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RETINA TODAY

PART IV

BEYOND THE CLINICAL TRIALS

An educational series on the implications of managing the ocular manifestations of diabetes in the real world.

It is much easier to demonstrate a benefit of a drug within the confines of a clinical trial with a carefully selected patient population than it is to intervene in a patient's disease in a real world setting. This difference may reflect that patients in the clinic may be ones who were ineligible or were not enrolled in clinical trials; or, it may be accounted for by the fact that in the real world, external and uncontrollable elements are a factor in the effectiveness of treatment.

In part 4 of this ongoing series, two retina specialists present clinical cases that reflect the sometimes challenging aspects of dealing with patients in the clinic on a day-to-day basis. First, Sunir J. Garg, MD, an associate professor of ophthalmology with the Retina Service of Wills Eye Hospital and Thomas Jefferson University, presents a case of a patient who was nonadherent to medical advice—and as a consequence, she may have left vision on the table. Then, Rishi P. Singh, MD, a staff physician at Cole Eye Institute, Cleveland Clinic, medical director of the clinical systems office in Cleveland Clinic, and an assistant professor of ophthalmology at Case Western Reserve University, offers a case of a patient with history of glaucoma but who previously was responsive to intravitreal steroid injections but not to anti-VEGF therapy. Would additional steroid therapy in this patient wind up causing unwanted adverse outcomes?

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Inconsistent Patient Follow-Up May Affect Outcomes

BY SUNIR J. GARG, MD

Our ability to help patients preserve their vision is not always a byproduct of the effectiveness of the drug we use or the surgery we perform. Sometimes the willingness or ability of our patients to follow our advice is a limiting factor in the outcomes and benefit they derive. This may be particularly true in a disease like diabetic macular edema (DME), a disease state in which patients are frequently simultaneously under the care of several medical specialists as a consequence of their systemic disease and which they may be experiencing an associated treatment burden.

The difficult nature of noncompliance among DME patients is compounded by the fact that we have a limited time window within which to intervene and effect a positive outcome. Treating DME is in some regard a race against the clock, because the pathology has the potential to cause irreversible vision damage. Late intervention in the disease course, regardless of whether with pharmacologic agents, surgery, laser, or some combination of all three, may not restore visual acuity.

I will present a case that demonstrates the effect of a patient's nonadherence with follow-up and the deleterious effect it may have had on her final visual outcome.

CASE

First Consultation

This is a case of a 58-year-old woman who was first referred to me in 2010. She presented with 20/200 visual acuity in each eye and she had received focal laser treatment, which can be seen in Figure 1. A fluorescein angiogram (FA) taken at the time of consultation showed diffuse leakage in the right eye. There was diffuse leakage apparent in the mid to late frame, but the status of the foveal avascular zone was difficult to assess on imaging or on physical examination (Figure 2). Based on the FA, we were concerned there may have been some destruction of the foveal avascular zone and numerous leaking microaneurysms.

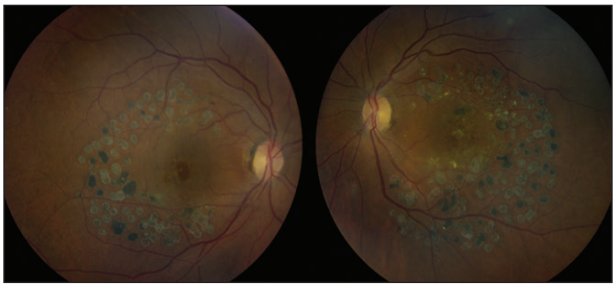


Figure 1. Extensive focal laser spots are present around the macula in each eye.

Second Consultation

This patient was then lost to follow-up for 1 year. During that time, she received panretinal photocoagulation (PRP) in each eye elsewhere. However, when she returned to our clinic for a second consultation, her visual acuity was still 20/200 in each eye. Except for

