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CME ACTIVITY

Steroid Delivery in Patients With Diabetic Macular Edema in the Presence of a Cataract

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CONTENT SOURCE:

A CME dinner series in Boston, New York, Phoenix, San Francisco, and Washington, DC, that took place between June and October 2015.

INTENDED AUDIENCE

This certified CME activity is designed for retina specialists and general ophthalmologists involved in the management of concurrent diabetic ocular disease and cataract.

LEARNING OBJECTIVES

Upon completion of this activity, the participant should be able to:

- Discuss why referrals to retina specialists in the cataract patient are warranted, and discuss the most effective timelines for these referrals.
- Discuss the most recent clinical studies elucidating the treatment paradigms in this higher-risk patient group.
- Develop plans to explain to patients the need for additional monitoring in the pre- and postoperative cataract surgery periods.
- Develop plans to initiate comanagement strategies between retina specialists, cataract surgeons, general ophthalmologists, other eye care specialists, and endocrinologists.

STATEMENT OF NEED

Diabetes affects about 382 million people worldwide, and that number is expected to grow to 592 million people within the next 25 years.[1] In the US alone, just under 26 million people are affected by diabetes.[2] Further taxing the US health care system, an estimated 60% of those with diabetes have one or more of the complications associated with the disease.[3]

Large population-based studies have documented an association between diabetes and cataract, with some linking impaired fasting glucose levels (even in the absence of clinical diabetes) to an increased risk of developing cortical cataract.[4,5] Cataract formation occurs at an earlier age in a diabetic patient than in those without diabetes.[4,6] Surgical intervention for the cataract coupled with ongoing diabetes management can be challenging for eye care providers, as patients with diabetes have a higher risk of postoperative complications after cataract surgery, including cystoid macular edema (CME).

The ASRS 2014 Preferences and Trends Membership Survey found almost 80% of US respondents would perform cataract surgery if the patient had diabetes with microaneursyms but no edema, and would evaluate the retina postoperatively.[7] Of interest, a smaller majority (57%) of international respondents would evaluate/treat the patient in a similar manner. While a scant number of US physicians (2.8%) would treat the patient with an intravitreal steroid or antivascular endothelial growth factor (VEGF) at the time of cataract surgery, 22% of international respondents would concomitantly treat.[7] Conversely, close to 80% of anterior segment surgeons do not perform any intravitreal injections, and the majority report up to 25% of their overall patient population has concurrent retinal disorders.[8] For ophthalmic surgeons, comanagement of these patients is of critical importance.

AT INCREASED RISK

It is already well established that a substantial number of patients undergoing cataract surgery have concomitant disease, with about one in five having diabetes mellitus ("diabetes").[9] More than 90 million people will be older than 65 years in 2060, increasing from 43 million in 2012,[10] meaning a substantially greater number of patients will be seeking care from both anterior and posterior segment surgeons. Recognizing the early symptoms of either cataract or diabetic ocular disease will continue to be at the forefront of preventing visual loss from either disorder.

Cataract surgery in patients with diabetes but no retinopathy (or mild retinopathy) does not typically result in postoperative complications, but in patients with diabetic macular edema or proliferative diabetic retinopathy, complications are more common and additional caution is necessary when planning cataract surgery.[11] Some reported adverse events after cataract surgery in this patient population include vitreous hemorrhage, iris neovascularization, and decreased vision.[12]

The diabetic cataract patient is also at an increased risk of postoperative CME, which may be difficult to differentiate from diabetic disease progression.[13-19] CME has been reported in 31% to 81% of patients with diabetes during the cataract surgery postoperative period.[20-22]

Even the timing of cataract surgery in patients with diabetic complications is shifting; in the 1990s cataract surgery was not recommended at all in patients where visual acuity had decreased to 20/100-20/200, noting the low percentage of eyes that could achieve 20/40 postoperatively.[22]

During the postoperative period after cataract surgery, it is becoming commonplace to use postoperative nonsteroidal anti-inflammatory agents for much longer in patients with diabetes or diabetic ocular disease than the on-label designated 2 weeks.[23-25] Unfortunately, the ability to delay or prevent cataract in this patient population remains elusive.[26]

LEARNING GAPS

With the ASCRS 2014 Clinical Survey results finding very few anterior segment surgeons prepared or willing to perform intravitreal injections, ensuring timely referrals to retina specialists is even more important.[7]

Eye care specialists need an improved understanding of the pathogenic mechanisms of the systemic disorder as well as its ophthalmic complications. This is perhaps of paramount importance in patients with concomitant cataract, as this patient population is at a much higher risk of postoperative complications.

Finally, cataracts are the most common cause of visual impairment in diabetic patients, and the rate of cataract surgery in this population is equally high.[12] As the population ages, there will be a significant and increased need to comanage patients with both diabetes and cataract. Particular attention needs to concentrate on recognizing newer non-laser treatments for the diabetic patient, understanding how to treat the potential complications of cataract

surgery in a diabetic patient, and how to best minimize irreversible vision loss.

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Treatment Options for Diabetic Macular Edema: A Review of Clinical Data

BY SRINIVAS R. SADDA, MD, AND CARL D. REGILLO, MD

Diabetes is a major public health concern. Around 21 million individuals in the United States have been diagnosed with diabetes, with as many as 8 million additional undiagnosed cases.[1] Diabetes is associated with a high rate of complications, such as heart disease, stroke, and various organ and macro- and microvascular complications.[1] Data from a multinational study in Europe suggest a complication rate as high as 60% among individuals with type 2 diabetes.[2] Rates of complications are believed to be lower among individuals with type 1 diabetes.[3] One such complication is the early development of cataract.[4] However, surgical intervention for patients with cataract and diabetes can be challenging, as these patients are at higher risk for complications such as cystoid macular edema or exacerbation of underlying diabetic retinopathy. Furthermore, it can be challenging to know how to manage patients with diabetic macular edema (DME) and a cataract, as treatment of these two disease states is often segmented in the US health care system, with subspecialist retina specialists typically handling the former and anterior segment surgeons managing the latter.

Yet, the emerging diabetes crisis in the United States suggests a need for all ophthalmologists to become aware of current DME treatment paradigms. It is becoming increasingly apparent that comanagement strategies are needed to ensure proper management of diabetic eye disease and whatever consequences may occur as a result, ie, cataract. As well, certain treatment paradigms for DME, which will be discussed below, may result in cataract development. Lastly, there is debate as to the utility of having treatment "on board" among phakic patients at the time of cataract surgery.

To help add clarity to the management of patients with diabetic eye disease, this review will discuss the most common treatment strategies for DME based on clinical trial data available at the time of publication. It is important to note that while pharmacotherapy has largely become the preferred treatment strategy for DME, all of the pharmacotherapy clinical trials discussed herein recruited patients with center-involving disease. Thus, it may not be possible to extrapolate the data to non–center-involving cases. This article will also discuss the rationale for laser and pars plana vitrectomy in eyes with DME.

BACKGROUND

Treatment of DME is an evolving paradigm, although a wealth of clinical data suggests that pharmacotherapy plays a primary and central role. However, questions remain regarding which patient types will benefit from each of the agents and about how best to use them in clinical practice. To date, there are no formal guidelines to codify evidence-based practice, while there is growing evidence that responses to therapy are highly individualized and contextualized. Thus, it seems prudent for physicians who regularly treat patients with DME to be aware of the data so that treatment decisions can be customized to the needs of the individual patient.

Overall, there has been a shift in the understanding of macular edema (ME). It used to be common to think of patients as having nonclinically significant versus clinically significant ME; today, it is more common to discuss patients as either having center-involving (ie, foveal-involving) or non–center-involving ME, the former of which is much more common. Center-involving ME (assuming it is thick enough to be detected clinically) is actually a subset of clinically significant ME that is more likely to affect visual acuity; the term refers to whether the ME is affecting an area of the retinal central subfield defined on optical coherence tomography.

PHARMACOTHERAPY

Anti-VEGF Therapy

In the absence of any treatment guidelines, antivascular endothelial growth factor (anti-VEGF) agents are the de facto first-line therapy for center-involving DME. Several well-controlled clinical trials support that anti-VEGF agents have superior safety and efficacy compared with laser, which was the previous gold-standard established in the Early Treatment of Diabetic Retinopathy Study (ETDRS; this will be discussed in more detail below).

RISE and RIDE

RISE and RIDE were parallel phase 3 studies that tested ranibizumab (Lucentis; Genentech) in doses of 0.3 or 0.5 mg compared with placebo.[5] After 3 months, patients in any arm could receive laser treatment. Patients in the ranibizumab arms gained between 10 and 12 letters in the study eye at 24 and 36 months, and visual acuity results corresponded with anatomic changes in central field thickness (CFT): at 2 years, patients in the active treatment arms had a 117 µm (0.5 mg group) and 119.5 µm (0.3 mg group) greater reduction in CFT compared with sham (Table 1). Decreases in CFT in the sham arm were likely secondary to use of rescue laser: about 72% in the sham arm required laser (and about 50% of these required two or more laser treatments) compared with 38% of medically treated patients.

TABLE 1. SUMMARY OF POOLED VISUAL AND ANATOMIC OUTCOMES IN RISE AND RIDE AT 24 AND 36 MONTHS COMPARED WITH BASELINE

	Visual Acuity (ETDRS)	CFT (µm)	Visual Acuity
	24 months		**36 months**
0.3 mg	+11.7	-253.1	+12.4
0.5 mg	+12.0	-250.6	+11.2
Sham	+2.5	-133.6	+4.5

There are other important lessons from this trial, especially from an extension follow-up trial, which will be discussed later. Nevertheless, this trial prompted the US Food and Drug Administration (FDA) to approve an indication for ranibizumab for DME at a dose of 0.3 mg.

