Use of Corticosteroids in the Treatment of Patients With Diabetic Macular Edema Who Have a Suboptimal Response to Anti-VEGF: Recommendations of an Expert Panel

Carl D. Regillo, MD; David G. Callanan, MD; Diana V. Do, MD; Howard F. Fine, MD, MHS; Nancy M. Holekamp, MD; Baruch D. Kuppermann, MD, PhD; Michael A. Singer, MD; Rishi P. Singh, MD

BACKGROUND AND OBJECTIVE: Guidance on the use of corticosteroids in the treatment of diabetic macular edema (DME) is lacking. This study aimed to develop a clinically recommended treatment paradigm for DME with emphasis on the role of corticosteroids.

PATIENTS AND METHODS: An expert panel of nine retinal specialists in the United States developed consensus recommendations for DME treatment through a modified Delphi process.

RESULTS: The panelists typically use intravitreal injections of vascular endothelial growth factor (VEGF) antagonists as first-line treatment of DME and switch patients with an inadequate response to anti-VEGF therapy (failure of best-corrected visual acuity to improve to 20/40 or better because of edema after three to six monthly injections, or a less-than-50% reduction in excess macular thickness after three to four monthly injections) to intravitreal corticosteroid treatment.

CONCLUSION: Intravitreal corticosteroids have a potentially useful role in the treatment of patients with DME who have an inadequate response to intravitreal anti-VEGF therapy.

is commonly used via an intravitreal injection in an off-label fashion for treatment of DME; a formulation approved for systemic cancer therapy is repackaged in syringes by a compounding pharmacy for off-label intravitreal ophthalmic use. Many studies have demonstrated that intravitreal anti-VEGF treatment has a favorable tolerability profile and is effective in reducing central retinal thickness and improving best-corrected visual acuity (BCVA) in patients with DME. Even with monthly administration of anti-VEGF, however, the response to anti-VEGF therapy is suboptimal in a substantial proportion of patients. After 2 years of monthly ranibizumab 0.3 mg injections for the treatment of DME in the RISE/RIDE registration trials, central foveal thickness remained greater than 250 μm on time-domain optical coherence tomography (OCT) in 24.8% of patients, and BCVA was worse than 20/40 in 42.8% of patients. Corticosteroids are also available for the treatment of DME. Although intraocular corticosteroid treatment is commonly associated with adverse effects of cataract and increases in intraocular pressure (IOP), intravitreal corticosteroids have demonstrated efficacy in improving central retinal thickness and BCVA in DME and, therefore, are viable treatment options. In the United States, dexamethasone intravitreal implant 0.7 mg (DEX implant) (Ozurdex; Allergan plc, Dublin, Ireland) is FDA-approved for treatment of DME, and intravitreal fluocinolone acetonide insert (FAc) (Iluvien; Alimera Sciences, Alpharetta, GA) is approved for treatment of DME in patients who have been previously treated with a course of corticosteroids and did not have a clinically significant rise in IOP. In addition, intravitreal triamcinolone acetonide (TA) has been used off-label for many years and has demonstrated beneficial effects in patients with DME.
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<td>First-line treatment for center-involved DME</td>
<td>Intravitreal anti-VEGF injections</td>
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<td>2. Improvement in visual acuity (secondary)</td>
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<td>Definition of inadequate response to anti-VEGF therapy</td>
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<td>than-50% reduction in excess macular thickness after three to four monthly anti-VEGF injections</td>
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<td>4. Monthly injections are too burdensome (ie, poor compliance)</td>
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<td>Reasons to potentially consider switching or stopping anti-VEGF</td>
<td>1. Fluid still present on the retina</td>
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<td>treatment</td>
<td>2. Lack of anatomical improvement (eg, CRT)</td>
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<td>3. Lack of improvement in BCVA</td>
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<td>4. Monthly injections are too burdensome (ie, poor compliance)</td>
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<td>Importance of treating the inflammatory versus the VEGF component</td>
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<td>FDA-approved corticosteroid is preferred</td>
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<td>Use of macular laser in center-involved DME</td>
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<td>Frequency of monitoring</td>
<td>1. Monthly for patients on anti-VEGF</td>
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<td></td>
<td>2. Every 1 to 2 months for patients on corticosteroid</td>
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<td>3. Every 1 to 2 months for patients newly on combination of anti-VEGF and corticosteroid</td>
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<td></td>
<td>4. Every 2 months for patients established on combination of anti-VEGF and corticosteroid</td>
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<tr>
<td>Management of IOP increases during corticosteroid treatment</td>
<td>1. Treat elevated IOP of 30 mm Hg or less with topical IOP-lowering medication (single medication</td>
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<td>or fixed combination)</td>
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<td></td>
<td>2. For patients with IOP higher than 30 mm Hg, treat with fixed-combination IOP-lowering eye</td>
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<td>drop and/or refer the patient to a glaucoma specialist</td>
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*BCVA = best-corrected visual acuity; CRT = central retinal thickness; DEX implant = dexamethasone intravitreal implant; DME = diabetic macular edema; FDA = U.S. Food and Drug Administration; IOP = intraocular pressure; VEGF = vascular endothelial growth factor*
There is a need for guidelines on how DME should be treated to provide patients with the best possible outcomes when the response to anti-VEGF therapy is inadequate. To address this need, a panel of clinical experts in retinal ophthalmology was brought together to develop consensus recommendations for DME treatment through a modified Delphi process. The objective was to develop a clinically recommended treatment paradigm for DME, with particular focus on how corticosteroids fit within the treatment paradigm.

**PATIENTS AND METHODS**

The Delphi technique is a widely used and accepted method for building consensus from experts in a field through iterations of a survey and anonymous feedback; in each round of the survey, the participants review and assess the results and feedback from the previous round, then respond to the survey again, and the process is repeated until consensus is reached. A modified Delphi approach incorporating a face-to-face meeting led by a moderator has been used in previous studies to develop recommendations for the assessment and management of ophthalmic diseases and was used in this study to develop a recommended treatment paradigm for DME. A panel of nine retina specialists with expertise in the treatment of diabetic retinopathy and DME were invited and agreed to participate in the development of the treatment guidelines. After a literature review was conducted to identify current treatment patterns in DME, a survey including 22 multipart, multiple-choice, and open-ended questions regarding treatment scenarios and clinical decision-making was developed by Endpoint Outcomes and Allergan. The questions were designed to elucidate key elements of the treatment paradigm including assessment of the response to anti-VEGF therapy, the role of corticosteroids in the treatment paradigm, differentiation of available corticosteroid treatment options, and corticosteroid use and side effects.