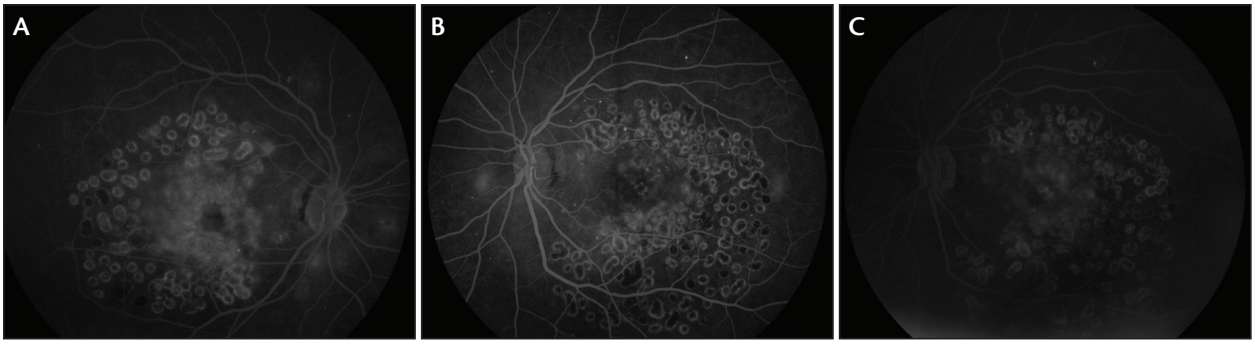


Figure 2. The baseline FA shows the prior laser spots (A and B) as well as what appears to be mild macular ischemia in the left eye (A) and diffuse leakage in the right eye (B). The leakage is even more apparent in the mid to late frame (C).

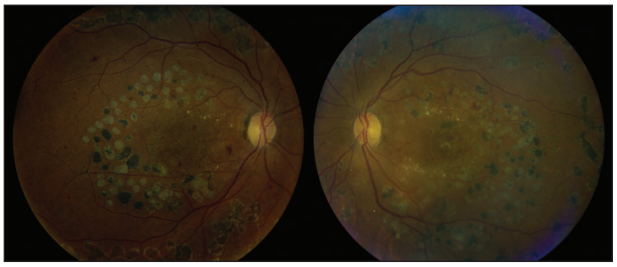


Figure 3. After being lost to follow-up for 1 year, the patient returned after receiving PRP elsewhere. Her visual acuity was still 20/200 in each eye.

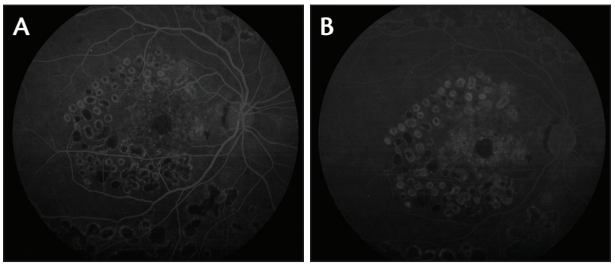


Figure 4. The FA shows definite ischmia, leaking microaneurysms, and enlargement of the foveal avascular zone (A). In the late frames, the extent of the leakage can be appreciated (B).

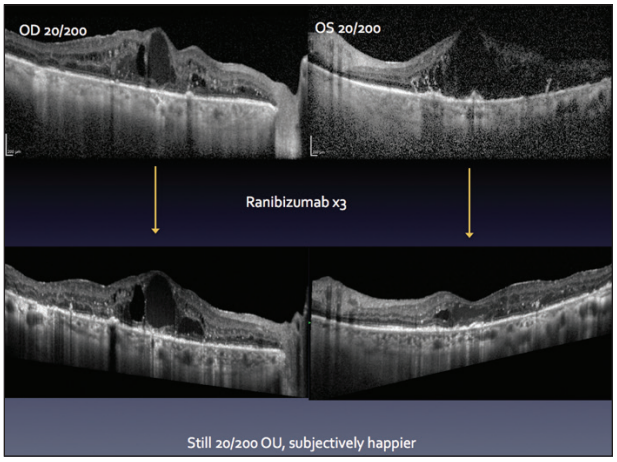


Figure 5. OCT at baseline (top) and a month after the last injection of ranibizumab (bottom).

