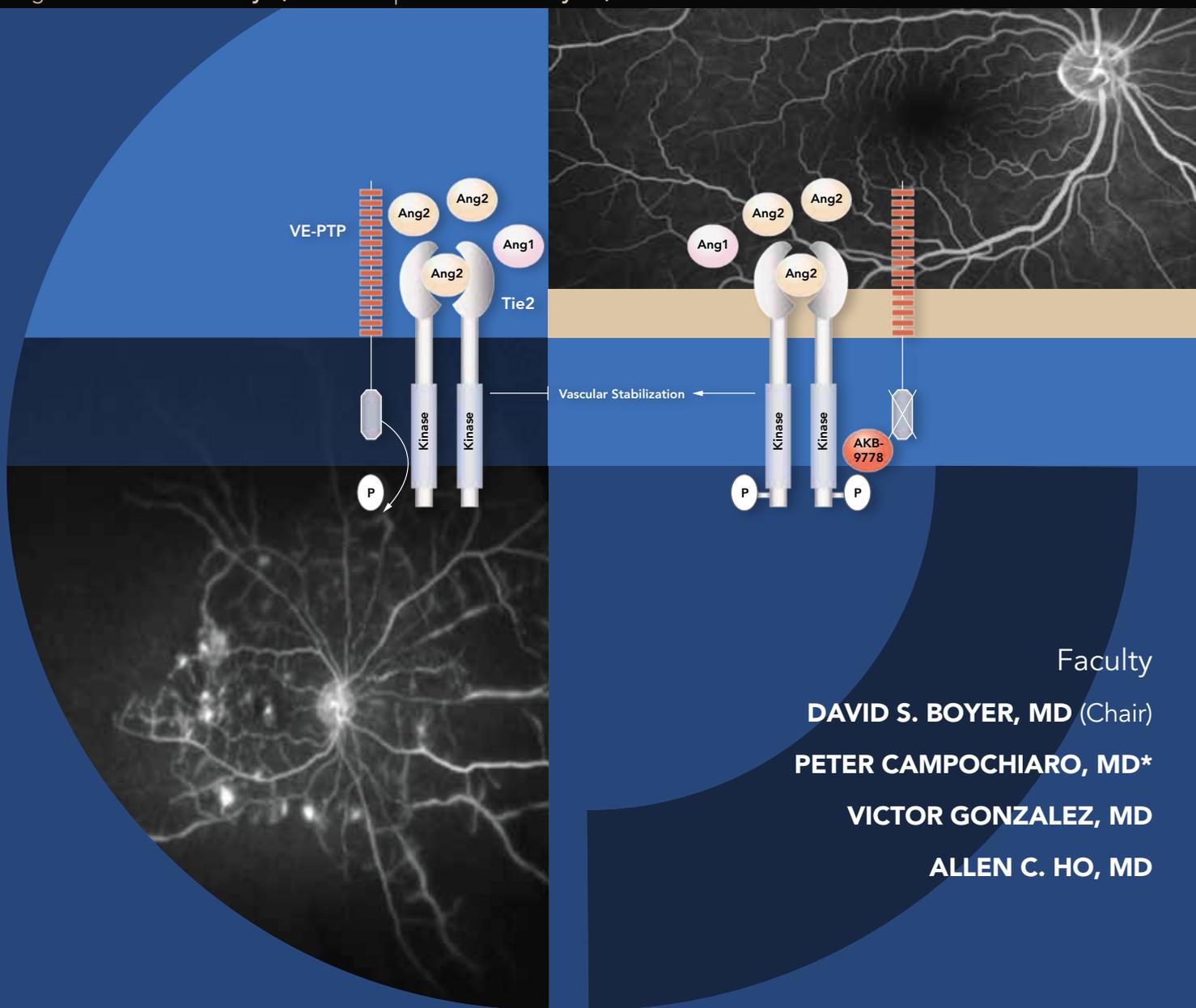


NEW FRONTIERS IN THE TREATMENT *of* Diabetic Macular Edema

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Purpose and Target Audience

Diabetic macular edema (DME) is the most common cause of visual impairment and vision loss in individuals with diabetic retinopathy. Treatment for DME has undergone a paradigm shift in the past few years, with intravitreal anti-vascular endothelial growth factor replacing laser therapy and steroid implants replacing traditional formulations. However, one-half to two-thirds of patients do not benefit from these treatments. New therapies are in development to meet the needs of these patients. The purpose of this monograph is to provide a review of current treatment options for DME and agents currently in clinical trials that might fill the unmet medical need in this disease. This activity is intended to educate retina specialists and other ophthalmologists.

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Learning Objectives

Upon completion of this activity, participants should be able to:

- Discuss current treatments for patients with DME
- Review the pathophysiology of DME
- Describe the mechanism behind Tie2 activation for treating DME
- Examine the potential role of Tie2 activation in the treatment of DME

Hardware & Software Requirements – Digital Edition

High-speed Internet connection (Broadband, Cable, or DSL)

Windows 2000 or higher

256 MBs or more of RAM

Internet Explorer 6.0 or higher

Windows Media Player 10.0 or higher

Adobe Acrobat 7.0 or higher

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*Participation by Dr Peter Campochiaro in this activity does not constitute or imply endorsement by The Johns Hopkins University, The Johns Hopkins Hospital, or The Johns Hopkins Health System.

INTRODUCTION