The panel responded to the survey in two formal rounds of feedback. The first round of the survey was conducted on the SurveyMonkey online platform. The panel was provided with a list of patient scenarios and asked to rate their likelihood of requiring corticosteroid treatment. The panel's consensus was recorded and used to develop the treatment paradigm.

**TABLE 2**

<table>
<thead>
<tr>
<th>Patient Scenario</th>
<th>Definite or Likely Candidate for Corticosteroid Treatment</th>
<th>Unlikely Candidate for Corticosteroid Treatment</th>
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<tr>
<td>Inadequate responder to anti-VEGF after three to six injections</td>
<td>✅</td>
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<tr>
<td>Inadequate responder to anti-VEGF who is pseudophakic</td>
<td>✅</td>
<td></td>
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<tr>
<td>Inadequate responder to anti-VEGF who is phakic and older than 60 years old</td>
<td>✅</td>
<td></td>
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<tr>
<td>Inadequate responder to anti-VEGF who is phakic and younger than 60 years old</td>
<td>✅</td>
<td></td>
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<tr>
<td>Patient in need of rescue</td>
<td>✅</td>
<td></td>
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<tr>
<td>Patient who is scheduled to undergo cataract surgery</td>
<td>✅</td>
<td></td>
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<tr>
<td>Patient with a history of vitrectomy</td>
<td>✅</td>
<td></td>
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<tr>
<td>Patient with persistent DME</td>
<td>✅</td>
<td></td>
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<tr>
<td>Patient with severe edema</td>
<td>✅</td>
<td></td>
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<tr>
<td>Suboptimal response to anti-VEGF treatment after three injections</td>
<td>✅</td>
<td></td>
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<tr>
<td>Patient who is resistant to laser photocoagulation</td>
<td>✅</td>
<td></td>
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<tr>
<td>Patient who had successful filtration surgery to control IOP</td>
<td>✅</td>
<td></td>
</tr>
<tr>
<td>Patient with POAG well controlled on one glaucoma drop</td>
<td>✅</td>
<td></td>
</tr>
<tr>
<td>Patient with POAG well controlled on two glaucoma drops (status of optic nerve)</td>
<td>✅</td>
<td></td>
</tr>
<tr>
<td>Patient with POAG well controlled on two glaucoma drops and a healthy optic nerve</td>
<td>✅</td>
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DME = diabetic macular edema; IOP = intraocular pressure; POAG = primary open-angle glaucoma; VEGF = vascular endothelial growth factor.
survey platform (www.surveymonkey.com). Nine panelists participated in the survey and provided anonymous feedback. Following the first round, the results were summarized and provided to the panelists. Eight of the panelists then participated in the second round of the survey at a “real-time” Delphi panel meeting on June 4, 2016, in Philadelphia, Pa. At the meeting, the anonymous summary results of the first round were presented to the panelists. Answers to open-ended questions in the first round were used to frame multiple-choice answers to survey questions for the second round (Appendix B available at www.Healio.com/OSLI-Retina). For each survey question, if consensus was not reached in the first round, the results were discussed and debated by the panelists. The panelists then voted for their chosen response. An electronic audience response system (ResponseCards; Turning Technologies, Youngstown, OH) was used to capture anonymous votes during the Delphi panel discussion, and all panelists were required to vote before results were displayed. Discussion was continued and voting was repeated until consensus was reached, or it was clear that it was impossible to achieve consensus. During this process, modification of survey questions and possible responses, based on opinions expressed during the discussion, was allowed to facilitate the achievement of consensus. Consensus was defined as agreement by at least six of nine panelists in the first round (66.7%), or by at least six of eight panelists at the Delphi panel meeting (75%).

RESULTS

The panelists reached consensus on many issues in the treatment of DME (Table 1) and developed a recommended treatment paradigm for center-involved DME in patients who have an incomplete response to anti-VEGF treatment (Figure).

The key aspects of the treatment paradigm are as follows.

Disease Classification

The majority of panelists (75%; six of eight) agreed that clinical decision-making on whether and how to treat DME begins with the classification of the DME as center-involved or non-center-involved.

First-line Treatment for Center-Involved DME: Anti-VEGF Therapy

Members of the expert panel typically use intravitreal bevacizumab, ranibizumab, and aflibercept as first-line treatment for center-involved DME. In the first round (online) survey, there was consensus agreement (77.8%; seven of nine) that if there was a suboptimal response to anti-VEGF injections early in treatment (after three or fewer injections), the patient is typically switched to another anti-VEGF agent. In the discussion at the Delphi meeting, panelists clarified that insurance coverage and reimbursement can affect the choice of anti-VEGF agent initially used. When the early response to anti-VEGF is poor, they may switch to a different anti-VEGF agent that is believed to be more efficacious, but they generally limit the total time on anti-VEGF-only therapy to 6 months for patients who have an inadequate response.

The response to anti-VEGF treatment is variable among patients. All panelists agreed that the relative roles of VEGF and other inflammatory cytokines in the edema is the most important factor contributing to different levels of patient response to anti-VEGF. The panelists also all agreed that the chronicity of the edema is a second key factor contributing to different levels of patient response to anti-VEGF.

There was unanimous agreement that long-term DME results in poorer outcomes. Panelists stated that chronic DME may be less responsive to anti-VEGF therapy and is likely to involve inflammatory pathways and cytokines other than VEGF that can cause tissue damage. Photoreceptor damage and permanent loss of visual acuity can occur in chronic DME. Prompt treatment of center-involved DME with anti-VEGF is recommended for optimal outcomes.