VIVID and VISTA

The next agent to gain FDA approval for DME was aflibercept (Eylea; Regeneron) based on results from the parallel VIVID and VISTA trials. This was a sophisticated trial design, with patient randomized to laser or 2.0 mg aflibercept every 4 weeks (2q4) or every 8 weeks (2q8) after a loading dose phase in which injections were given once a month for 3 consecutive months.[6] At the studies' primary endpoints of 52 and 100 weeks, patients receiving aflibercept treatment gained between 10 and 12 ETDRS letters, regardless of treatment frequency group in both studies. Patients also exhibited significant reductions in CFT from baselines in the 2q4 and 2q8 groups compared with laser (Table 2).

TABLE 2. SUMMARY OF VISUAL AND ANATOMIC OUTCOMES IN VIVID AND VISTA AT 52 AND 100 WEEKS COMPARED WITH BASELINE

	Visual Acuity (ETDRS)	CFT (µm)	Visual Acuity	CFT (µm)
	52 weeks		100 weeks	
VIVID				
2q4	+10.5	-195	+11.4	-212
2q8	+10.7	-192	+9.4	-196
Laser	+1.2	-66	+0.7	-86
VISTA				
2q4	+12.5	-186	+11.5	-191
2q8	+10.7	-183	+11.1	-191
Laser	+0.2	-73	+0.9	-84

BOLT

Both ranibizumab and aflibercept are FDA approved for use in DME; a third agent, bevacizumab (Avastin; Genentech) is often used intravitreally in an off-label fashion for DME. In the BOLT study, investigators studied bevacizumab compared with laser in a prospective study.[7] The small patient population (n=80) limits its applicability; nonetheless, the trial demonstrated that bevacizumab-treated patients (n=37) demonstrated improvement in ETDRS letters (+8.6) at 24 months, whereas patients in the laser group (n=28) lost 0.5 letters at 24 months. These results seem to be in accordance with a growing understanding of the role of VEGF blockade in treating DME.

Protocol T

The most recent clinical trial to evaluate anti-VEGF therapy in DME was the Protocol T study by the DRCR.net, in which bevacizumab, ranibizumab, and aflibercept were compared in a head-to-head fashion. The drugs were dosed more or less on an as-needed (prn) basis, essentially monthly until the macula was at its "successful" best degree; followed by prn thereafter, depending on specific protocol criteria. The DRCR.net Protocol T was a reasonably powered study with good follow-up.[8] The top-line finding was that, overall, patients gained +10, +11, and +13 letters in the bevacizumab, ranibizumab, and aflibercept groups, respectively, at 52 weeks (aflibercept vs bevacizumab $P < .001$; aflibercept vs ranibizumab $P = .034$; ranibizumab vs bevacizumab $P = .12$). The study authors noted the statistically significant difference in visual acuity change between the aflibercept and the other drugs, but also stated that the difference was not clinically significant.

The real differences in the study were noted in preplanned analyses of patients according to baseline visual acuity. Patients with entry Snellen acuity of 20/50 or worse fared much better in the ranibizumab and aflibercept arms, with a difference favoring the latter, compared with bevacizumab (Figure 1). Change in central subfield thickness on optical coherence tomography showed a similar pattern among patients with 20/50 or worse initial visual acuity: -101 µm reduction in the bevacizumab group, -147 µm reduction in the ranibizumab group, and a -169 µm reduction in the aflibercept group (aflibercept vs bevacizumab $P < .001$; aflibercept vs ranibizumab $P = .036$; and ranibizumab vs bevacizumab $P \leq .001$).

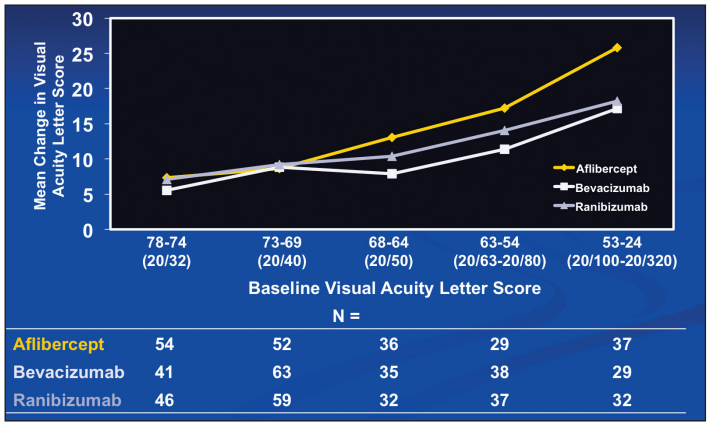

Figure 1. Patients with entry Snellen acuity of 20/50 or worse fared much better in the aflibercept arm.

Above and beyond its implications for treatment of DME, the results from Protocol T represent a novel finding for the anti-VEGF literature. In all of the trials comparing these agents in age-related macular degeneration there have not been significant differences noted in terms of efficacy. It is interesting that the differences in Protocol T corresponded with parallel anatomic outcomes, which speaks to the validity of the findings. Because there was no difference in visual and anatomic results among patients with acuity of 20/40 or better, any of the drugs could be considered good options for such patients. However, in patients with worse acuity, aflibercept may be the preferred primary therapy.

RISE and RIDE Extension

DME is a disease that has both functional and anatomic (structural) consequences. Although visual outcomes are an important measure of pharmacotherapy outcome, structural improvements vis-à-vis reduction in central subfield thickness is equally important. These facts are well known to those who manage patients with DME, and many have speculated that failure to resolve the anatomy in a timely manner might have

implications for the probability of visual improvement. In fact, the RISE and RIDE extension study was valuable for demonstrating this fact.[9]

In the extension component of the RISE and RIDE study, patients from the pivotal trial were followed with open-label, prn therapy with 0.5 mg ranibizumab from months 36 to 60. The results showed what many had long suspected. Patients who began the study in the sham treated arm never gained as much visual acuity as those who began with pharmacotherapy, even after the intended crossover at 24 months (Figure 2). The critical point from this study is that, although it is not emergent to start therapy right away (the visual consequences from delayed therapy are not as immediately apparent as in, say, age-related macular degeneration), there is a critical time window to reduce the swelling before leaving vision on the table. The point is made all the more salient by patients' compliance with therapy or lack thereof, in that failure to attend regular injection clinic appointments may have a similar effect.

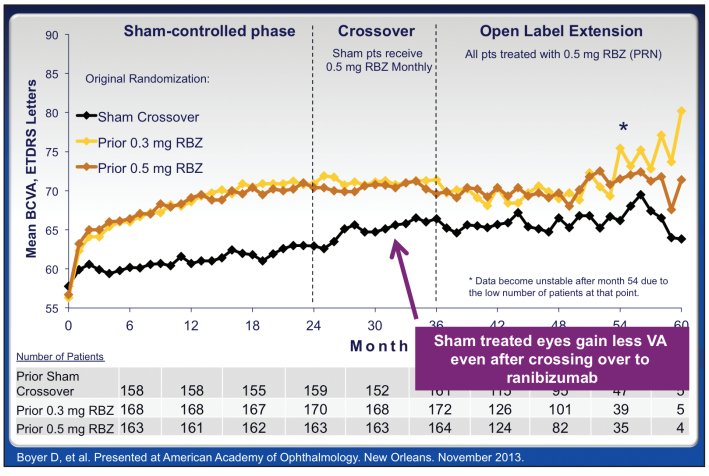

Figure 2. Patients in the sham treated arm never gained as much VA as those with pharmocotherapy, even after 24 months.

Anti-VEGF and Diabetic Retinopathy – RISE/RIDE and VIVID/VISTA

In a deeper analysis of both RISE and RIDE[10] and VIVID and VISTA,[11] there is evidence that anti-VEGF therapy has an impact on the underlying diabetic retinopathy (DR). In RISE and RIDE, the time to progression to proliferative DR was slowed significantly; as well, many patients demonstrated improvement in ETDRS retinopathy classification at 24 months (Table 3). In VIVID and VISTA, about one-third of patients showed a substantial reduction in DR severity (Table 4). The DRCR.net is currently studying anti-VEGF drugs in the treatment of DR. As a result of both of these studies, the labels for ranibizumab and aflibercept were modified to acknowledge that these agents can be used to treat DR in the presence of DME. It would not be on-label to treat DR without DME with either ranibizumab or aflibercept; however, the label change is an acknowledgement from the FDA that these drugs do favorably affect the underlying DR in the setting of DME.

As-Needed Therapy – Protocol I and RISE and RIDE

Both RISE and RIDE and VIVID and VISTA employed monthly dosing strategies per FDA requirements. However, in clinical practice, such a treatment protocol may not always be realistic, as it may be burdensome to the patient and/or practitioner. Equally as important,

TABLE 3. CHANGE IN DR SEVERITY SCORES AMONG PATIENTS TREATED IN RISE AND RIDE

	% Improved ≥3 steps	% Improved ≥2 steps	% Worsened ≥3 steps	% Worsened ≥2 steps
RISE				
0.5 mg	17.6	36.1	0	0
0.3 mg	17.1	38.5	1.7	1.7
Sham	2.4	4	10.6	5.6
RIDE				
0.5 mg	11.3	35.7	4.3	1.7
0.3 mg	9.4	35.9	1.7	0.9
Sham	0	7	8.7	4.3

TABLE 4. CHANGE IN DR SEVERITY SCORES AMONG PATIENTS TREATED IN VIVID AND VISTA

	% Improved ≥2 steps
VIVID	
2q8	27.7
2q4	33.3
Laser	7.5
VISTA	
2q8	29.1
2q4	33.8
Laser	14.3

it may expose patients to additional risk from multiple doses of pharmacotherapy. Additionally, patients with diabetes traditionally have high health care utilization, with up to 25 visits per year to various care providers.[9] Kiss et al showed in a claims analysis that patients with DME received between two and four anti-VEGF injections per year while visiting their ophthalmologist between 4 and 6 times a year.[12] This data, although a retrospective review of data garnered from a hospital network, highlights that once-a-month dosing is not followed in the real world while raising questions about whether patients are receiving optimal therapy.

