-based MIGS procedure, and MIGS procedures generally have more favorable safely profiles than more traditional glaucoma surgeries.[17]

Case Conclusion

The patient underwent an uncomplicated gel stent implantation. For the first week, her IOP was in the range of 4 to 6 mm Hg, and her BCVA dipped briefly to 20/60. One month postoperatively, her IOP rose to 20 mm Hg, and she required a needling procedure with adjunctive mitomycin C that restored the diffuse nature of the bleb and lowered IOP to 13 mm Hg. By 1 year postoperatively, her BCVA was 20/20, and her IOP was 13 mm Hg using the timolol/dorzolamide fixed combination.

Case 3. Woman With Pseudophakic Diabetic Macular Edema

From the Files of Baruch D. Kuppermann, MD, PhD
(Courtesy of Anat Lowenstein, MD, and Michaella Goldstein, MD)

- 65-year-old woman with diabetes mellitus and an extensive history of therapies for both proliferative diabetic retinopathy (DR) and DME
- Had undergone multiple sessions of panretinal photocoagulation for proliferative DR in the right eye, which is now fully regressed
- Left eye had severe nonproliferative DR and had not yet received panretinal photocoagulation
- Bilateral DME, which was much worse in the right eye
- Right eye had undergone focal laser treatment and 3 prior intravitreal bevacizumab injections
- Left eye had not yet been treated for DME
- BCVA was 20/70 OD, and central macular thickness (CMT) was 840 µm
- BCVA was 20/30 OS, and CMT was 349 µm
- Right eye subsequently received another round of 3 monthly bevacizumab injections, with no improvement in BCVA or CMT

Commentary

Dr Kuppermann: The pathophysiology of DME is complex and dependent in part on inflammation.[33] Recent studies demonstrate that many inflammatory cytokines are elevated in the aqueous humor of eyes with diabetes.[36,37] The concentrations of these cytokines are directly proportional to the severity of the DR,[36,37] and steroid therapy more effectively reduces these concentrations than does anti-VEGF therapy **(Table 2)**.[36] The DRCRnet's (Diabetic Retinopathy Clinical Research Network's) Protocol I study found that triamcinolone plus focal laser treatment yielded comparable structural improvement, but inferior functional improvement, compared with ranibizumab plus deferred laser treatment through 12 months of follow-up.[38] However, only approximately half of the eyes manifested an early and consistent response to anti-VEGF therapy (at least 20% reduction in central subfield thickness of the macula on OCT imaging) by the first 16 weeks of treatment,[39] and those short-term nonresponders and suboptimal responders tended to have attenuated long-term responses to anti-VEGF therapy compared with responders.[40] Duration of DME predicts response to therapy with anti-VEGF: eyes with longstanding DME tend to respond to anti-VEGF therapy substantially less well than eyes with shorter-duration DME,[41,42] so it is crucial to identify the anti-VEGF suboptimal responders quickly and move on to alternate therapy while there is still benefit to be gained.

Table 2. Steroid Treatment Reduces the Levels of Several Inflammatory Mediators More Effectively Than Does Anti–Vascular Endothelial Growth Factor Treatment[36]

Cytokine Concentration, pg/mL	IVTA (n = 11)			Bevacizumab (n = 11)		
	Preinjection	Postinjection	*P* Value*	Preinjection	Postinjection	*P* Value*
IL-6	29.9	13.8	< .01	26.7	24.0	.477
IL-8	28.2	25.3	.597	23.9	23.6	.374
IP-10	366.0	249.0	.013	401.0	433.0	.110
MCP-1	3850.0	1090.0	.010	3770.0	3840.0	.594
PDGF-AA	68.7	37.1	.016	81.0	72.7	.722
VEGF	55.0	10.5	.050	61.5	0.1	< .01

Abbreviations: IL, interleukin; IP, interferon-inducible protein; IVTA, intravitreal injection of triamcinolone; MCP, monocyte chemotactic protein; PDGF, platelet-derived growth factor; VEGF, vascular endothelial growth factor.
* Wilcoxon signed rank text
Reprinted from *American Journal of Ophthalmology,* 152, Sohn HJ, Han DH, Kim IT, et al, Changes in aqueous concentrations of various cytokines after intravitreal triamcinolone versus bevacizumab for diabetic macular edema, 686-694, Copyright 2011, with permission from Elsevier.