Evaluating the Response to Anti-VEGF Therapy

All panelists agreed that the most important determinant of an ideal response to anti-VEGF therapy is the resolution of edema. Most of the panelists (87.5%; seven of eight) further agreed that improvement in visual acuity is the second most important determinant of an ideal response to anti-VEGF therapy. Improvement in visual acuity is important, but it is a secondary factor in evaluation of the treatment response because other factors beyond DME can affect vision.

A patient can be determined to be an inadequate responder to anti-VEGF therapy based on anatomic criteria, or a combination of BCVA and anatomic criteria. Almost all (87.5%; seven of eight) of the panelists agreed that a DME patient who after three to four monthly anti-VEGF injections has a less than 50% reduction from baseline in the excess macular thickness (defined as thickness over the upper limit of normal) is an inadequate responder to anti-VEGF
therapy. In addition, the majority of panelists (75%; six of eight) agreed that a DME patient whose BCVA after three to six monthly anti-VEGF injections has failed to improve to 20/40 or better because of edema is an inadequate responder to anti-VEGF therapy.

The panel was unable to agree on a value for the central subfield thickness on OCT that indicates an inadequate response to anti-VEGF therapy. Although the central subfield thickness measurement is valuable for evaluation of changes in retinal thickness over time and after treatment, qualitative assessment of the persistence of edema, which is associated with visual acuity loss, may drive treatment decisions.

Almost all panelists (87.5%; seven of eight) agreed that they are prepared to tolerate persistent edema for 4 to 6 months in patients who are receiving monthly anti-VEGF injections. Panelists agreed that waiting longer than 6 months to move on to other modalities of treatment is potentially detrimental. It was noted that DME may be present for months before patients are seen by a clinician and initiate treatment, so the persistence of edema through 6 months of treatment may indicate the development of chronic DME, which involves inflammatory pathways and cytokines other than VEGF and potentially has reduced responsiveness to anti-VEGF therapy. Panelists cited clinical data (the EARLY Study) showing that the BCVA outcomes of patients in the DRCR.net Protocol I study after 3 years of ranibizumab 0.5 mg treatment could be predicted by results at week 12. The results support a change in therapy when edema persists and BCVA does not improve after 3 months of ranibizumab treatment, because most patients who had less-than-five-letter BCVA gain from baseline after 3 months continued to have less-than-five-letter BCVA gain from baseline after 3 years of ranibizumab administration.

Reasons to Change Therapy

In the first round of the survey, all panelists reported that they were somewhat or very likely to use treatment options in addition to anti-VEGF if monthly injections were too burdensome for the patient (ie, there was poor compliance with frequent injections). After discussion at the Delphi panel meeting, the majority of panelists (62.5%; five of eight) agreed that they typically would be likely to consider switching anti-VEGF treatment to other therapy if monthly injections are too burdensome. Panelists emphasized that to facilitate compliance, it is important to discuss with patients the importance of frequent injections to preserve vision.

The panelists agreed that persistent edema and lack of improvement in BCVA are important factors driving decisions to change therapy. In the first round of the survey, all panelists reported that they would be somewhat or very likely to incorporate additional treatment modalities beyond anti-VEGF if fluid was still present on the retina, and all but one of the panelists responded that they would be somewhat or very likely to consider switching or stopping anti-VEGF treatment in this scenario. Similarly, all panelists reported that they would be somewhat or very likely to incorporate additional treatment modalities beyond anti-VEGF if there was lack of anatomical improvement (eg, in retinal thickness). In the second round, consensus was reached regarding switching treatment, and 75% (six of eight) of panelists agreed that they typically would be likely to consider switching from anti-VEGF to another treatment modality if there was a lack of anatomical improvement. Consensus was reached in the first round of the survey with respect to the effect of lack of improvement in BCVA on treatment decisions. Most panelists (77.8%; seven of nine) reported that they would be very likely to incorporate additional treatment modalities in patients who had no improvement in BCVA with anti-VEGF therapy, and almost all panelists (88.9%; eight of nine) reported that they would be somewhat or very likely to switch or stop anti-VEGF treatment.

Most panelists (87.5%; seven of eight) also agreed that they typically would be likely to consider switching from anti-VEGF to another treatment modality in patients who have had a recent stroke or cardiovascular event.

The panelists were unable to reach consensus on the relative importance of treating the VEGF component of DME compared with the inflammatory component of DME. However, all panelists agreed that it is more important to treat the inflammatory component of DME than the VEGF component of DME after it has been established that the response to anti-VEGF therapy is suboptimal.

Treatment When the Response to Anti-VEGF Is Inadequate

The panelists agreed unanimously that they would be most likely to switch a patient who is an inadequate responder after three to six monthly injections of anti-VEGF agents to corticosteroid treatment. All panelists reported they are most likely to switch an anti-VEGF inadequate responder to DEX implant treatment, and their second most likely choice for corticosteroid therapy is intravitreal TA (Triescence; Alcon, Fort Worth, TX).

All panelists further agreed that laser photocoagulation should be used as an adjunct treatment in patients with center-involved DME, but should not
be considered a rescue treatment. Panelists agreed that the rescue treatment for patients with suboptimal anti-VEGF response is a corticosteroid.

**Role of Corticosteroids in the Treatment Paradigm**

Consensus was reached that intravitreal corticosteroid treatment is appropriate in multiple scenarios of DME (Table 2). Phakic as well as pseudophakic patients who have an inadequate response to anti-VEGF therapy can be candidates for corticosteroid treatment, and corticosteroid treatment can be used in patients with severe edema and those who have undergone vitrectomy. Corticosteroid treatment can also be considered in DME patients with co-existing glaucoma as long as IOP is controlled on one or two medications and the optic nerve is healthy. Several panelists indicated that patients who have had successful filtering surgery can be candidates for corticosteroid therapy as long as the cup-to-disc ratio does not exceed 0.8.