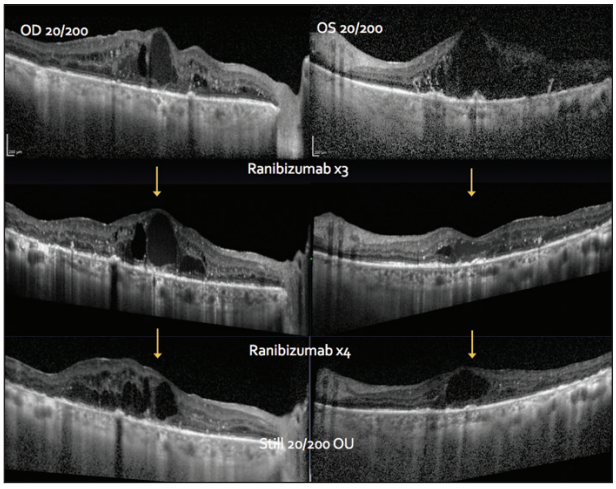


Figure 6. Continued anti-VEGF therapy resulted in improvements in macular edema over the course of treatment, especially in the left eye.

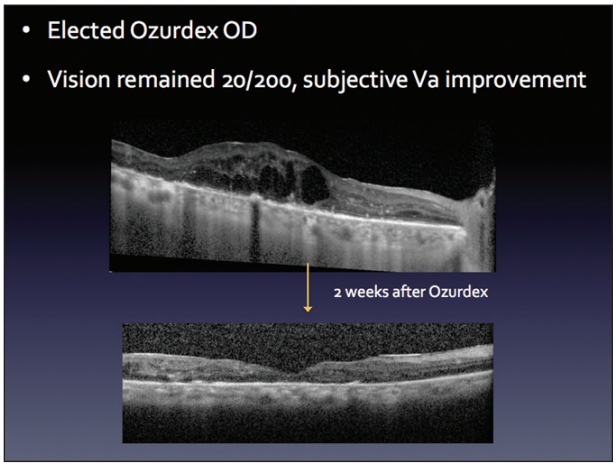


Figure 7. The dexamethasone intravitreal implant yielded a dramatic improvement in macular edema after 2 weeks.

some notable formation of hard exudates in the macula of each eye and the additional laser spots from the PRP, not much was different in this patients color fundus photographs compared with her first visit (Figure 3).

The FA of the right eye at this second visit was somewhat revealing. Macular ischemia is apparent as is enlargement of the foveal avascular zone. The multiple areas of leakage were also a cause for concern (Figure 4).

Third Consultation and Follow-Up

Unfortunately, we lost this patient for another 2 years. This time she had received intermittent intravitreal bevacizumab (Avastin, Genentech) in each eye. Her visual acuity was still 20/200 in each eye. She had not received treatment for a year before we saw her on this third visit. During this visit, we decided to try monthly injections with intravitreal ranibizumab (Lucentis, Genentech) for three injections.

As seen on optical coherence tomography (OCT) taken a month after the third injection, there was significant resolution of the macular edema, especially in the left eye (Figure 5). The patient reported subjectively better visual acuity, but upon refraction, she was still 20/200 in each eye.

We performed four additional intravitreal ranibizumab injections over the next 8 months. That said, her follow-up was still very inconsistent, and, as a result, the

The increase in mean IOP was seen with each treatment cycle, and the mean IOP generally returned to baseline between treatment cycles (at the end of the 6 month period).

USE IN SPECIFIC POPULATIONS

Pregnancy Category C

Risk Summary

There are no adequate and well-controlled studies with OZURDEX® in pregnant women. Animal reproduction studies using topical ocular administration of dexamethasone were conducted in mice and rabbits. Cleft palate and embryofetal death in mice and malformations of the intestines and kidneys in rabbits were observed. OZURDEX® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Animal Data

Topical ocular administration of 0.15% dexamethasone (0.375 mg/kg/day) on gestational days 10 to 13 produced embryofetal lethality and a high incidence of cleft palate in mice. A dose of 0.375 mg/kg/day in the mouse is approximately 3 times an OZURDEX® injection in humans (0.7 mg dexamethasone) on a mg/m2 basis. In rabbits, topical ocular administration of 0.1% dexamethasone throughout organogenesis (0.13 mg/kg/day, on gestational day 6 followed by 0.20 mg/kg/day on gestational days 7-18) produced intestinal anomalies, intestinal aplasia, gastroschisis and hypoplastic kidneys. A dose of 0.13 mg/kg/day in the rabbit is approximately 4 times an OZURDEX® injection in humans (0.7 mg dexamethasone) on a mg/m2 basis.

Nursing Mothers: Systemically administered corticosteroids are present in human milk and can suppress growth and interfere with endogenous corticosteroid production. The systemic concentration of dexamethasone following intravitreal treatment with OZURDEX® is low. It is not known whether intravitreal treatment with OZURDEX® could result in sufficient systemic absorption to produce detectable quantities in human milk. Exercise caution when OZURDEX® is administered to a nursing woman.