Dr Sheybani: How effective are steroids in treating DME that does not respond to anti-VEGF treatment?

Dr Kuppermann: The MEAD study evaluated DEX in eyes with DME and found that significantly more DEX 0.7 mg-treated eyes (n = 351) gained 15+ ETDRS (Early Treatment Diabetic Retinopathy Study) letters in BCVA over 3 years than did sham-treated eyes (n = 350) (22% vs 12%; $P < .001$).[43] Compared with anti-VEGF therapy, DEX provided better improvement in BCVA than did anti-VEGF therapy in a meta-analysis of nearly 4000 patients in 15 real-world trials.[44] Likewise, the FAME study of the fluocinolone acetonide implant (FA) for DME found 15+ letter gains through 3 years of follow-up in 27.8% of 376 eyes receiving low-dose FA and

Table 3. Preplanned Subgroup Analysis of Change in Visual Acuity by Baseline Lens Status*[47]

	Dexamethasone + Ranibizumab (n = 63)		Sham Treatment + Ranibizumab (n = 64)		Adjusted Difference: Combination-Ranibizumab (95% CI)†	*P* Value for Interaction
	No. of Eyes	Mean (SD)	No. of Eyes	Mean (SD)		
Pseudophakic	25	+5.1 (9.7)	32	+2.0 (7.6)	+3.1 (-2.1, +8.3)	.08
Phakic	38	+1.1 (9.7)	32	+4.1 (6.4)	-3.0 (-7.7, +1.7)	

Abbreviations: CI, confidence interval; SD, standard deviation.
* Observed data only, including participants who completed the 24-week visit
† Treatment group differences and the corresponding 95% CIs and *P* values were obtained from a linear mixed model mimicking the primary analysis model by adding an interaction between subgroup and treatment. No imputation for missing data was performed.

in 28.7% of 395 eyes receiving high-dose FA vs in only 18.9% of 185 eyes receiving sham therapy ($P = .018$).[45] When choosing between these implants, it is important to keep in mind that DEX lasts approximately 3 to 6 months, whereas FA lasts up to 3 years. FA is indicated only in patients who have been treated previously with a course of corticosteroids who did not develop a clinically significant rise in IOP.[46]

Dr Yeu: Steroids can contribute to the development of cataracts. Is phakic status an important consideration when selecting DME therapy?

Dr Kuppermann: The DRCRnet Protocol U study evaluated the incremental benefit of adding DEX to ranibizumab in eyes with persistent DME after 6 or more anti-VEGF injections.[47] Both phakic and pseudophakic eyes were enrolled, and overall, there was no significant difference in visual acuity between the groups after 24 weeks, even though the steroid group had a significantly greater improvement in CMT on OCT. Although the study was not powered adequately to compare outcomes by lens status, there was a trend ($P = .08$) toward better BCVA outcomes with combination therapy in pseudophakic eyes that was not seen in phakic eyes **(Table 3)**, although the potential effects of cataract development/progression in the phakic group could have skewed these results against combination therapy.

Dr Sheybani: Steroids can also raise IOP. What was the incidence of IOP spikes in these steroid studies?

Dr Kuppermann: Comparing approved steroid treatments for DME, IOP elevations ≥ 10 mm Hg were seen with DEX in 27.7% of 347 eyes in the MEAD study and in 23% of 65 eyes in the Protocol U study **(Table 4)**.[47,48] In the FAME study, 37.1% of 375 eyes receiving low-dose FA and 45.5% of 393 eyes receiving high-dose FA had IOP elevations, of which 4.8% and 8.1%, respectively, required filtering surgery **(Table 4)**.[45]

Dr Sheybani: What is the approach to managing steroid-related IOP elevations in retina practice?