The management of diabetic macular edema (DME) has been greatly improved by the shift from laser therapy to inhibition of vascular endothelial growth factor (VEGF) and suppression of inflammation. Multiple anti-VEGF agents have been shown in numerous clinical trials to produce rapid and substantial improvements in vision that persist over years. More recently, novel sustained-release steroid delivery systems also have been approved for the treatment of DME via suppression of inflammation. With the entry of these new treatment options, clinical practice patterns are changing. Despite progress, many patients do not respond to newer therapies and some patients have suboptimal responses. The goals of this monograph are to summarize the state of the art in DME therapy, provide guidance on the appropriate selection of therapy, and to preview the pipeline of innovative therapies in development to address unmet medical need for patients with DME. Clinical scenarios will be used to tie the discussion to clinical practice.

CASE STUDY, Part 1

Mr Williams, a 58-year-old factory worker with long-standing type 2 diabetes, presents with symptomatic decreased vision in the left eye. His visual acuity is 20/40 OD and 20/25 OS, with classic DME on clinical examination and optical coherence tomography (OCT) revealing central retinal thickness (CRT) of 325 μm (Figure 1).

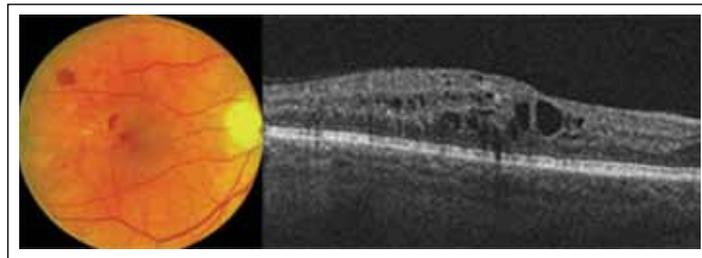


Figure 1: Diabetic macular edema in a patient with type 2 diabetes. Images Courtesy of David M. Brown, MD

ANTI-VEGF THERAPY: THE PREFERRED FIRST-LINE CHOICE FOR DIABETIC MACULAR EDEMA

Dr Boyer: This case represents a patient we often see in the clinic: a working-aged man with diabetes, some vision loss, and a 9-to-5 job.

Given the many therapeutic choices available for the treatment of DME—from laser to anti-VEGF therapy to steroids—what is the current treatment paradigm for such patients?