The DRCR.net Protocol I study supplies some important data with regard to prn therapy.[13] In the study, patients were randomized to sham plus prompt laser, triamcinolone plus prompt laser, ranibizumab plus prompt laser, or ranibizumab plus deferred laser. Per protocol, after 6 months, all patients in the medical therapy groups were followed with as-needed therapy plus laser used at the investigator's discretion. Patients needed eight to nine injections of ranibizumab on average in the first year of the study; at the 2-year follow-up, patients in the ranibizumab plus prompt laser required a median 11 injections and the patients in the ranibizumab plus deferred laser required a median 13 injections, while visual acuity gains remained persistent (triamcinolone plus laser did not fare well in terms of visual acuity, likely due to onset of cataracts). This means that patients were adequately controlled with less than monthly dosing.

At the end of 5 years, patients needed 14 and 17 injections overall, respectively.[14] Interestingly, prompt laser appeared to reduce the need for injections, but the difference was negligible, bringing into question whether first-line laser therapy with anti-VEGF therapy is beneficial. Patients in the deferred laser group did slightly better with visual outcomes at 2 and 5 years—with the important caveat that Protocol I enrolled an all-comers population. That said, we (the authors) are not aware of any clinical trials that demonstrate an additional benefit of laser plus pharmacotherapy for the average patient, although there may be circumstances that warrant use of laser in DME (see page 9).

The notion that prn therapy may be of use in clinical practice is reinforced by data from the RISE and RIDE open-label extension.[9] After 2 years, 25% of patients did not require additional therapy,

Case Demonstrating Rationale for Monthly Anti-VEGF Until Resolution of Edema

By Carl D. Regillo, MD

This is a case of a 58-year-old man with diabetic macular edema in the right eye. The patient is phakic and visual acuity is 20/100 (Figure 1).

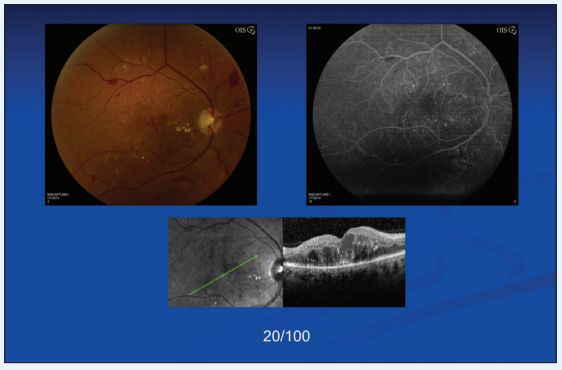

Figure 1. Baseline imaging demonstrating DME.

The patient was treated with monthly injections of ranibizumab (Figure 2A-D). The macular edema improved slightly month to month, but visual acuity improved only to 20/70 after the fourth injection.

This case raises some interesting questions. For example, there is a demonstration of a response, although at this point, there is not complete resolution of the edema and visual acuity has not recovered. Should this prompt a change in therapy? If so, because there was at least partial response, is another anti-VEGF agent a plausible choice? Or does the lack of complete response signify a need to switch classes of therapy?

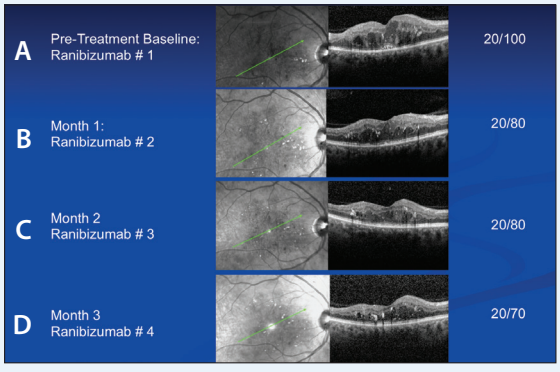

Figure 2. Anti-VEGF therapy was successful in resolving the anatomy, although visual function remained decreased.

In fact, the DRCR.net Protocol I study supplies data for a similar situation. Although the per-protocol suggestion was that patients may be switched to prn therapy following the loading phase, patients in Protocol I were only moved off of monthly therapy if the edema resolved. Thus, there is a frank suggestion that monthly therapy should be continued if the edema is not completely resolved, so long as there is continual, month-to-month improvement in the edema.[1]

Furthermore, we know from pivotal phase 3 studies with ranibizumab (RISE and RIDE) that it was not unusual for improvement in vision and edema to take many more months to reach maximal benefit.[2]

This case supports that practice. Monthly ranibizumab injections were continued from month 4 to 6, with continued improvement in edema and visual acuity (Figure 3A-C). At month 7, visual acuity was 20/30 and the edema was nearly completely resolved (Figure 3D). At this time point, it may be appropriate to consider prn therapy.

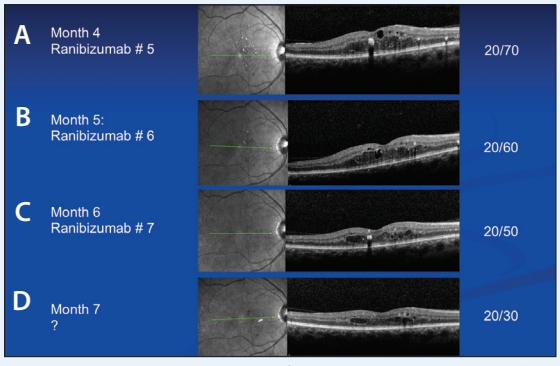

Figure 3. Continued use of the same anti-VEGF drug eventually restored visual acuity, reinforcing learnings from the DRCR.net Protocol I study.

1. The Diabetic Retinopathy Clinical Research Network. Rationale for the Diabetic Retinopathy Clinical Research Network Intravitreal Anti-VEGF treatment and follow-up protocol for center-involved diabetic macular edema. *Ophthalmology.* 2011;118:e5-e14.
2. Brown DM, Nguyen QD, Marcus DM, Boyer DS, Patel S, Feiner L, Schlottmann PG, Rundle AC, Zhang J, Rubio RG, Adamis AP, Ehrlich JS, Hopkins JJ; RIDE and RISE Research Group. Long-term outcomes of ranibizumab therapy for diabetic macular edema: the 36-month results from two phase III trials: RISE and RIDE. *Ophthalmology.* 2013;120(10):2013-2022.

Multiple Mechanisms for DME and the Rationale for Long-Acting Corticosteroid Implants

By SriniVas R. Sadda, MD

A 77-year-old woman complaining of slowly progressive blurring of vision OD for 4 months was seen in my clinic. I had seen this patient 9 months previously and noted moderate nonproliferative diabetic retinopathy but no diabetic macular edema. There was a 10-year history of hypertension, a 15-year history of diabetes, history of hypothyroidism, and, at the current examination, the A1C was 7.7.

Optical coherence tomography (OCT) examination revealed fovea-involved edema, lipid exudates, and mild subretinal fluid. Visual acuity in the right eye was 20/70. Fluorescein angiography revealed many microaneurysms; however, the leakage pattern was diffuse, suggesting telangiectatic capillaries (Figure 1). It is commonly believed that focal leakage follows from microaneurysms, while diffuse patterns indicate telangiectatic capillaries; further, it is widely believed that focal leakage is better suited to laser treatment, while diffuse leakage suggests a need for earlier corticosteroid therapy.

However, should the leakage pattern really drive treatment choice? In reality, there is no good evidence to suggest that the leakage pattern provides a rationale for any particular treatment choice. In the RESTORE study,[1] investigators did not note any difference in the efficacy of laser according to whether the leakage pattern was diffuse or focal; instead, antivascular endothelial growth factor (anti-VEGF) therapy demonstrated a greater response in all leakage pattern types.

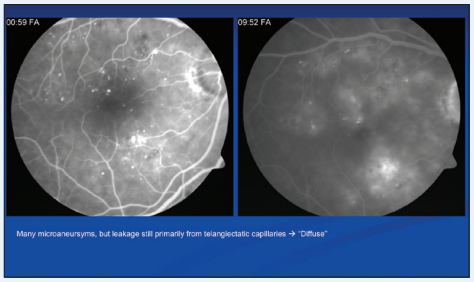

Figure 1. OCT of a 77-year-old woman demonstrating hallmark fovea-involved edema, lipid exudates, and subretinal fluid.

This patient was started on anti-VEGF therapy (ranibizumab). As seen on OCT and in the visual acuity scores, there was month over month improvement from baseline to month 3 (Figure 2A-D). However, the visual acuity appeared to have leveled off and the edema was still present. Evidence from DRCR.net Protocol I suggest a utility for continued therapy as long as there is anatomic improvement,[2] and so we opted to continue ranibizumab injections through month 6. At that time, the visual dropped to 20/50 at month 6 and the edema was not fully resolved (Figure 2E).

The regression in outcomes raised the possibility of tachyphylaxis or vitreomacular traction. A fluorescein angiogram revealed that although the edema was still present, the leakage had gone down. To me, this suggested that perhaps other factors were involved in the edema other than the leakage. I opted for a trial of aflibercept (Eylea; Regeneron); the edema resolved a little, but the visual acuity did not rebound after three treatments.

At this point, it was pretty clear that anti-VEGF yielded a suboptimal response, and perhaps a switch in class was called for. Laser was an option, but there is not good evidence that delayed laser is all that beneficial. Instead, I opted to use a 0.7 mg dexamethasone intravitreal implant.