Dr Kuppermann: A panel of experts developed guidelines to address this common issue.[49] In general, IOP values ≤ 25 mm Hg can be managed with a single topical medication. Intraocular pressure elevations between 26 and 30 mm Hg are better managed with a fixed combination. Once IOP exceeds 30 mm Hg, a fixed combination is encouraged, and these patients might require referral to a glaucoma specialist.

Dr Yeu: How did you manage this patient who clearly failed anti-VEGF therapy?

Dr Kuppermann: She received bilateral DEX. Both eyes required 2 implants.

Dr Sheybani: What is the duration of efficacy of DEX?

Dr Kuppermann: The peak release of drug is at 2 months.[50] By 90 days, it is still therapeutic, but the drug level is dropping. By 120 days, it is subtherapeutic in many but not all eyes. According to data from the MEAD trial using DEX, IOP elevations tended to peak 1.5 to 3 months after implantation,[48] at the same time of peak drug release. Thus, it is important to schedule follow-up visits during this time to identify potential IOP spikes so they can be treated accordingly.

Table 4. Summary of Intraocular Pressure Elevations in Trials Evaluating Corticosteroid Therapy for Diabetic Macular Edema

Trial	Treatment	Patients With IOP Elevation ≥ 10 mm Hg, %	Patients Requiring Incisional Surgery, %
FAME[45]	FA 0.2 µg/d (n = 375)	37.1*	4.8
	FA 0.5 µg/d (n = 393)	45.5*	8.1
	Sham (n = 185)	11.9*	0.5
MEAD[48]	DEX 0.7 mg (n = 347)	27.7	1.2
	DEX 0.35 mg (n = 343)	24.8	1.2
	Sham (n = 350)	3.7	0.3
Protocol I[38]	IVTA† 4 mg + laser (n = 186)	38	1
	Sham + laser (n = 293)	5	< 1
Protocol U[47]	DEX 700 µg/ Ranibizumab 0.3 mg (n = 65)	23	0
	Sham/Ranibizumab 0.3 mg (n = 64)	0	0

Abbreviations: DEX, dexamethasone implant; FA, fluocinolone acetonide implant; IOP, intraocular pressure; IVTA, intravitreal triamcinolone injection.
* In the FAME study, the degree of IOP increase was not noted.
† IVTA is used off-label for the treatment of diabetic macular edema.

Case Conclusion

The patient's final BCVA was 20/40 in both eyes, with CMT of 222 µm OD and 236 µm OS **(Figure 7)**. After the second implant, she developed an IOP spike to 32 mm Hg in the left eye that responded well to fixed-combination therapy.

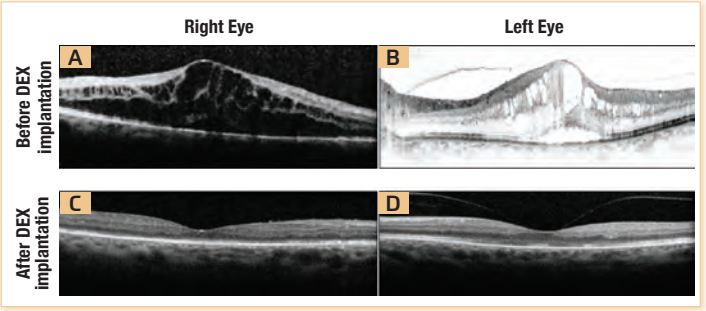


Figure 7. Macular optical coherence tomography images of the eyes of the patient presented in Case 3: before dexamethasone (DEX) implantation (A and B) and 11 and 8 weeks postimplantation in the right and left eye, respectively (C and D). Note the presence of diabetic macular edema in both eyes—worse in the right eye—before treatment (A and B), and the substantial improvement in macular architecture after treatment (C and D).