**Patient Monitoring**

Most panelists (77.8%; seven of nine) reported that their patients who are on anti-VEGF therapy are monitored monthly. There was no consensus regarding the frequency of monitoring for patients on corticosteroid-only therapy. Two panelists reported that they monitor patients monthly, four monitor patients at intervals of 6 to 8 weeks, and two monitor 1 month after the corticosteroid injection and 2 to 3 months afterward, depending on the IOP. During subsequent discussion, it was pointed out that these results indicate that the panelists typically monitor patients on corticosteroid-only therapy every 1 to 2 months. Patients who receive a sustained-release implant may be monitored at 4 to 6 weeks after their first corticosteroid injection, then subsequently at extended intervals not exceeding 3 months.

For patients receiving a combination of anti-VEGF and corticosteroid treatment, the frequency of monitoring is dependent on whether patients are new to or established on the combination treatment. Most panelists (75%; six of eight) agreed that patients who are new to combination therapy should be monitored every 1 to 2 months, and almost all panelists (87.5%; seven of eight) agreed that patients who are established on combination therapy should be monitored every 2 months.

**Choosing Among Corticosteroid Options**

All panelists agreed that they would prefer to use a corticosteroid approved by the FDA for DME treatment (DEX implant or FAc) when considering efficacy, safety, and duration of effect, and all panelists reported that they use an FDA-approved corticosteroid in most cases. In their comments on the first-round survey, panelists indicated that they usually treat patients with DEX implant and sometimes use the FAc implant after DEX implant treatment in patients who are not steroid responders, who have shown a good response to multiple DEX implants, and who need long-term treatment.

Some panelists reported that they occasionally use a nonapproved corticosteroid (TA) when lack of insurance coverage or cost is an issue.

**Management of the Side Effects of Corticosteroid Treatment**

All panelists agreed that side effects of corticosteroid treatment are monitored in conjunction with efficacy, and no additional office visits are scheduled to monitor for side effects, unless a problem is detected and requires follow-up. Panelists commented that side effects of cataract are manageable and side effects of increases in IOP are generally manageable. The panelists reached consensus on how they treat increased IOP in patients on corticosteroid therapy. For patients who have elevated IOP of 25 mm Hg or less, six panelists (75%) agreed that they would prescribe a single topical IOP-lowering medication, and for patients with IOP between 26 mm Hg and 30 mm Hg, almost all panelists (87.5%; seven of eight) agreed that they would prescribe a fixed-combination IOP-lowering eye drop. For patients with IOP higher than 30 mm Hg, all panelists agreed that they would prescribe a fixed-combination IOP-lowering eye drop or refer the patient to a glaucoma specialist, and most agreed that they would both prescribe the fixed combination and make the referral.

**DISCUSSION**

The introduction of anti-VEGF treatment has greatly improved visual outcomes in patients with DME, but a significant proportion of patients have an incomplete response to anti-VEGF treatment. Corticosteroids are a rational approach to the treatment of DME because inflammatory mediators and pathways in addition to VEGF appear to be involved in the development of DME. However, there has been limited practical guidance on when and how to use corticosteroids in the treatment regimen. The consensus recommendation of this panel is that corticosteroids be used in patients with an inadequate response to anti-VEGF treatment, and guidance is provided on how to identify patients who are inadequate responders to anti-VEGF, and when to progress to corticosteroid therapy.

The recommendation of the panel is that center-involved DME with some degree of decreased visual acuity should be treated promptly with anti-VEGF therapy. Most patients with DME respond well to
anti-VEGF treatment. Currently bevacizumab is used more frequently than ranibizumab or aflibercept for treatment of ophthalmic disease in clinical practice because of its lower cost. In the DRCR.net Protocol T study comparing these anti-VEGF agents in patients with DME, after 1 year of treatment, aflibercept was more effective than ranibizumab or bevacizumab in improving BCVA in patients with baseline BCVA worse than 20/40, whereas the anti-VEGF agents showed comparable efficacy in patients with baseline BCVA of 20/32 to 20/40. After 2 years of treatment, aflibercept and ranibizumab provided similar improvement in BCVA, and aflibercept continued to be more effective than bevacizumab in improving BCVA in patients with baseline BCVA worse than 20/40. Although the efficacy of switching among anti-VEGF therapies has not been well studied, favorable outcomes have been reported after patients with suboptimal response switched from bevacizumab to ranibizumab or from bevacizumab or ranibizumab to aflibercept. Therefore, if a patient has a poor early response to anti-VEGF, and the initial anti-VEGF agent used was not aflibercept because of considerations such as cost and reimbursement, the clinician may consider switching the patient to aflibercept. The consensus of the panel, however, is that whether or not there is a switch among anti-VEGF therapies, continued edema should be tolerated for no longer than 6 months.

There are three fundamental reasons why a patient with an inadequate response to anti-VEGF therapy typically should remain on anti-VEGF treatment for no longer than 6 months before proceeding to a corticosteroid. First, there is evidence that anti-VEGF treatment is most effective in early disease. In the RISE/RIDE registration studies of ranibizumab, patients in the initial sham group who crossed over to ranibizumab treatment at year 2 had less favorable outcomes after 12 months of ranibizumab treatment than patients in the initial ranibizumab groups, and patients with a longer duration of DME at baseline required more as-needed ranibizumab injections during the open-label study extension after year 3, suggesting that prompt treatment of shorter-term DME with ranibizumab results in better outcomes. Similarly, in the VIVID/VISTA registration studies of aflibercept, patients in the initial laser treatment group achieved a smaller gain in BCVA after receiving rescue aflibercept treatment compared with patients in the initial aflibercept treatment groups, suggesting that delaying aflibercept treatment results in poorer outcomes and that aflibercept treatment is more effective in shorter-term DME. Second, continuing anti-VEGF treatment when the early response to treatment is poor usually does not result in favorable outcomes. The EARLY study analysis of results from the DRCR.net Protocol I study showed that the majority of patients who had a less-than-five-letter gain in BCVA from baseline at week 12 (after three monthly ranibizumab injections) continued to have less-than-five-letter gains in BCVA from baseline at week 156 (after 3 years of monthly ranibizumab injections). Third, delaying effective treatment increases the risk of permanent vision loss, because chronicity of DME is associated with foveal atrophy and photoreceptor damage.