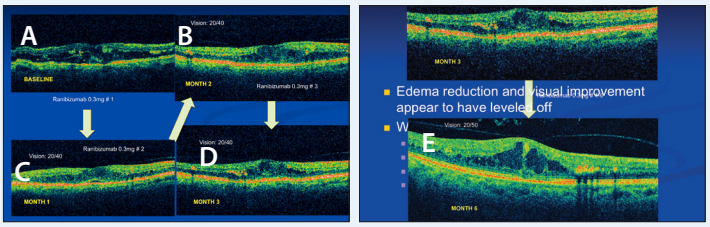

Figure 2. The patient demonstrated an initial response to anti-VEGF therapy for the first 6 months of therapy (A-D), but a regression following another injection (E), raising the possibility of tachyphylaxis or progression of the underlying disease.

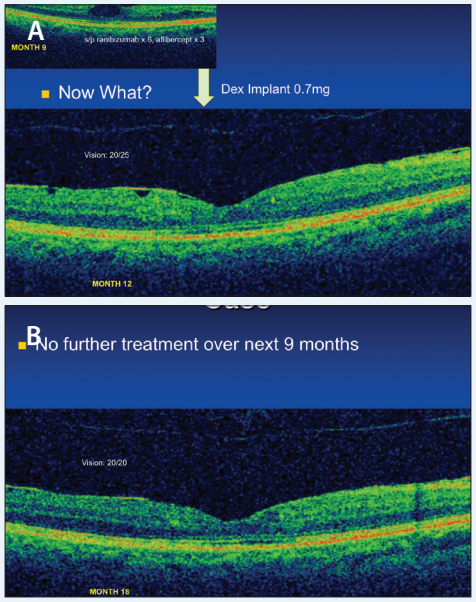

Figure 3. After a switch to a long-acting corticosteroid implant, the anatomy resolved and visual acuity rebounded despite an ERM that became apparent after treatment (A). Still, despite the ERM, the patient required no additional intervention to maintain treatment benefits 9 months later (B).

At the month 12 follow-up, the edema was completely resolved (Figure 3A). Interestingly, I was able to detect an epiretinal membrane that only became manifest after the edema went away. However, this patient did not require any additional treatment over the subsequent 9 months of follow-up (Figure 3B).

What is notable about this case is that it demonstrates a patient who had a partial response to anti-VEGF therapy but persistent edema that responded well to a switch to corticosteroid therapy. This case demonstrates that diabetic macular edema may be driven by multiple mechanisms, including inflammation, which may respond more robustly to corticosteroid therapy than anti-VEGF injections.

1. Mitchell P, Bandello F, Schmidt-Erfurth U, et al.; RESTORE study group. The RESTORE study: ranibizumab monotherapy or combined with laser versus laser monotherapy for diabetic macular edema. *Ophthalmology*. 2011;118(4):615-625.
2. Bressler SB, Qin H, Beck RW, et al; Diabetic Retinopathy Clinical Research Network. Factors associated with changes in visual acuity and OCT Thickness at 1 year after treatment for diabetic macular edema with ranibizumab. *Arch Ophthalmol.* 2012;30(9):1153–1161.

suggesting a diminishing need for the anti-VEGF component over time. This makes sense in that although VEGF is an important factor in ME secondary to diabetes, other factors, perhaps inflammatory in nature, also play a crucial role. Thus, VEGF may be an important factor in the initial disease stage, while additional biochemical factors may continue to or may become active in later stages of the disease—especially if either the underlying DR or systemic diabetes is poorly controlled.

CORTICOSTEROIDS

Prior to the availability of anti-VEGF agents, it was regular practice to use triamcinolone in an off-label fashion injected intravitreally to suppress the edema in eyes with diabetic eye disease. The first suggestion that intravitreal triamcinolone may be used for this purpose comes from a report by Martidis et al published in *Ophthalmology* in 2002.[15] The authors suggested that 4.0 mg intravitreal triamcinolone may have a role in refractory cases; shortly after its publication, there was a large upswing in the use of intravitreal triamcinolone for DME.

In clinical practice, it is well appreciated that corticosteroids can cause adverse effects, such as cataracts and glaucoma, which seemingly diminish their utility. In the DRCR.net Protocol B study, patients in the 4.0-mg group demonstrated a greater benefit in visual acuity gain at 4 months compared with the laser group ($P < .001$) or the 1.0-mg triamcinolone group ($P = .001$); however, this difference disappeared by 1 year, and at all time points from 16 months through 2 years, visual acuity was more favorable in the laser group.[16] Appreciable pressure rise (≥10 mm Hg at any visit) was more frequent in the 1.0- and 4.0-mg groups (16% and 33%, respectively) compared with laser (4%), and cataract surgery was more commonly performed in eyes in the 1.0- and 4.0-mg groups (23% and 51%, respectively) compared with laser 13%. Interestingly, the authors of the study noted that although cataract formation contributed to lower visual acuity scores in the steroid groups, not all differences could be attributed to cataract formation: central subfield thickness measure on optical coherence tomography paralleled the visual acuity findings (mean decrease of 139 ± 148 µm, 86 ± 167 µm, and 77 ± 160 µm in the laser, 1.0-mg, and 4.0-mg groups, respectively). As well, a subgroup analysis of pseudophakic eyes and those without lens changes showed no benefit for triamcinolone versus laser. Long-term follow-up out to 3 years confirmed these findings.[17]

Another DRCR.net study, Protocol I supports the notion that visual gains after treatment with triamcinolone are largely negated by the onset of cataracts.[14] In this study, among the subset of patients who were pseudophakic at baseline, triamcinolone plus prompt laser demonstrated remarkably similar visual outcomes as patients treated with ranibizumab (Figure 3).

In sum, what this suggests is that strong evidence points to a utility for corticosteroids in treatment of DME; however, results from clinical trials and clinical practice indicate that there may be important context for deployment of particular agents within the class. This second point readily follows from emerging data implying that corticosteroids cannot be thought of categorically, and that there are, in fact, important differences among the agents and formulations within the corticosteroid category.

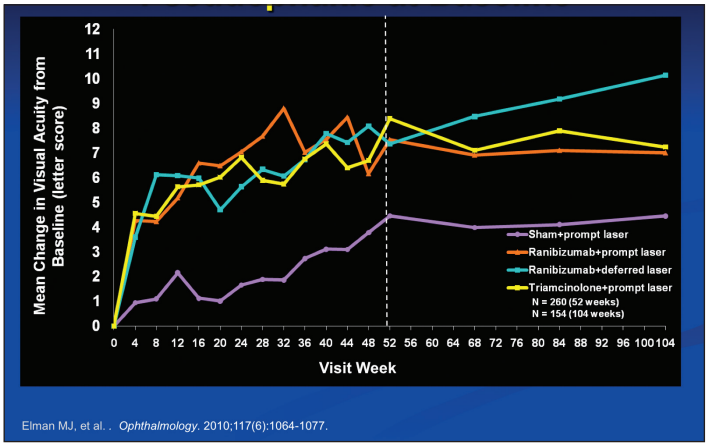

Figure 3. In DRCR.net Protocol I, patients who were pseudophakic at baseline had similar outcomes.

Dexamethasone Sustained-Release Implant

The dexamethasone intravitreal implant 0.7 mg (Ozurdex; Allergan) is a bioerodable implant that is injected via a 23-gauge needle into the vitreous cavity. It was first approved for use in vein occlusion edema. It later gained an indication for use in DME as a result of the MEAD study.[18] When it was cleared by the FDA, the dexamethasone intravitreal implant became the first corticosteroid officially approved for use in DME, as all other agents used for this purpose previously were used in an off-label fashion.

In pooled analysis of the phase 3 MEAD study, a higher percentage of patients treated with the implant achieved a 15 or greater improvement in ETDRS letters at 3 years compared with sham (22.2% in the 0.7 mg group [$P <$. 001 vs sham] vs 18.4% in the 0.35 mg group [$P = .018$ vs sham] vs 12.0% in the sham group). The improvement in BCVA in the active treatment group was reduced starting at the 15-month time point compared with sham, which correlated with onset of cataracts during the second year of the study. The idea that the final visual acuity was influenced by cataract development is supported by a subgroup analysis demonstrating that visual acuity gain was much more consistent among eyes that were pseudophakic at baseline compared with results in the overall population (Figure 4).

The incidence of cataract-related adverse events (defined as cataract, cataract cortical, cataract nuclear, cataract subcapsular, or lenticular opacities) was predictably higher in phakic patients treated with the 0.7-mg implant compared with sham (67.9% vs 20.4%). Overall, 59.2% of patients who had a phakic study eye treated with the dexamethasone implant 0.7 mg required cataract surgery, compared to 7.2% of the sham-treated patients, with the majority of cataract surgeries reported in the second and third year (between 18 and 30 months). The mean time to cataract being reported as an adverse event was approximately 16 months in the 0.7-mg implant group and approximately 10 months in the sham group. In patients in the 0.7-mg implant group with a phakic study eye at baseline, the visual acuity achieved prior to cataract was reestablished upon removal of the cataract.

As for adverse events related to IOP, approximately one-third of patients on active treatment in MEAD required use of an IOP-lowering agent (41.5% in the 0.7-mg group and 37.6% in the 0.35-mg group vs

Variable Response to Individualized Therapy

By Szilárd Kiss, MD

Patients' response to therapy can be highly variable. Likewise, there is growing evidence that differences in the formulations of the various pharmacotherapy options may impart different treatment effects. Within the corticosteroid class, different pharmacokinetic profiles of the various agents suggest that patients may respond differently to each one.