Dr Ho: First-line therapy for center-involved DME is an anti-VEGF therapy as established by numerous phase 3 clinical trials of both ranibizumab and aflibercept.¹⁻⁴ (See Sidebar 1: **Pharmacotherapy for Diabetic Macular Edema**, page 8.) Anti-VEGF therapy represents a significant improvement in efficacy over laser therapy and has a more favorable safety profile than steroid therapy.⁵ The benefits and safety of anti-VEGF therapy for DME were first demonstrated by the READ1/2 studies and have been confirmed by the DRCR.net (Diabetic Retinopathy Clinical

Research Network) in Protocols I and T.^{2,6-8} We also should be aware of other interventions that can affect DME, including glycemic control; maintaining normal blood pressure, lipids, and weight; eating a healthy diet; and engaging in regular exercise.⁹

Dr Boyer: The ranibizumab phase 3 studies involved monthly dosing for a period of at least 2 years, whereas the aflibercept studies used 5 monthly doses and then either monthly or every-other-month dosing for up to 12 months.³ These regimens impose a significant treatment burden on patients in terms of regular office visits and the injections themselves.

How do you typically manage treatment over the first few months?

Dr Campochiaro: I tend to give an anti-VEGF injection monthly for approximately 3 to 6 months and monitor response by OCT. If the edema resolves, I begin to extend the duration between visits and injections with the goal of keeping the macula as dry as possible. If a patient has residual edema after I extend for a period, then I will shorten the between-visit interval to find the optimal spacing that maintains a dry macula.

Dr Gonzalez: My approach is similar. I begin to extend after 3 or 4 injections if I see improvement.

CASE STUDY, Part 2

Mr Williams agrees to treatment with an anti-VEGF agent and has received 3 monthly injections of ranibizumab. By his fourth office visit, visual acuity has not improved and OCT reveals persistent fluid with no change in CRT.

Dr Boyer: *When and how do we decide if primary therapy is effective? What is the next step when it is ineffective?*

Dr Gonzalez: If, at 3 months, I see inadequate improvement in CRT, I will consider switching to a different anti-VEGF agent. I have seen patients who did not respond to ranibizumab, but then responded to aflibercept, and vice versa. My general practice is to switch agents after 3 injections if a 50% reduction in CRT has not been achieved.¹⁰

Dr Campochiaro: If I do not see significant improvement of visual acuity and edema after the first 3 treatments, I usually continue with the same agent monthly and often see a delayed response.

Dr Boyer: If I do not see significant response in either vision or OCT after 2 or 3 injections, I might try a different anti-VEGF agent on the third visit.

Dr Ho: Overall, visual acuity tended to improve fairly quickly in the anti-VEGF age-related macular degeneration (AMD) trials, but more gradually in the DME trials (Figure 2).^{3,4} Because of this, I tend to be a little bit more patient with anti-VEGF therapy in DME.

Dr Boyer: At the doses we administer, we are very likely neutralizing all the VEGF present in eyes with DME.

Why, then, do we see a slower response in DME compared with AMD? Why do some patients respond poorly or not at all?

Dr Campochiaro: There are likely multiple permeability factors, including VEGF, that contribute to edema in DME. In some patients, VEGF might not be the primary driver of disease, and this might explain why some patients have a delayed response to VEGF suppression whereas others respond minimally or not at all.

CASE STUDY, Part 3

After a suboptimal response to 3 monthly anti-VEGF injections, Mr Williams is then treated with an alternate anti-VEGF agent for an additional 3 months. Visual acuity remains 20/40, and CRT is unchanged at 375 μm .

WHEN TO MOVE BEYOND ANTI-VEGF THERAPY: STEROIDS FOR DIABETIC MACULAR EDEMA

Dr Boyer: The beneficial effect of steroids in some cases supports this idea of multiple factors contributing to the pathophysiology of DME. Clearly, there is an inflammatory component to the disease.