Pediatric Use: Safety and effectiveness of OZURDEX® in pediatric patients have not been established.

Geriatric Use: No overall differences in safety or effectiveness have been observed between elderly and younger patients.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

No adequate studies in animals have been conducted to determine whether OZURDEX® (dexamethasone intravitreal implant) has the potential for carcinogenesis.

Although no adequate studies have been conducted to determine the mutagenic potential of OZURDEX®, dexamethasone has been shown to have no mutagenic effects in bacterial and mammalian cells *in vitro* or in the *in vivo* mouse micronucleus test. Adequate fertility studies have not been conducted in animals.

PATIENT COUNSELING INFORMATION

Steroid-related Effects

Advise patients that a cataract may occur after repeated treatment with OZURDEX®. If this occurs, advise patients that their vision will decrease, and they will need an operation to remove the cataract and restore their vision.

Advise patients that they may develop increased intraocular pressure with OZURDEX® treatment, and the increased IOP will need to be managed with eye drops, and, rarely, with surgery.

Intravitreal Injection-related Effects

Advise patients that in the days following intravitreal injection of OZURDEX®, patients are at risk for potential complications including in particular, but not limited to, the development of endophthalmitis or elevated intraocular pressure.

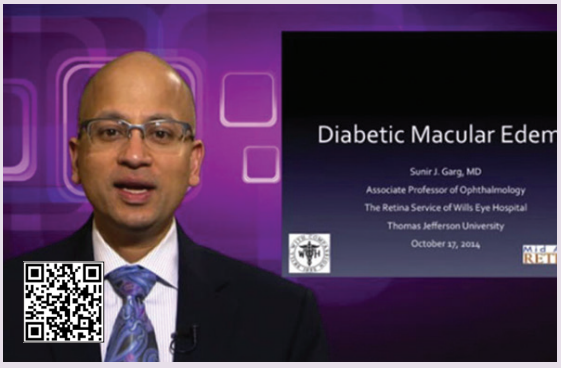
When to Seek Physician Advice

Advise patients that if the eye becomes red, sensitive to light, painful, or develops a change in vision, they should seek immediate care from an ophthalmologist.

Driving and Using Machines

Inform patients that they may experience temporary visual blurring after receiving an intravitreal injection. Advise patients not to drive or use machines until this has been resolved.

Video



interdose interval was irregular and not according to our ideal management plan. Yet, there was improvement in edema in both eyes on OCT examination (Figure 6) and the patient continued to report subjective improvement in visual acuity.

A Change in Therapy Approach

After a brief period of observing this patient, we opted to change course a bit and offered the patient the option of the dexamethasone intravitreal implant (Ozurdex, Allergan). As seen in the final OCT on this patient, there was dramatic improvement in the anatomy after 2 weeks (Figure 7). Unfortunately, the visual acuity was 20/200 even though the patient reported subjective improvement.

CONCLUSION

There are several important things to learn from this case. First, the dexamethasone intravitreal implant caused a marked improvement in the anatomy even after a long duration of an active disease process, and even after numerous anti-VEGF injections failed to produce a similar response.

There was not an improvement in visual acuity, but the patient reported subjective improvements in visual acuity. In our view, the lack of gain in final visual acuity is most likely due to macular ischemia as well as from chronic DME. We can only speculate whether we would have been able to salvage some additional visual improvement had we had the opportunity to intervene earlier in the disease process. ■

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Dexamethasone Implant in a Patient with History of POAG

BY RISHI P. SINGH, MD

Some patients in the pivotal clinical trials performed with the dexamethasone intravitreal implant (Ozurdex, Allergan) experienced a rise in intraocular pressure (IOP). However, most patients in the MEAD study had only transient elevations; those in whom elevated IOP persisted were easily managed with topical medications, and only 1 patient in the study required incisional glaucoma surgery.[1] Therefore, a concern over potential IOP elevation should not necessarily obviate the use of the implant among patients with diabetic macular edema, so long as there are not other risk factors suggesting the potential to damage the optic nerve secondary to a rise in IOP.