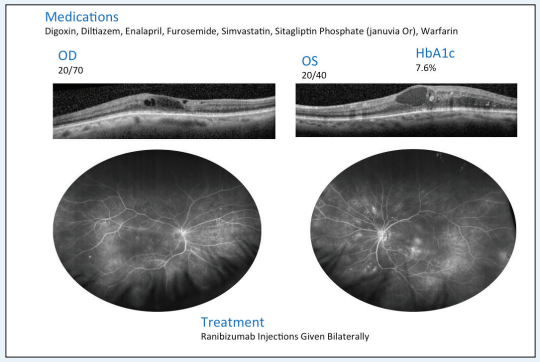

Figure 1. Initial presentation of a patient with 20/70 visual acuity OD and 20/40 OS.

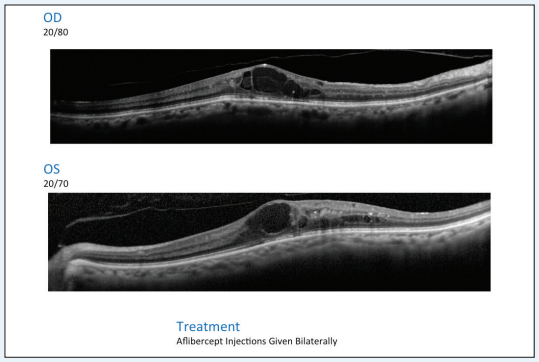

Figure 2. Monthly injections of ranibizumab failed to resolve the edema.

I had a patient who presented with diabetic macular edema in each eye. Visual acuity was 20/70 in the right eye and 20/40 in the left (Figure 1). The patient was on a variety of medications (digoxin, diltiazem, enalapril, furosemide, simvastatin, sitagliptin and warfarin) and the HbA1c was 7.6%. Ranibizumab was injected in each eye.

There was an unsatisfactory response after eight injections in each eye (Figure 2), and so the patient was switched to aflibercept. However, after three monthly injections, neither the edema nor the visual acuity had resolved (Figure 3). Treatment was again changed, this time to a 0.7-mg dexamethasone intravitreal implant 0.7 mg in each eye.

The patient was seen back in the clinic after 4 months (Figure 4). Due to insufficient response, therapy was switched again to a 0.19-mg fluocinolone acetonide intravitreal implant given bilaterally.

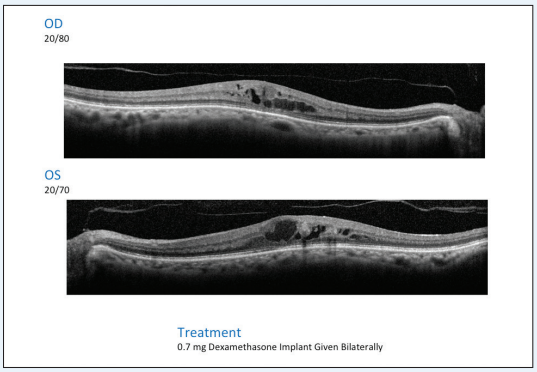

Figure 3. A switch to aflibercept, attempted for 3 consecutive months, did not provide a treatment benefit.

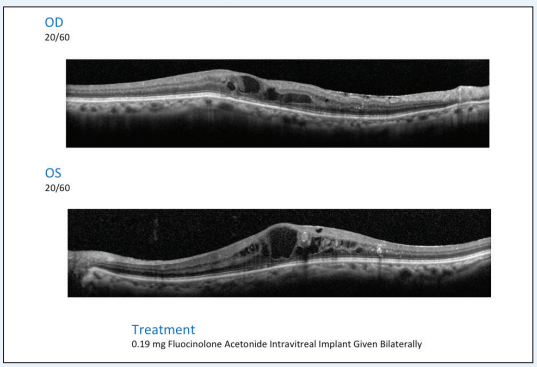

Figure 4. Four months after receiving a dexamethasone implant, the patient still had an insufficient response.

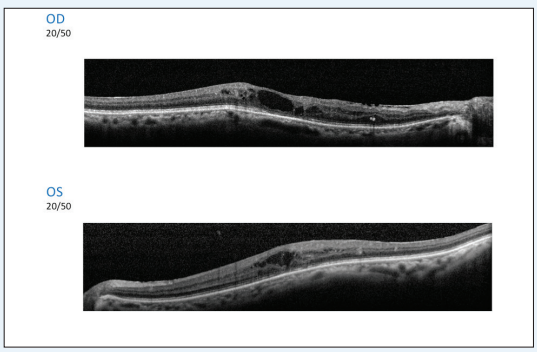

Figure 5. A switch to the long-acting fluocinolone acetate 0.19-mg implant finally yielded resolution of the edema and restoration of visual acuity.

Two months later, the edema resolved and the visual acuity improved to 20/50 OD and OS (Figure 5).

This case demonstrates that response to therapy is highly variable, even within the same class of pharmacotherapy. The improved functional and anatomic outcomes after switching to the fluocinolone acetonide intravitreal implant after prior use of the dexamethasone intravitreal implant supplies supporting rationale that differences in these agents' pharmacokinetics and formulations yield distinct treatment effects.

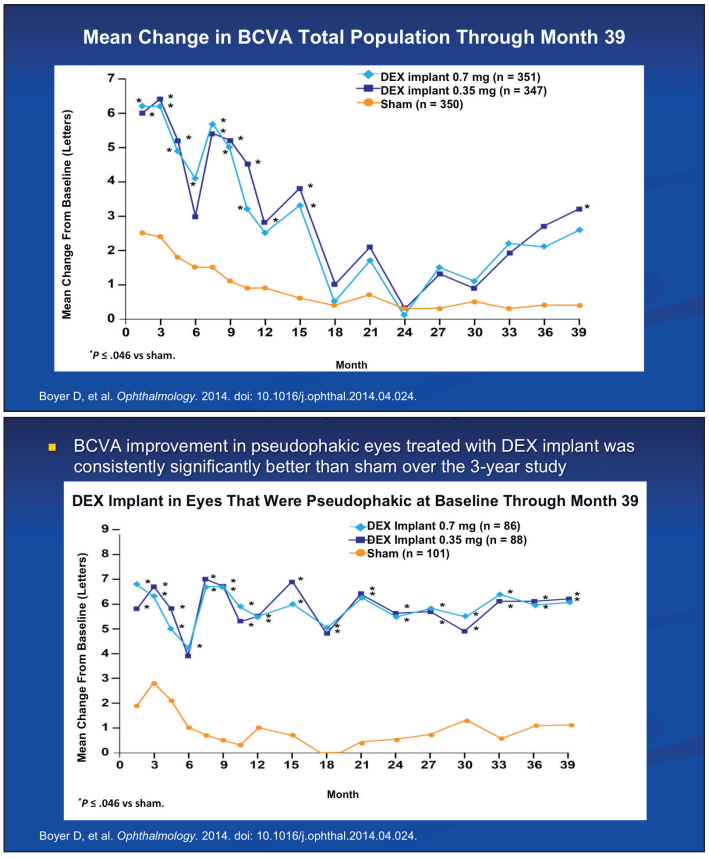

Figure 4. Visual acuity gain was much more consistent among eyes that were pseudophakic at baseline compared with results in the overall population.

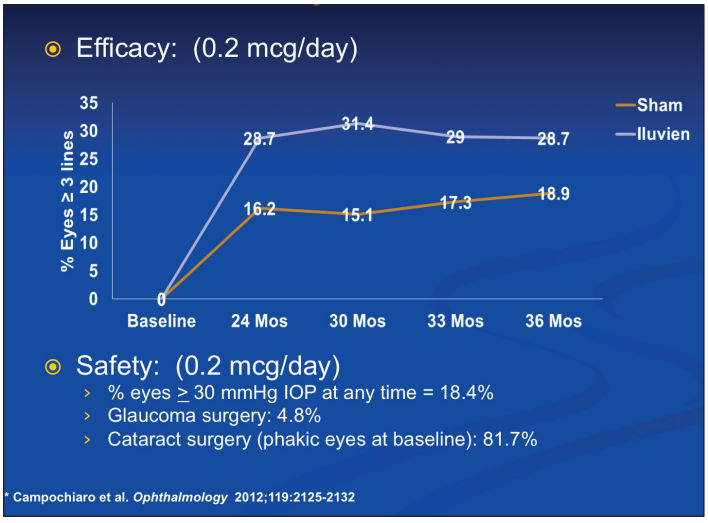

Figure 5. Salient outcomes of the phase 3 FAME study: Month 24: $P = 0.002$, Month 30: $P < .001$, Month 33: $P = .004$, Month 36: $P = .018$.

9.1% in the sham group). However, implant removal due to IOP elevation was not required in any patients, and only one patient in each of the 0.35- and 0.7-mg groups required incisional glaucoma surgery, for an overall incidence rate of 0.6%.

Fluocinolone Acetonide Implant

A second intravitreal implant was approved for use in DME late in 2014; however, the fluocinolone acetonide 0.19 mg intravitreal implant (Iluvien; Alimera) is notably different compared with the dexamethasone implant. The fluocinolone 0.19 mg implant is a non-bioerodable implant that is approved for use for up to 36 months (the dexamethasone implant was reimplanted every 6 months in MEAD, although its effects may wear off around 4 months after injection). The salient outcomes from the pivotal phase 3 FAME study[19] are shown in Figure 5. Close to 30% of patients gained 3 lines of visual acuity at 3 years, although there were a significant number of reports of cataracts and elevated IOP. In the FAME study, 4.8% of patients required incisional glaucoma surgery.

LASER THERAPY FOR DME

Laser therapy became the standard therapy for DME after the results of the ETDRS were published in 1985.[20] That this was a completely different era in DME therapy is evident in the primary endpoint: a significantly lower percentage of patients in the laser groups had moderate visual loss (13%) compared with patients who were followed without therapy (33%) at 3 years of follow-up. It should be noted that ETDRS enrolled patients with CSME, not just those with center-involved DME, and so the results cannot truly compare with results from pharmacotherapy trials.