Summary and Take-Home Points

- Aging eyes often have multiple coexisting ocular conditions that can affect management, and treatment plans for coexisting conditions must respect the effect of such plans on concurrent disease
- Treatments for complex, chronic diseases such as DED and glaucoma often necessitate a multifaceted therapeutic approach
- Treatments for DED are often multimodal and might include topical medications (tear replacements, anti-inflammatories), nutritional supplementation, or novel interventions such as neurostimulation
- Ocular surface inflammation should be minimized before any intraocular procedures, such as cataract or glaucoma surgery, are performed
- When considering toric IOLs in eyes with glaucoma, trabeculectomy can induce surgical astigmatism, but MIGS procedures generally do not
- Laser and surgical glaucoma therapies can minimize long-term ocular exposure to IOP medications and excipient ingredients that can worsen DED and impair visual function
- The optimal first-line therapy for DME is anti-VEGF therapy, although approximately half of eyes will manifest suboptimal responses to such therapy
- Steroids act on the inflammatory component of the pathophysiology of DME and can be effective when anti-VEGF therapy alone is inadequate

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1. From which of the following treatments would a patient with DED secondary to an inflammatory disease process likely benefit?
   a. Oral doxycycline
   b. Lifitegrast or cyclosporine
   c. Neurostimulation
   d. Artificial tears

2. Which is the correct treatment-and-effect combination for DED?
   a. Steroids increase tear production
   b. Neurostimulation stimulates goblet cell release of mucin
   c. Cyclosporine reduces tear break-up time
   d. Omega-3 fatty acids improve fluorescein staining patterns

3. A 60-year-old woman scheduled for cataract surgery presents with symptoms of DED despite treatment with preservative-free artificial tears. Testing reveals mild lissamine green corneal staining inferiorly, tear break-up time of 7 seconds, and damage to 30% of the meibomian glands. She took lifitegrast for 4 weeks before surgery. After surgery, which regimen would be the most appropriate to manage her DED?
   a. Punctal occlusion
   b. Lifitegrast or cyclosporine and neurostimulation
   c. Lifitegrast or cyclosporine
   d. Doxycycline and warm compresses

4. A pseudophakic patient with mild glaucoma has well-controlled IOP on 2 medications. Elective cataract surgery is planned. The patient also has DED and feels that the glaucoma medications worsen the disease. The best next step to achieve target IOP is to combine cataract surgery with a _____.
   a. Canal-based MIGS procedure
   b. Subconjunctival MIGS procedure
   c. Trabeculectomy
   d. Tube-shunt implantation

5. Implantation of which MIGS devices involve formation of a bleb?
   a. Hydrus and XEN
   b. MicroShunt and XEN
   c. MicroShunt and Hydrus
   d. None

6. A pseudophakic patient with glaucoma that is not well controlled with 3 classes of drops is scheduled for surgery. Of the following US Food and Drug Administration–approved devices, which is the most appropriate for this patient?
   a. XEN
   b. MicroShunt
   c. iStent
   d. Hydrus

7. Which cytokine is elevated in DR *AND* increases with severity of DR?
   a. Monocyte chemotactic protein-1
   b. Interleukin-2
   c. Vascular endothelial growth factor
   d. Platelet-derived growth factor

8. In the DRCRnet Protocol I study, ___ of patients with DME treated with ranibizumab injections had an early and consistent ≥ 20% improvement in OCT central subfield thickness by the first 16 weeks of therapy.
   a. 5%
   b. 20%
   c. 50%
   d. 75%

9. According to findings from Protocol U, which statement is supported for a female patient with DME who has had 3 ranibizumab injections, with no appreciable effect on visual acuity or edema?
   a. Adding DEX will improve her visual acuity significantly more than simply continuing the monthly injections alone
   b. She has failed anti-VEGF therapy and her vision cannot be improved
   c. Her edema will likely improve if DEX is added to her treatment
   d. If she receives DEX, she has a 5% chance of developing elevated IOP

10. Which of the following is true regarding FA?
    a. Significantly more patients gained ≥ 15 ETDRS letters after 3 years of FA treatment vs sham
    b. Fewer than 1% of FA-treated eyes saw improvement in their DR
    c. The therapeutic effect of FA lasts approximately 3 months before retreatment is necessary
    d. IOP elevations ≥ 10 mm Hg occur in approximately 25% of eyes receiving FA