I will present a case where the use of the dexamethasone intravitreal implant was particularly beneficial for a patient with a history of a glaucoma diagnosis in normalizing the retinal contour as depicted on optical coherence tomography (OCT) while also producing gains in visual acuity.

CASE REPORT

This was a 68-year-old woman with a history of proliferative diabetic retinopathy. She had a vitrectomy in her left eye for a tractional detachment, as well as cataract surgery with placement of an intraocular lens. She had been previously diagnosed with primary open-angle glaucoma (POAG) controlled with brimonidine drops three times daily in each eye.

After reviewing a fundus photograph captured at the initial evaluation, we determined there was mild to moderate cupping of the optic nerve. Panretinal laser scars were also evident on this photograph (Figure 1). The patient was unresponsive to prior therapy with topical corticosteroids and nonsteroidal agents. We attempted anti-VEGF therapy with bevacizumab (Avastin, Genentech) and ranibizumab (Lucentis, Genentech), but there was only a minimal response (Figure 2). The line scan shows diffuse cystoid edema, scant epiretinal membrane, and no evidence of subretinal fluid present in this patient.

Because of the inability to achieve a complete anatomic response, however, we decided to use intravitreal injections with preservative-free triamcinolone (Triescence, Alcon). As seen in Figure 3, there was marked improvement in the retinal contour, the patient achieved 20/50 visual acuity, and there was no rise in IOP. The average interdose interval was 2.5 months.

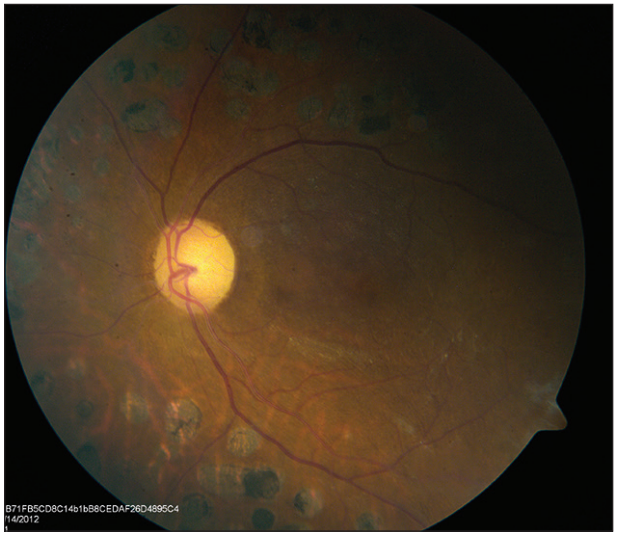

Figure 1. There was mild to moderate cupping of the optic nerve upon initial evaluation.

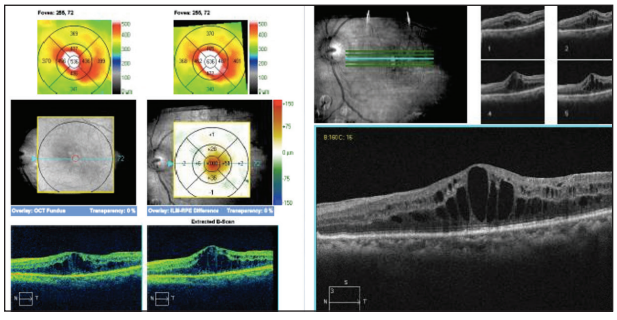

Figure 2. Change analysis before and after ranibizumab injections showed only modest declines in retinal thickness 1 month after the injection.

THERAPY CHANGE

At this point, we decided to switch therapy modalities to the dexamethasone intravitreal implant. Our rationale was that we might be able to lengthen the interval

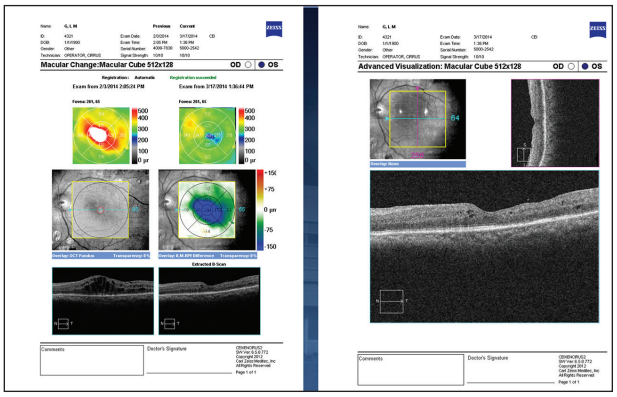

Figure 3. There was marked improvement in the retinal contour after intravitreal injections of preservative-free triamcinolone.