To date, laser remains the only proven option for patients with non–center-involved DME, which raises an interesting question as to whether this subset of patients should be treated. On the one hand, laser takes time to become effective after application; and if you wait for a patient with foveal-threatening DME to develop central involvement before treatment, there may be vision loss. But, while it may be arguably advantageous to offer laser therapy to avoid potential vision loss—especially for patients in whom compliance may be questionable—laser use can be associated with adverse outcomes such as scotoma and scarring of the retina. Thus, it may be plausible to follow the patient with non–center-involved DME for potential progression towards foveal involvement and offer pharmacotherapy should the disease become more vision threatening, with the important understanding that this (ie, treatment of non-foveal edema) is an off-label use of any of the available agents, and that it has never been studied in a controlled clinical trial.

In sum, laser appears to have a role in non–center-involved DME and perhaps as adjuvant therapy for pharmacotherapy (although no clinical trial data from controlled studies demonstrate this). However, in the era of pharmacotherapy, laser seems to have fallen into a category of adjunctive and special use. For example, in the Protocol I study, patients who received laser required three fewer injections, but the benefits may not outweigh the potential risks associated with laser use.

SURGERY

Pars plana vitrectomy is an infrequently used modality for patients with DME, yet it may still be important, as epiretinal membrane or vitreomacular traction may contribute to the edema, and the epiretinal membrane or traction may limit the effectiveness of pharmacotherapy.

CONCLUSION

Based on the available data, anti-VEGF therapy is the appropriate first-line therapy for patients with DME that involves the fovea. Corticosteroids are a viable choice for patients who may not respond to anti-VEGF therapy, although there may be circumstances that warrant earlier use of certain agents—for instance, patients who are pseudophakic and have ME. It should be noted that the original FDA indication for the dexamethasone intravitreal implant was for patients with DME who were pseudophakic or for whom cataract surgery was planned; this indication arose from data within MEAD demonstrating that pseudophakic patients had consistent benefit from the implant, as well as an analysis showing that patients who underwent cataract surgery with an implant on board seemed to have better outcomes in terms of ME.

Although laser was the gold standard therapy for DME following the publication of the ETDRS, pharmacotherapy has largely supplanted this. Still, there may be rationale for laser in certain circumstances, although the role of adjunctive laser is unclear. Vitrectomy is often reserved for patients with epiretinal memebrane or vitreomacular traction secondary to the DME. ■

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ERM Risk Factors and Classification

BY UDAY DEVGAN, MD

Cystoid macular edema (CME) was described by Gass in 1969 as a retinal thickening in the macula that results from disruption of the normal blood-retinal barrier, leading to capillary leakage and accumulation of fluid.[1] This explanation has become the basis for much of our understanding of CME all the way to the present day. Several pathways can lead to the development of CME, although the most common cause is vitreomacular traction, which can exert tractional forces and lead to release of inflammatory factors such as fibroblastic grown factor, vascular endothelial growth factor (VEGF), and platelet-derived growth factor; a consequence of this inflammatory cascade is a breakdown of the blood-retinal.

CME is a known risk factor of cataract surgery. Clinically apparent CME after cataract surgery (called Irvine-Gass syndrome) occurs in about 0.1% to 2.33% of cataract surgeries employing small incision techniques and phacoemulsification,[2,3] although subclinical CME may be apparent on optical coherence tomography scans in 4% to 11% of cases.[4,5] The incidence is dramatically reduced compared to historical precedent, when CME occurred in as many as 60% of cases employing intracapsular cataract extraction and in 15% to 30% of extracapsular cataract cases.[6]

Regardless of the particular surgical technique employed, certain factors may contribute to a higher risk of developing CME after cataract surgery in the postoperative period, including capsule break, vitreous loss, vitreous traction, epiretinal membrane (ERM), diabetes (especially with prior macular edema from the diabetes), uveitis, retinal vein occlusion, and prior history of CME in the fellow eye—this last risk factor may contribute a 50% higher risk of CME development.[7]

Of these risk factors, ERM and diabetes are particularly noteworthy. ERM occurs in about 7% of patients older than 55 and in about 20% of those 75 years and older; however, ERM is also more common among patients with diabetes.[8] Therefore, diabetes is both an independent risk factor for development of CME as well as a contributing factor for ERM, which is in itself an independent risk factor for CME.

An ability to recognize the severity of ERM in a patient with a cataract will help with counseling about prognosis and outcome, and it may change the surgical plan; as well, it may contribute to a greater understanding of the risk for developing CME and thus guide an appropriate treatment plan.

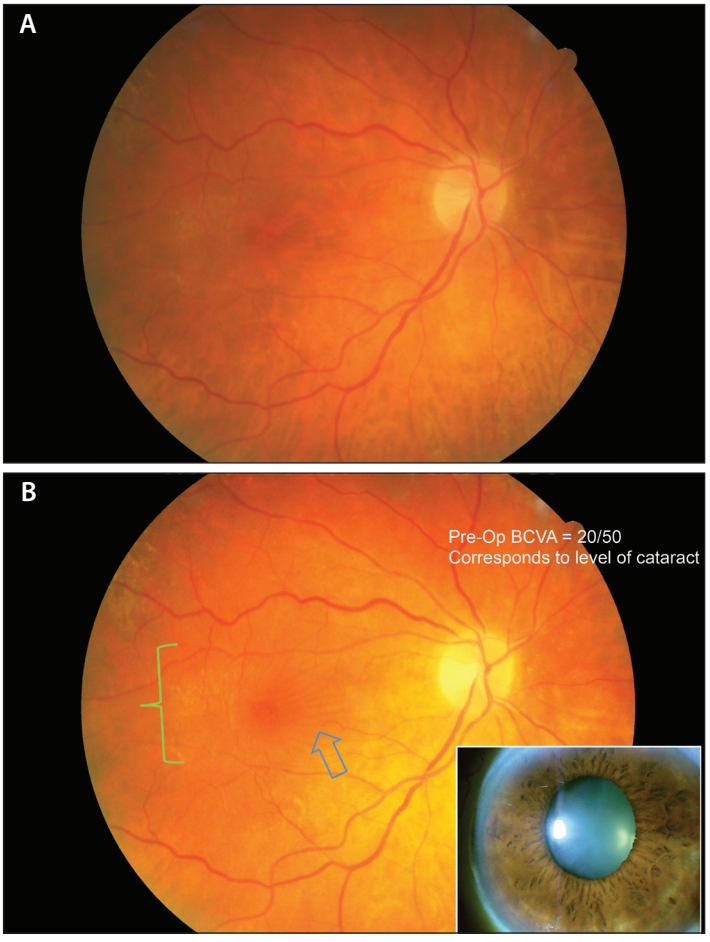

Figure 1. Fundus photograph of a patient with a cataract and a Gass Level Zero ERM. On standard resolution (A), it is difficult to appreciate the subtle appearance. An enhanced imaged (B) may be necessary to view the wrinkling (indicated by arrow).

GASS CLASSIFICATION SYSTEM

Gass ERM Level Zero

ERM Level Zero on the Gass classification scale is characterized by cellophane maculopathy and minimal wrinkling with no vascular distortion. It is a subtle and often difficult to appreciate on fundus photography (Figure 1). Aside from the ERM, the OCT will appear normal in appearance. These patients are likely to recover good visual acuity after cataract surgery; however, prolonged therapy with nonsteroidal anti-inflammatory drugs (NSAIDs) in combination with steroids will help lower the risk of developing CME. Although there is a wealth of data demonstrating the benefits of combined steroid and NSAID therapy for reducing the risk of CME,[9-29] this is an off-label use of these medications in the setting of cataract surgery. In my clinic, I have observed that NSAIDs can help resolve CME in the postoperative period (Figure 2).

Gass ERM Level 1

Gass ERM Level 1 is slightly more apparent on fundus photography compared with Level Zero, although enhanced photographs are still helpful for identifying it (Figure 3). ERM Level 1 is characterized by crinkled cellophane maculopathy, the vessels are often pulled or twisted, and there is apparent retinal surface wrinkling. Because of pre-existing macular edema at the time of cataract surgery, patients are unlikely to recover good visual acuity after surgery. Thus, it may

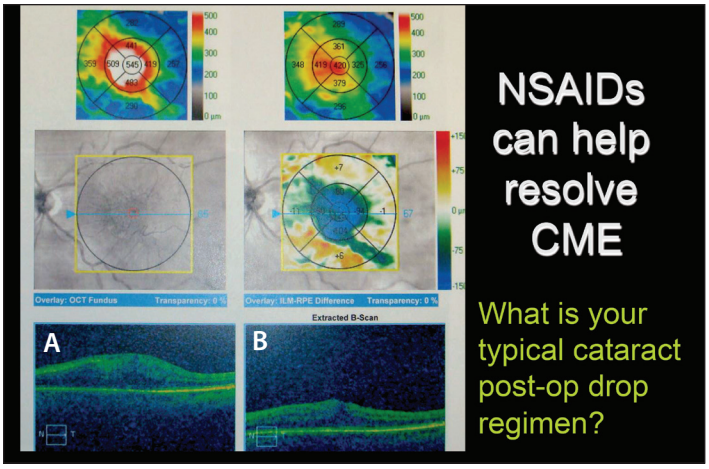

Figure 2. Before (A) and after (B) OCT images of a patient treated with NSAID therapy for CME in the postoperative period following cataract surgery.