Members of the panel agreed that the balance of VEGF versus other inflammatory cytokines appears to be an important factor contributing to the different levels of anti-VEGF response observed in patients with DME. The importance of this balance goes hand-in-hand with the importance of the chronicity of DME in the variability observed in patient response to anti-VEGF treatment, because it is generally believed that DME is primarily mediated by VEGF in its early phase, whereas the involvement of other cytokines and inflammatory mechanisms becomes more important in chronic disease. Low-grade inflammation has been postulated to be responsible for the retinal damage that occurs in chronic DME.

It may be important to treat the inflammatory component of DME in patients who do not respond adequately to anti-VEGF treatment. Studies have demonstrated the effectiveness of corticosteroid treatment in long-standing and refractory DME. In the MEAD registration studies for DEX implant, the treatment effects of DEX implant relative to sham were similar in subgroups defined by the duration of DME at baseline: DEX implant had beneficial effects in longer-term (duration of more than 3 years) as well as short-term (less than 1 year in duration) DME. Furthermore, in the FAME registration studies for FAC, the percentage of patients with 15-letter or greater gains in BCVA from baseline was superior with FAC relative to sham only in the subgroup of patients with long-standing DME (duration of 3 years or longer), consistent with an important role of inflammatory pathways amenable to corticosteroid treatment in the pathophysiology of persistent DME.

The panel recommends that a patient who has a less than 50% reduction from baseline in the macular thickness after three to four monthly anti-VEGF injections, or whose BCVA has not improved to 20/40 after three to six monthly injections

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**Efficacy of Switching Among Anti-VEGF Therapies**

Although the efficacy of switching among anti-VEGF therapies has not been well studied, favorable outcomes have been reported after patients with suboptimal response switched from bevacizumab to ranibizumab, or from bevacizumab or ranibizumab to aflibercept. Therefore, if a patient has a poor early response to anti-VEGF, and the initial anti-VEGF agent used was not aflibercept because of considerations such as cost and reimbursement, the clinician may consider switching the patient to aflibercept. The consensus of the panel, however, is that whether or not there is a switch among anti-VEGF therapies, continued edema should be tolerated for no longer than 6 months.

**Chronicity of DME**

Chronicity of DME in the variability observed in patient response to anti-VEGF treatment, because it is generally believed that DME is primarily mediated by VEGF in its early phase, whereas the involvement of other cytokines and inflammatory mechanisms becomes more important in chronic disease. Low-grade inflammation has been postulated to be responsible for the retinal damage that occurs in chronic DME.

**Corticosteroid Treatment**

Studies have demonstrated the effectiveness of corticosteroid treatment in long-standing and refractory DME. In the MEAD registration studies for DEX implant, the treatment effects of DEX implant relative to sham were similar in subgroups defined by the duration of DME at baseline: DEX implant had beneficial effects in longer-term (duration of more than 3 years) as well as short-term (less than 1 year in duration) DME. Furthermore, in the FAME registration studies for FAC, the percentage of patients with 15-letter or greater gains in BCVA from baseline was superior with FAC relative to sham only in the subgroup of patients with long-standing DME (duration of 3 years or longer), consistent with an important role of inflammatory pathways amenable to corticosteroid treatment in the pathophysiology of persistent DME.

The panel recommends that a patient who has a less than 50% reduction from baseline in the macular thickness after three to four monthly anti-VEGF injections, or whose BCVA has not improved to 20/40 after three to six monthly injections...
because of edema, be switched to corticosteroid treatment. The definitions of inadequate response include a range in the number of anti-VEGF injections, because the decision of whether to change treatment should take into account the trajectory of the response. A patient with continual improvement in edema after three or four sequential injections typically would be re-treated with anti-VEGF, whereas a patient with no improvement in edema after three or four anti-VEGF injections typically would be switched to a corticosteroid.

The panelists recommend that patients on anti-VEGF therapy receive frequent (monthly) injections and have monthly assessments to evaluate the trajectory of the response to treatment and identify inadequate responders. However, they recognize that some practitioners may see patients monthly for anti-VEGF injections but wait until after three to four injections before doing a full examination and OCT, rather than doing full exams at every visit. With this approach, the decision of whether to continue anti-VEGF treatment or switch to a corticosteroid is still made 3 to 4 months after the initial anti-VEGF injection, consistent with the suggestion from the EARLY study that this is an appropriate timeframe for deciding whether to switch therapy, since BCVA outcomes at week 12 in the Protocol I study were predictive of long-term outcomes. Although this approach does not consider the trajectory of the treatment response, there are cost savings associated with fewer examinations, and there is little risk of overtreatment, since edema is unlikely to resolve after one to three anti-VEGF injections. The panelists also recognize that the frequency of anti-VEGF injections required can be burdensome for patients, but in the experience of the panelists, patients are likely to adhere to frequent injections if they are educated on the alternative of risk of permanent loss of vision. The consensus opinion of the panel is that frequent monitoring is also needed for patients who have switched to corticosteroid implant treatment, but the recommended interval between visits for these patients is longer (1 to 2 months) than that recommended for patients on anti-VEGF therapy.

The panel’s consensus choice of corticosteroid for treatment of DME in inadequate responders to anti-VEGF is DEX implant, primarily because DEX implant has a more favorable safety profile compared with FAc and intravitreal TA. The increases in IOP associated with intraocular corticosteroid use are less frequent, less severe, and more easily managed with DEX implant than with FAc or intravitreal TA. Accordingly, the FDA-approved indication for FAc in DME is limited to patients who have been demonstrated to have no clinically significant IOP response to a corticosteroid. Disadvantages of use of intravitreal TA include its lack of FDA approval for treatment of DME and the possible need for more frequent injections. DEX implant has been demonstrated to be effective in patients with previous vitrectomy, patients with previously treated DME, and patients with DME that has been demonstrated to be resistant to anti-VEGF treatment.