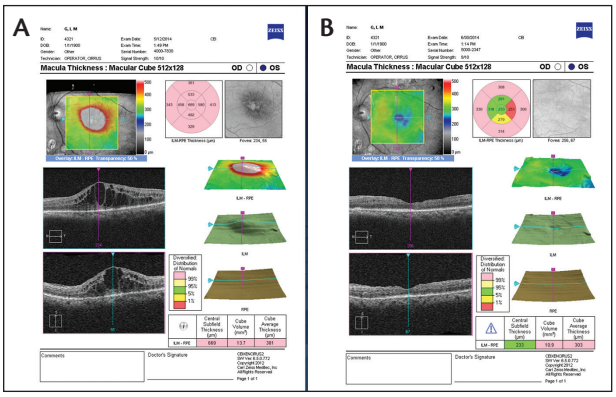

Figure 4. Baseline (A) and follow up OCT 1 month after injection of the dexamethasone intravitreal implant (B). There is significant normalization of the retinal contour and the patient achieved improvement in visual acuity from 20/50 to 20/25.

between steroid injections. However, we were cognizant of the potential for an IOP elevation, especially with her history of POAG and moderate to severe cupping. Again, just to reiterate, this patient had not had a steroid response with triamcinolone.

The patient had improvement in visual acuity from 20/50 to 20/25 and significant normalization of the retinal contour on OCT 1 month after injection with the dexamethasone intravitreal implant (Figure 4). At the 4-month follow up visit, we noted a slight thickening of the retina and the presence of retinal fluid, and the patient had 20/30 visual acuity at this time. We readministered the dexamethasone intravitreal implant, and 1 month after, there was again normalization of the retinal contour and visual acuity improved to 20/25 (Figure 5). The patient subsequently received a third injection after another 4 months of follow-up, and we saw a similar response as with the second implant.

CONCLUSION

This was a 68-year-old woman with proliferative diabetic retinopathy responsive to preservative-free triamcinolone but non-responsive to anti-VEGF therapy who now

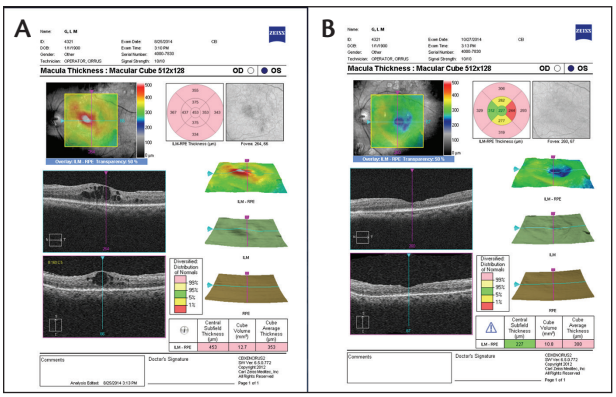

Figure 5. Four months after initial injection of a dexamethasone intravitreal implant, the patients OCT started to show indices of returning pathology (A). One month after a second implant was used, the retinal architecture again appeared to normalize (B).

seems to be responding to the dexamethasone intravitreal implant. It is important to note that we did not see any rise in IOP despite the patient's history of a diagnosis of POAG. This patient did have an improvement in visual acuity, despite the presence of a very chronic disease and disease state, and we were able to lengthen the interval between the time we gave her steroid injections up to 4 months. ■

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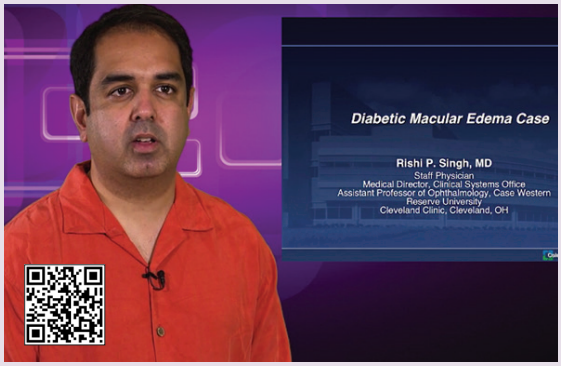
Video



1. 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.