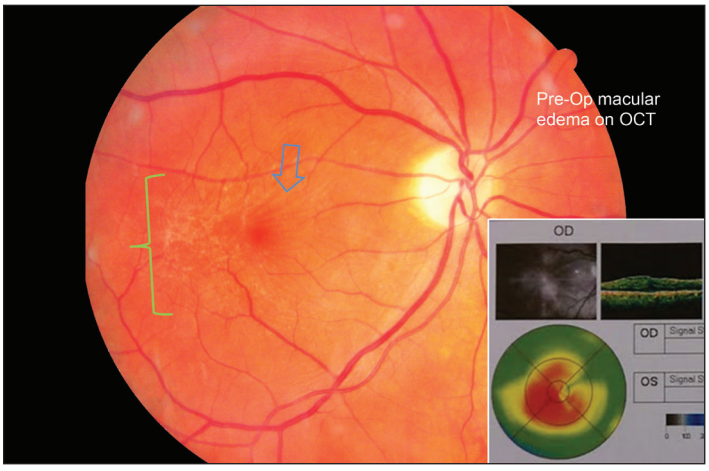

Figure 3. Enhanced fundus photograph of a patient with a moderate ERM (Gass Level 1) and cataract. This patient had a preoperative visual acuity of 20/160, which did not correspond to the severity of the cataract, suggesting that a separate issue was affecting the vision.

be warranted to steer such patients away from premium IOLs and to advise that a vitrectomy to manage the ERM will most likely be necessary. Such patients require prolonged postoperative anti-inflammatories to mitigate the risk of CME.

Gass ERM Level 2

Macular pucker is a hallmark of severe ERM, and a thick membrane, extensive retinal surface wrinkling, and vessels pulled or twisted into the pucker will be evident. Furthermore, a macular hole may develop. Although more apparent than Level Zero or Level 1, ERM Level 2 may require enhancement of fundus photographs to fully appreciate its severity (Figure 4).

CONCLUSION

A history of diabetes in a cataract surgery candidate is noteworthy for several reasons. The underlying systemic vascular disease may contribute to earlier development of cataracts (particularly subcapsular cataract) compared with individuals without diabetes. As well,

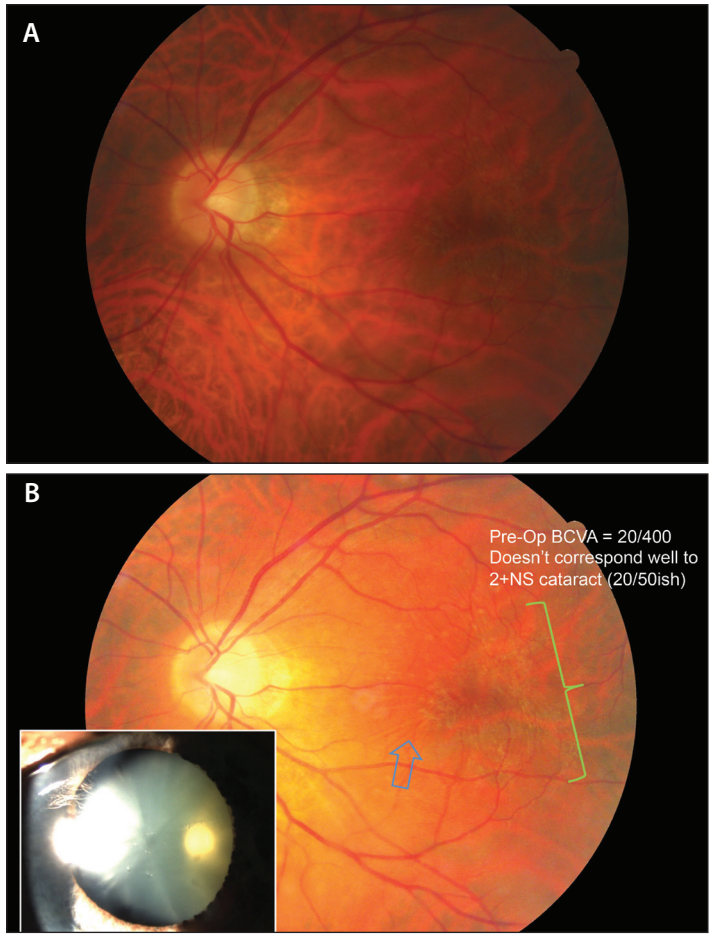

Figure 4. A patient with severe ERM (Gass Level 2) and a cataract. In this patient, the preoperative BCVA of 20/400 did not correlate with a 2+ nuclear sclerotic cataract. Note that these findings are much more apparent on the enhanced image (B) compared with the untouched photograph (A).

increased body mass index and hypertension, both of which may contribute to the development of type 2 diabetes, are also independent risk factors for progression of lens opacities.

In addition to diabetes potentially causing cataract development, it may also complicate the surgical course. Patients with diabetes undergoing cataract surgery are at increased risk of complications (including CME) and consequential loss of visual potential. It is well known that patients with diabetes may develop ocular complications, such as diabetic retinopathy and diabetic macular edema. Equally as important, diabetes is a risk factor for ERM development, which, in turn, is a risk factor for CME.

Although an off-label indication, combination NSAID and corticosteroid therapy in the postoperative period is an effective strategy for prevention of CME.[9-23] There may be additional rationale for having an NSAID and steroid on board at the time of cataract surgery to reduce the potential for CME.[10] Lastly, use of NSAID and corticosteroid therapy is a plausible treatment strategy for CME in the postoperative period. Intravitreal corticosteroid therapy is a viable choice, although the recent market availability of sustained release corticosteroid implants offers the theoretical benefit of supplying anti-inflammatory efficacy both at the time of injection and for the

entire postoperative healing period.

Patients with diabetes constitute a high-risk category for cataract surgery. A careful preoperative evaluation with emphasis on evaluating for diabetic eye disease is warranted. Of note, the level of the presenting cataract should correspond to the patient's visual acuity and reported symptoms; symptomatology that appears in discordance with the severity of cataract may be a tip off to the existence of retinal pathology. If present, treatment of diabetic eye disease should take precedent over managing the cataract.

Despite all of these challenges, patients with diabetes can still achieve excellent postoperative vision after cataract surgery, especially if a careful pre- and postoperative evaluation and follow-up are performed, the surgeon performs meticulous and minimally traumatic surgery, and appropriate medical therapy is offered pre- and postoperatively. ■

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NSAID Use in Cataract Surgery: Rationale and Clinical Applications

BY MICHAEL B. RAIZMAN, MD

Innovations in the technology and techniques used for cataract surgery have reduced the risk that patients will develop cystoid macular edema (CME) postoperatively while also improving visual outcomes after surgery. However, a byproduct of the increased success with cataract surgery is raised patients' expectation, making the appearance of even mild CME problematic. Despite advancements in the understanding of CME—its causes, treatment paradigms, and risk factors—it remains the leading cause of unexpected poor vision after otherwise successful cataract surgery. In addition to affecting visual acuity as measured on the Snellen chart, CME may also affect quality of vision, with patients reporting symptoms of metamorphopsia and loss of contrast sensitivity. Thus "clinically significant" CME may not be based solely on acuity, and its impact may be highly individualized and contextualized to the patient.

Depending on the population assessed, the skill level of the surgeon involved, and the particular techniques used, rates of CME after cataract surgery range from about 1% to 30%. However, patients with diabetes are at the upper end of this range, with about a 32% risk and perhaps as high as 81% if there is pre-existing diabetic retinopathy.[1] Patients with more severe diabetic macular edema will almost assuredly have CME postoperatively even after uncomplicated cataract surgery. Given that diabetes is a risk factor for cataract development, it is highly advantageous for the anterior segment/cataract surgeon to understand the role of prophylaxis and treatment of CME for patients undergoing cataract surgery.

PREVENTION

Given the negative impact CME can have on quantity and quality of postoperative vision after cataract surgery, some form of prophylaxis has become common, even if there are not specific agents approved by the US Food and Drug Administration for this indication.

I conducted a small trial in the 1990s where 60 patients were randomized to either corticosteroids alone for 4 weeks postoperatively or corticosteroids plus a nonsteroidal anti-inflammatory drug (NSAID) for the same duration. All patients received a course of NSAID therapy for 2 days prior to surgery with the intention of maintaining mydriasis during the operation[2] At the 6-week evaluation, 12% of patients using steroid alone had some degree of macular thickening on optical coherence tomography compared with zero patients in the combined corticosteroid plus NSAID group.

Although suggestive of a benefit, this small trial is not definitive by itself to warrant a recommendation for universal prophylaxis. To date, there have not been any large multicenter clinical trials examining the question of whether NSAIDs play a role in CME prophylaxis, nor is it likely that such a study will ever be conducted, given the cost and resources required.

While there are no definitive studies, there are a plethora of smaller trials conducted to date that supply suggestive evidence of a benefit for NSAID therapy in the cataract postoperative period for preventing CME. Since 1999, a number of studies have investigated diclofenac, ketorolac, and nepafenac in the postoperative management of cataract agents, and despite the use of different agents, they have shown remarkably similar outcomes.[3-8] There have not been studies comparing NSAIDs to steroids alone for prophylaxis, but it appears that NSAIDs are the more important element in the postoperative regimen. At the same time, use of an NSAID alone would likely provide insufficient coverage to eliminate inflammation in some cases, and prolonged inflammation in the anterior chamber can result in the breakdown of the blood-retinal barrier which produces CME.

RATIONALE FOR PREVENTIVE USE

At a minimum, based on the available evidence, NSAID prophylaxis should be used for high-risk cases, such as those involving patients with diabetes even without evidence of diabetic retinopathy, as this population is at high risk for CME. As well, patients with any epiretinal membrane, vitreomacular disorder, retinal vascular disease, uveitis, retinitis pigmentosa, history of CME in the fellow eye, or pre-existing macular edema of any type should also receive pre- and postoperative NSAID therapy. A broken capsule during surgery should also prompt initiation of NSAID therapy.