The primary role of corticosteroids in the treatment paradigm for DME is as alternative treatment after a suboptimal anti-VEGF response, but corticosteroids may also be considered for treatment in patients who discontinue anti-VEGF therapy because of systemic safety concerns. Although intravitreal anti-VEGF treatment is generally believed to be systemically safe, it has been difficult to determine whether anti-VEGF might increase the risk of stroke, arteriothrombotic events, or cardiovascular events because studies have been underpowered and patients with DME may be at increased risk of these events regardless of treatment. However, the majority of panelists agreed that they typically would likely consider a change in therapy if a patient being treated with anti-VEGF had a recent stroke or cardiovascular event. In a recent meta-analysis that pooled systemic safety data from patients treated with ranibizumab 0.5 mg or aflibercept in clinical studies, the risk of cerebrovascular accidents and vascular deaths was significantly higher in patients treated monthly for 2 years with anti-VEGF injections than in patients treated with sham, suggesting that frequent anti-VEGF injections over the long term may increase the risk of serious systemic adverse events.

There is a lack of evidence from clinical studies concerning some aspects of care in DME, such as the benefits of using combination therapy with an anti-VEGF agent and a corticosteroid. In their discussion at the Delphi meeting, panelists indicated that they generally use combination anti-VEGF and corticosteroid therapy only for patients with severe and persistent DME. Furthermore, based on their clinical experience, the panelists believe that a patient with a suboptimal response to anti-VEGF has better improvement in retinal drying if the patient is switched to a corticosteroid than if the patient is switched to a different anti-VEGF agent, but supporting data from clinical trials are lacking.

The clinically recommended treatment paradigm for DME presented here includes recommendations for the medical treatment of DME, and it was developed with the understanding that the recommen-
lications should be general and applicable in 80% of cases. The authors recognize that there are exceptions and that there is a need for individualized patient care, as well as a need for surgery in cases of epiretinal membrane or vitreomacular traction. Some patients will lose vision irretrievably even if the recommendations are followed. The recommendations are based on evidence from reported studies and the clinical experience of the panelists, and they may be modified when more data become available. It is anticipated that results of the ongoing DRCR.net Protocol U study (clinicaltrials.gov identifier: NCT01945866), comparing ranibizumab monotherapy to combination therapy with ranibizumab and DEX implant in patients with an incomplete response to three monthly injections of ranibizumab, may further help guide corticosteroid use in the treatment of DME.

REFERENCES

34. Shea AM, Curtis LH, Hammill BG, et al. Resource use and costs...


Appendix A
Draft Questions for DME Round 1 Delphi Survey [via SurveyMonkey]

Instructions: Thank you for your participation in the diabetic macular edema (DME) Delphi panel. In this survey, we will be asking you open and closed-ended questions about your experience with DME treatment scenarios. Your answers will remain anonymous, however the results of this survey will be summarized along with other panelists’ answers in order to inform our discussion during the Delphi meeting on [June 4th].

Section 1: Defining Treatment Response to Anti-VEGF Therapy

1. Do you classify DME patients into types before deciding on treatment options?
   a. Response options: Yes/No
   b. If Yes, how do you classify DME patients?
      i. [Open-ended]

2. What would you consider to be an adequate response to anti-VEGF therapy? Please describe in a few brief sentences.
   a. [Open-ended]

3. When would you consider someone an inadequate responder to anti-VEGF treatment?
   a. [Open-ended]
   b. Please fill in the blanks:
      i. After X injections failed to improve best-corrected visual acuity to 20/XX
      ii. After X injections failed to improve best-corrected visual acuity by X lines
      iii. After X injections, OCT-measured retinal thickness is equal to or above X µm
      iv. After X injections, OCT-measured retinal thickness has not improved by X% from baseline

4. How long are you prepared to tolerate persistent edema despite treatment with multiple anti-VEGF injections? Please explain.
   a. [Open ended]

5. What are the reason(s) for different levels of response to anti-VEGF therapy?
   a. [Open ended]

6. What do you consider an optimal response when treating DME with an anti-VEGF?
   a. [Open ended]

7. Does long-term presence of DME result in poorer outcomes? Please explain why.
   a. [Open ended]

8. Listed below are various scenarios for DME patients that are being considered for, or are on, anti-VEGF treatment. How likely are you to consider incorporating additional treatment modalities (eg, introducing steroid) based on each scenario?
   a. Monthly injection is too burdensome for patients (poor compliance by patients):
      i. Response options for a-f:
         1. Very likely to discontinue anti-VEGF treatment
            a. [please explain open-ended question after each response option]
         2. Somewhat likely to discontinue anti-VEGF treatment
         3. Somewhat unlikely to discontinue anti-VEGF treatment
         4. Very unlikely to discontinue anti-VEGF treatment
   b. Systemic considerations (patients with increased risk of stroke/cardiovascular events)
9. Listed below are various scenarios for DME patients that are being considered for or are on anti-VEGF treatment. How likely are you to consider switching or stopping treatment based on each scenario?
   a. Monthly injection is too burdensome for patients (poor compliance by patients):
      i. Response options for a-f:
         1. Very likely to discontinue anti-VEGF treatment
         a. [please explain open-ended question after each response option]
         2. Somewhat likely to discontinue anti-VEGF treatment
         3. Somewhat unlikely to discontinue anti-VEGF treatment
         4. Very unlikely to discontinue anti-VEGF treatment
   b. Systemic considerations (patients with increased risk of stroke/cardiovascular events)
   c. Lack of improvement in best corrected visual acuity
   d. Lack of anatomical improvement (central retinal thickness)
   e. Fluid still present on the retina
   f. Other (please specify):

10. How important is it to treat the inflammatory component of DME compared to the VEGF component? Please select one answer below:
    a. Response options:
       i. Inflammation most important to treat
       1. Please explain [open-ended] after each response option
       ii. Inflammation somewhat more important to treat
       iii. Inflammation and VEGF equally important to treat
       iv. VEGF somewhat more important to treat
       v. VEGF most important to treat