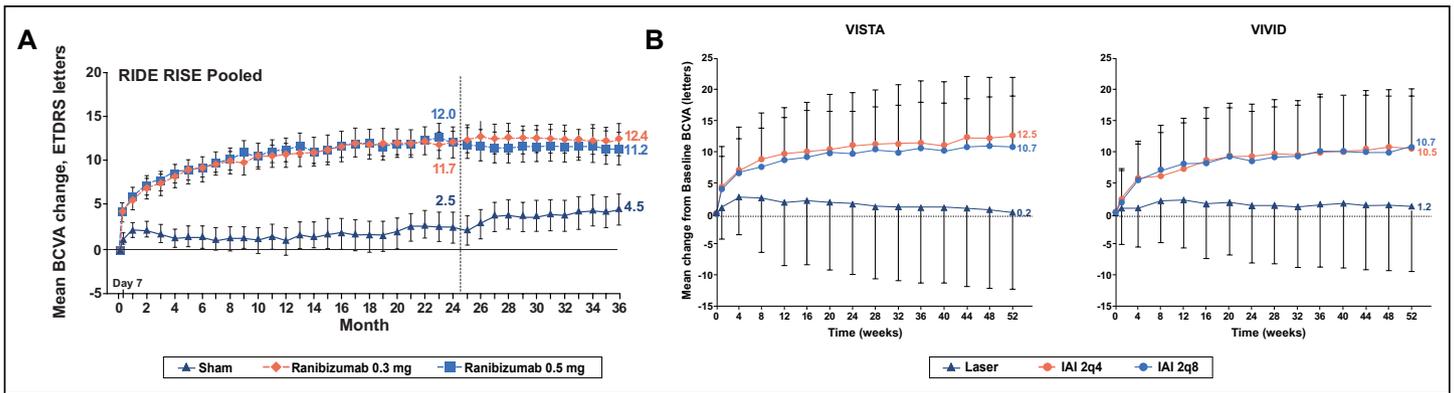
What is the current role of steroid therapy for DME?

Dr Ho: Certainly there are cases in which steroids can be very helpful. In comparison with anti-VEGF therapy, steroids for DME can often produce rapid and dramatic improvements (Figure 3).^{11,12} They have a less favorable safety profile than anti-VEGF agents, so it remains prudent to begin with anti-VEGF therapy. My approach, if I see no substantial benefit from the first anti-VEGF therapy at 3 months, is to switch to a second anti-VEGF agent. If, after 3 injections of the second agent, I see little improvement, I then consider intravitreal steroid therapy.

Dr Campochiaro: Patient characteristics also inform our choices. We are less inclined to use steroid therapy in phakic patients given its propensity for causing cataract formation. In addition, steroids can produce significant rises in intraocular pressure (IOP), so they should be used with caution in patients with known glaucoma or those who are known steroid responders. For pseudophakic patients with minimal response after 5 to 6 anti-VEGF injections, steroids are a very reasonable consideration.

Dr Boyer: There are currently 2 steroid products approved for DME: dexamethasone and fluocinolone (Figure 3).^{11,12} (See Sidebar 1: **Pharmacotherapy for Diabetic Macular Edema**, page 8.) The dexamethasone device can deliver sustained-release dexamethasone for 2 to 6 months, whereas the fluocinolone implant delivers sustained-release fluocinolone acetonide for up to 36 months. In addition, intravitreal triamcinolone is used off-label for this indication.

What is the panel's experience with these products, and how are they optimally utilized for DME?



BCVA=best corrected visual acuity; ETDRS=Early Treatment Diabetic Retinopathy Study; IAI=intravitreal aflibercept injection.

Figure 2. Phase 3 results of [A] RISE/RIDE³ ranibizumab and [B] VIVID/VISTA⁴ aflibercept studies in DME. Note the gradual improvement of visual acuity over time.