In my practice, for routine cases, I prefer to use the NSAID one day prior to surgery (along with an antibiotic), as the newer agents in this class are potent enough to deliver benefit without 2 to 3 days of therapy. I do not believe longer duration of therapy will be harmful; however, a single day of use may be more convenient for patients. I then continue NSAID therapy for 4 weeks postoperatively.

For high-risk cases, my paradigm changes: NSAIDs for 7 days before surgery and for 6 weeks after. I also use OCT to monitor for CME and base a decision on whether to withdraw or continue therapy on the imaging study. Visual acuity is, in my opinion, a secondary measure of whether continued NSAID use is needed.

ARGUMENTS AGAINST ROUTINE NSAID USE

Several questions have been raised over the years regarding the use of NSAIDs in all cases following cataract surgery. For example, some have claimed that there is a lack of demonstrated efficacy for NSAID use. As noted earlier, multicenter trial data is not available; yet, evidence from a number of studies suggest a benefit.[3-8] Thus, efficacy of NSAID for this purpose has been well demonstrated.

Another commonly cited notion is that CME occurs too rarely following cataract surgery to warrant use of prophylaxis, especially if cases can be treated after they occur or if NSAIDs may expose patients to safety risks. Historical studies of intracapsular and extracapsular cataract surgery techniques suggest a CME rate of 60% and

NSAID Pretreatment in a Second Eye Cataract Surgery

By Jay L. Schwartz, DO

Previous history of cystoid macular edema (CME) in a contralateral eye has been suggested as a significant risk factor for CME development during second eye cataract surgery. Some studies report a risk as high as 50%.[1] At the current time, there are no evidence-based guidelines for prevention of CME during second eye surgery, although anecdotal evidence suggests the utility of offering nonsteroidal anti-inflammatory drugs (NSAIDs), a practice that is supported by several case series and data from published clinical studies.

CASE

In my practice, a 67-year-old man underwent uneventful cataract surgery for a 2+ nuclear sclerotic cataract in the right eye. He was implanted with a multifocal lens, and a femtosecond laser was used for the operation. The preoperative BCVA was 20/20.

On postoperative day 1, the visual acuity was 20/40, edema was minimal, and the lens was well centered. At the 1-week checkup, the visual acuity had improved to 20/25 and the patient was J2+ at near. Imaging with optical coherence tomography was normal, yet the patient complained of worse vision than before surgery.

The facts of the case raised three distinct possibilities: the visual symptoms were part of the normal healing process; that the patient needed more time to neuroadapt to the multifocal IOL; or that CME may be present, even if it was not detectable on optical coherence tomography.

DIAGNOSIS AND MANAGEMENT

The patient demonstrated normal macular findings with some leakage on fluorescein angiography. However, the strongest clue was the subjective complaint of worse vision than before surgery, which suggested CME. There was certainly a possibility that delayed adaption could be a factor; yet, if CME is a plausible possibility, it may be warranted to treat empirically to avoid visual complications due to delayed treatment.

The patient was treated with topical NSAIDs and steroids, but there was no improvement after 3 weeks. An intravitreal steroid injection was performed, and there was complete resolution 2 weeks later. Visual acuity was 20/20 and J1 at near. Importantly, the patient was finally happy with his vision.

SECOND EYE SURGERY

Noting that the risk of CME in this second eye surgery was significantly enhanced, we opted to start aggressive prophylaxis protocols, which included 7 days of NSAIDs instead of the 3 days I typically pretreat with. The surgery was uneventful, and the patient was 20/20 and J1 at 1 week and extremely happy.

CONCLUSION

This case demonstrates the utility of preventive treatment with NSAIDs in settings in which there is an increased risk of CME. Although this patient's first eye was successfully treated with steroid and NSAID therapy after the occurrence of CME, this is not always the case, as CME results from altered macular structural integrity, which, if left untreated, may yield lost visual potential. Lastly, this case demonstrates that CME is not always clinically apparent or recognizable on imaging, but may still affect patients' subjective assessment of their own vision. Thus, a high index of suspicion for CME is prudent, as is a low threshold for treatment; additionally, pretreatment should be considered in high-risk cases.

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30%, respectively.[9] Modern small incision surgery is associated with much lower rates of about 2%[10,11]; however, evidence of CME may be apparent on OCT following small incision cataract surgery with phacoemulsification in as many as 11% of cases.[12,13] If CME is known to affect quantity and quality of vision, then these so-called subclinical cases with only OCT evidence should garner as much attention as those in which patients report visual symptoms. Any macular thickening can be clinically significantly, independently or as a contributing risk factor in the development of other retinal conditions.

Some have suggested waiting for CME to occur and then treating, rather than using preventive treatment. Treating CME after it occurs is certainly an option. However, not all patients will respond to treatment, which may indicate that once the anatomy of the macula is altered, it may not resolve in such a way that yields a full return of visual potential.

Safety concerns with NSAIDs arise primarily from reports of corneal melts after introduction of a formulation of diclofenac sodium ophthalmic solution by Falcon Pharmaceuticals in 1999. Shortly after its release, there was a rise in reports of corneal melts; however, this may have been due to misuse of the agent, as it was frequently prescribed 6 to 8 times a day. Some researchers attribute the propensity for this single agent to cause corneal melts to the presence of vitamin E based solubilizer tocophersolan in the formulation.[14] Incidence of corneal melts have not been reported with other NSAID agents.[14] More frequently cited complications of NSAID use include minor burning, stinging, and conjunctival hyperemia,[15] as well as keratitis, corneal infiltrates, and corneal lesions, although these complications may be associated with use of ophthalmic medications that contain preservatives.[16]

Most toxicity with NSAIDs tends to occur in eyes with dry eye, which makes sense given the breakdown of the epithelium. Patients with keratojunctivitis sicca and heavy punctate staining preoperatively may require efforts to get the ocular surface healthy enough to endure the NSAID therapy (there are actually a multitude of reasons to desire a healthy tear film before any ophthalmic surgery, and the implications for NSAID therapy is just one reason). It may be wise to avoid NSAID use on patients in whom the eye is severely dry, such as

those with Sjögren syndrome or graft-versus-host disease; these cases may need to be followed closely, monitored for any sign of CME, and treated appropriately.

Another objection to wider adoption of NSAIDs is the issue of compliance. Certainly, adding a drop to the postoperative regimen risks poor compliance. Several studies show a negative correlation between patients' compliance and the number of drops they take.[17] However, if patients are properly educated that the drop is intended to prevent inflammation and subsequent loss of vision, it may help.

Related to the issue of compliance is the cost of medication. But, again, I have found that if I explain to patients the need for the drop and why I am prescribing it, then the investment is evident. On a larger scale, per-patient use of NSAIDs is much less taxing to the health care system then the additional office visits, diagnostic testing, and as-needed therapy that would be required to follow patients and treat when cases occur.

Surgeons are increasingly judged on outcomes. We need our patients to see better as soon as possible. NSAIDs may hasten the improvement in visual acuity after cataract surgery.

CONCLUSION

Although usage guidelines for NSAID for prevention of CME are debatable, efforts are being made to introduce evidence-based practice into the postoperative care of cataract patients.[18] It seems apparent that a growing body of evidence suggests the utility of diabetic macular edema prophylaxis with a steroid and an NSAID agent. In the future, the advent of so-called dropless cataract surgery—in which a compounded injection is used at the end of cataract surgery to deliver multiple agents (formulations exist that contain a steroid and antibiotic or a steroid, an antibiotic, and an NSAID agent; Imprimis Pharmaceuticals)—may obviate cost and compliance concerns. However, the practice is currently still an off-label indication. A number of drug delivery devices are also under investigation. Lastly, a product that is infused into the balanced salt solution during surgery containing phenylephrine and ketorolac recently gained FDA approval; its potential effect on CME is unclear, although there is suggestive evidence that it may reduce COX 1 and 2 in the postoperative period.[19] ■

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STEROID DELIVERY IN PATIENTS WITH DIABETIC MACULAR EDEMA IN THE PRESENCE OF A CATARACT

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1. Which of the following is a proven treatment for non–foveal-involved DME:
a. Aflibercept
b. Ranibizumab
c. Photocoagulation
d. Aflibercept or ranibizumab
e. Dexamethasone intravitreal implant

2. The year 1 results of DRCR.net Protocol T showed that in patients with baseline Snellen equivalent visual acuity of 20/50 or worse:
a. Ranibizumab achieved the best improvement in visual acuity.
b. Bevacizumab achieved the best improvement in visual acuity.
c. Aflibercept achieved the best improvement in visual acuity.
d. All three anti-VEGF agents had similar outcomes.

3. In the phase 3 trial of the dexamethasone intravitreal implant, approximately what percentage of patients required glaucoma surgery?
a. 25% to 50%
b. 5% to 25%
c. 1 to 5%
d. < 1%

4. A large multicenter clinical trial demonstrated conclusively the value of topical NSAIDs in preventing macular edema after cataract surgery.
a. True
b. False

5. Which of the following is the least likely risk factor for cystoid macular edema after cataract surgery:
a. Epiretinal membrane
b. Use of oral prednisone
c. Background diabetic retinopathy
d. Retinitis pigmentosa

6. Which clinical condition poses the highest risk of toxicity from topical NSAIDs?
a. Collagen vascular disease
b. Retinitis pigmentosa
c. Marfan syndrome
d. Sjögren syndrome

7. What factors have contributed to a lower incidence of cystoid macular edema following cataract surgery compared with historical precedence?
a. Adoption of pre- and postoperative topical drug regimens that include NSAIDs and corticosteroid agents
b. The adoption of small-incision techniques
c. The introduction of phacoemulsification
d. All of the above

8. A patient with normal OCT findings, but who has cellophane maculopathy and minimal wrinkling with no vascular distortion on fundus photography most likely falls into what category of the Gass Classification System?
a. Level Zero
b. Level 1
c. Level 2
d. It cannot be determined based on the information provided.