11. What would you typically do for a patient that does not respond optimally to anti-VEGF early in their treatment? Please choose all that apply:
    a. Continue anti-VEGF therapy with the same agent
       i. For how many injections? [1, 2, 3, etc.]
    b. Switch anti-VEGF therapy to a different agent within the anti-VEGF class
       i. Which anti-VEGF treatment would you typically start with?
          1. Intravitreal bevacizumab
          2. Intravitreal ranibizumab
          3. Intravitreal aflibercept
       ii. Which anti-VEGF treatment would you typically switch to?
          1. Intravitreal bevacizumab
          2. Intravitreal ranibizumab
          3. Intravitreal aflibercept
iii. For how many injections? [1, 2, 3, etc.]

c. Introduce a steroid
   i. How would you introduce the steroid? Please choose one:
      1. Monotherapy
      2. In combination with anti-VEGF agent
   ii. Which steroid would you typically introduce? Please rank in the order of steroid you would most likely use, to steroid you would least likely use [ranking exercise 1-4]
      1. Dexamethasone intravitreal implant (DEX)
      2. Fluocinolone acetonide implant (FA)
      3. Intravitreal triamcinolone acetonide
      4. Other:

d. Incorporate laser treatment
   i. How would you incorporate laser treatment? Please choose one.
      1. In combination with anti-VEGF agent
      2. In combination with steroid
      3. In isolation

Section 2: Steroid Treatment Options

12. Listed below are various DME patient scenarios. Please indicate how likely you would be to recommend steroid treatment for each type of patient listed:
   a. Persistent diabetic macular edema
      i. Response options for a-k:
         1. Definite candidate for steroid treatment
         2. Likely candidate for steroid treatment
         3. Unlikely candidate for steroid treatment
         4. Not a candidate for steroid treatment
   a. If 3 or 4 are chosen, please explain why [open ended]:
   b. Cases with severe edema
   c. Patients who do not respond optimally to anti-VEGF treatment after 3 injections
   d. Patients who do not respond optimally to anti-VEGF treatment after 6 injections
   e. Anti-VEGF suboptimal responders who are pseudophakic
   f. Anti-VEGF suboptimal responders who are phakic and older than 60 years of age
   g. Anti-VEGF suboptimal responders who are phakic and younger than 60 years of age
   h. Patients scheduled to undergo cataract surgery
   i. Patients resistant to laser photocoagulation
   j. Patients with a history of vitrectomy
   k. Patients with POAG well controlled on 1 glaucoma drop
   l. Patients with POAG well controlled on 2 glaucoma drops
   m. Patients who have had successful filtration surgery to control IOP
   n. Patients that cannot afford branded anti-VEGF treatment?
o. Other (please specify):
13. How frequently do you monitor subjects who are on anti-VEGF treatment?
   a. Monthly
   b. Every 2 months
   c. Every 3 months
   d. Other (please specify):

14. How frequently do you monitor subjects who are on combination anti-VEGF treatment and steroids?
   a. Monthly
   b. Every 2 months
   c. Every 3 months
   d. Other (please specify):

15. How frequently do you monitor subjects who are on steroid only treatment?
   a. Monthly
   b. Every 2 months
   c. Every 3 months
   d. Other (please specify):

16. What clinical observations occur after a DME patient has either switched treatments from anti-VEGF therapy to steroid therapy, or steroid therapy has been incorporated in addition to anti-VEGF therapy?
   a. [Open ended]

17. Considering your choice of steroids in the management of patients with DME:
   a. When would you use a FDA approved steroid? [Open ended]
   b. When would you use a non-approved steroid? [Open ended]
   c. Which would you prefer when thinking about each of the following items:
      i. Efficacy. Please choose from below:
         1. Prefer FDA-approved steroid
         2. Prefer non-approved steroid
      ii. Safety. Please choose from below:
         1. Prefer FDA-approved steroid
         2. Prefer non-approved steroid
      iii. Duration of effect. Please choose from below:
         1. Prefer FDA-approved steroid
         2. Prefer non-approved steroid
      iv. Cost/cost effectiveness. Please choose from below:
         1. Prefer FDA-approved steroid
         2. Prefer non-approved steroid

18. Which type of implant do you prefer to use, and why? If you use both, please select both options and describe the scenarios for using each type of implant:
   a. Short acting implant [please explain]
   b. Long acting implant [please explain]
### Section 3: Steroid Use and Side Effects

19. Approximately how frequently do you monitor patients for possible side effects of steroid use?
   - a. At first follow-up only
   - b. Once every month
   - c. Every 2 to 3 months after the first month from an injection
   - d. Once every 6 months
   - e. Once a year
   - f. Other (please specify):

20. To what extent are the side effects of steroid use manageable?
   - a. [open ended]

21. How do you treat an increase in intraocular pressure following steroid use?
   - a. [open ended]
   - b. Is the treatment for increased IOP effective?
     - i. [open ended]

22. How do you treat glaucoma following steroid use?
   - a. [open ended]
   - b. Is the treatment for glaucoma following steroid use effective?
     - i. [open ended]

DME = diabetic macular edema; VEGF = vascular endothelial growth factor; IOP = intraocular pressure; POAG = primary open-angle glaucoma; FDA = U.S. Food and Drug Administration
## Final Questions

1. How do you classify DME patients?
   - a. Center-involved or non-center-involved
   - b. Focal areas of leakage, peripheral non-perfusion, or diffuse leakage
   - c. Focal versus diffuse (level of diabetic retinopathy matters)
   - d. Do not classify DME patients
   - e. Other

2. Out of the following, which do you consider to be the most important factor determining an ideal response when treating DME with an anti-VEGF?
   - a. Resolution of edema
   - b. Improvement in VA
   - c. Improvement in OCT thickness
   - d. Other

3. Out of the following, which do you consider to be the second most important factor determining an ideal response when treating DME with an anti-VEGF?
   - a. Resolution of edema
   - b. Improvement in VA
   - c. Improvement in OCT thickness
   - d. Other

4. An inadequate responder to anti-VEGF treatment is determined when after monthly three to four injections, OCT-measured retinal thickness has not improved by what percent of excess thickness from baseline?
   - a. 50%
   - b. 33%

5. An inadequate responder to anti-VEGF treatment is determined after what number of injections failed to improve BCVA to 20/x attributable to edema? (Value of “x” be defined in the next question.)
   - a. One to three
   - b. Three to six
   - c. Six to 10
   - d. Other

6. An inadequate responder to anti-VEGF treatment is determined after three to six monthly injections failed to improve BCVA to 20/x attributable to edema, with “x” = what value?
   - a. 40
   - b. 20
   - c. 30

7. Do you use the number of lines of BCVA improvement in determining inadequate responders to anti-VEGF treatment?
   - a. Yes
   - b. No

8. How long are you prepared to tolerate persistent edema despite treatment with monthly anti-VEGF injections (including any type of anti-VEGF used)?
   - a. 3 months
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<th>Answer</th>
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<td>9. Out of the following, what are two key factors that contribute to the</td>
<td>two answers from below:</td>
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<td>different levels of anti-VEGF response?</td>
<td>a. Level of diabetic retinopathy</td>
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<td>b. Balance of VEGF versus other inflammatory cytokines</td>
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<td>c. Glycemic control (in diabetes)</td>
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<td>d. Previous laser treatments</td>
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<td>e. Chronicity of DME</td>
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<td>f. Other</td>
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<td>10. Out of the following, what is the most important factor that</td>
<td>contributes to the different levels of anti-VEGF response?</td>
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<td>contributes to the different levels of anti-VEGF response?</td>
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<td>f. Other</td>
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<td>11. If monthly injection is too burdensome for patients (eg, poor</td>
<td>compliance by patients), how would you typically proceed?</td>
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<td>compliance by patients), how would you typically proceed?</td>
<td>a. Likely to consider incorporating additional treatment modalities</td>
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<td>b. Likely to consider switching treatment modalities</td>
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<td>c. Likely to stop current treatment</td>
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<td>d. Likely to continue current treatment</td>
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<td>e. Provide better education to improve compliance</td>
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<td>f. Other</td>
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<td>12. Due to systemic considerations (eg, patients with recent stroke/</td>
<td>cardiovascular events), how would you typically proceed?</td>
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<td>cardiovascular events), how would you typically proceed?</td>
<td>a. Likely to consider incorporating additional treatment modalities</td>
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<td>e. Other</td>
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<td>13. If there is lack of improvement in best-corrected visual acuity,</td>
<td>how would you typically proceed?</td>
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<td>e. Other</td>
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14. If there is a lack of anatomical improvement (eg, central retinal thickness), how would you typically proceed?
   a. Likely to consider incorporating additional treatment modalities
   b. Likely to consider switching treatment
   c. Likely to stop current treatment
   d. Likely to continue current treatment
   e. Other

15. When is it important to treat the inflammation component of DME compared to the VEGF component?
   a. From the beginning
   b. After a suboptimal response to anti-VEGF therapy
   c. Never
   d. Always

16. What would you most likely do for a patient that does not respond optimally to anti-VEGF agents early (three to six monthly injections) in their treatment?
   a. Continue anti-VEGF therapy
   b. Switch anti-VEGF therapy to a different agent within the anti-VEGF class
   c. Switch to a steroid
   d. Add a steroid
   e. Incorporate laser treatment

17. Which steroid would you most typically introduce?
   a. Dexamethasone intravitreal implant
   b. Fluocinolone acetonide implant
   c. Intravitreal triamcinolone acetonide
   d. Kenalog
   e. Triescence

18. Which steroid would be your second most likely choice for initial steroid therapy?
   a. Dexamethasone intravitreal implant
   b. Fluocinolone acetonide implant
   c. PFTA compounding therapy
   d. Kenalog
   e. Triescence

19. In a patient being treated for DME, do you use a steroid to help to protect against edema from cataract surgery?
   a. Highly likely
   b. Somewhat likely
   c. Somewhat unlikely
   d. Highly unlikely

20. Do you agree that steroid is the most preferred rescue modality?
   a. Strongly agree
   b. Somewhat agree
   c. Somewhat disagree
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<th>Options</th>
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   b. Rescue  
   c. First line  
   d. Never |
| 22. Would you recommend steroid treatment for a patient with POAG and healthy nerve that is well controlled on two glaucoma drops? | a. Potential candidate  
   b. Not potential candidate |
   b. 6 to 8 weeks  
   c. Every 2 months  
   d. Every 3 months  
   e. 1 month after steroid and 2 to 3 months afterwards depending on IOP  
   f. Other |
| 24. How frequently should you monitor subjects who are new to combination anti-VEGF treatment and steroids? | a. Monthly  
   b. 1 to 2 months  
   c. 2 to 3 months depending on IOP  
   d. Other |
| 25. How frequently should you typically monitor subjects who are established on combination anti-VEGF treatment and steroids? | a. Monthly  
   b. Every 2 months  
   c. Every 3 months  
   d. Other |
| 26. After the first steroid injection, approximately how frequently do you monitor patients for possible side effects? | a. Every 2 to 3 months after the first month from an injection  
   b. Every 6 to 8 weeks  
   c. Every month for the first one to three injections, then just every 3 months  
   d. Other |
| 27. Do you do any additional screening for side effects after steroid use beyond efficacy monitoring? | a. Yes  
   b. No |
| 28. After a problem is detected, do you do any additional monitoring? | a. Yes  
   b. No |
29. How do you typically treat an increase in intraocular pressure (25 mm Hg or below)?
   a. Single agent
   b. Fixed combination
   c. Refer to glaucoma specialist
   d. Observe

30. How do you typically treat an increase in intraocular pressure (26 mm Hg to 30 mm Hg)?
   a. Single agent
   b. Fixed combination
   c. Refer to glaucoma specialist
   d. Observe

31. How do you typically treat an increase in intraocular pressure (above 30 mm Hg)?
   a. Single agent
   b. Fixed combination
   c. Refer to glaucoma specialist
   d. Fixed combination and refer to a glaucoma specialist

DME = diabetic macular edema; IOP = intraocular pressure; OCT = optical coherence tomography; PFTA = preservative-free triamcinolone acetonide; POAG = primary open-angle glaucoma; VA = visual acuity; VEGF = vascular endothelial growth factor