Dr Campochiaro: We do not have head-to-head studies comparing these steroid formulations for DME, so the relative-efficacy issue is difficult to address. In a patient with DME who has not responded well to anti-VEGF therapy, I will treat with the dexamethasone implant. I then follow the patient to see if we get a response and also to see how long it lasts. In my experience, the response is usually quite rapid and lasts for approximately 3 months. If I observe at least 3 months of control, I will repeat the dexamethasone. There are no published data on repeat injections, but in my personal experience, response to a second or third injection of a dexamethasone implant is similar to that after the first injection. If there is not complete resolution of edema 2 months after a dexamethasone implant, I may also re-treat with anti-VEGF therapy to see if it is more effective once the steroids have reduced the inflammatory component of the disease. If the patient responds well to dexamethasone, I will repeat it once or twice more before considering the longer-acting fluocinolone acetonide implant. I do not start with a fluocinolone acetonide implant because it has a higher risk for IOP elevation and remains bioactive longer, so that the risk for increased IOP that cannot be controlled with medical management is higher unless you have prior knowledge that the patient is not at risk, according to response to shorter-acting steroids.

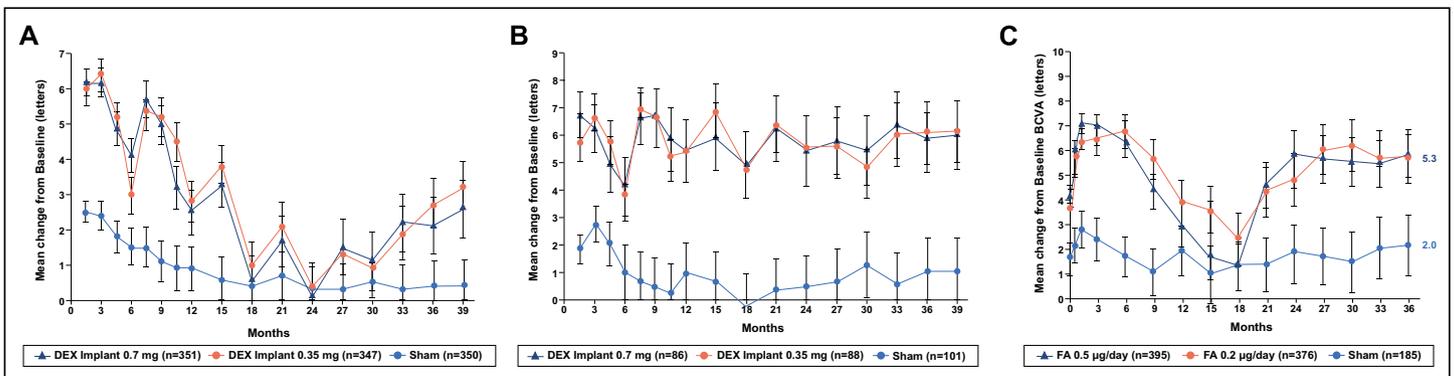
Dr Gonzalez: In some patients, dexamethasone works for a long time. If I can get 6 or 8 months of disease

control from dexamethasone, I will stay the course and repeat the dexamethasone implant injections. If, however, dexamethasone provides only 2 or 3 months of control before the edema returns, fluocinolone is an entirely appropriate therapy in this setting.

Dr Boyer: There is consensus among the panel members that dexamethasone is an appropriate first step in steroid therapy for DME, and that fluocinolone is useful for patients who tolerate steroids but get only short-term benefit from dexamethasone. We previously discussed that switching between anti-VEGF agents is a reasonable approach based on observations of differential response that is likely due to differences in pathophysiology.

Should we expect to see differential efficacy or safety responses to steroids such as triamcinolone, dexamethasone, and fluocinolone?

Dr Campochiaro: Both the dexamethasone implant and the fluocinolone implant can cause increased IOP, but because the dexamethasone is gone by 3 months after injection, if high IOP occurs, it can almost always be managed medically, whereas the long duration of fluocinolone release can result in high IOP that cannot be controlled with medical management. In the MEAD dexamethasone implant trial, approximately 40% of patients required IOP-lowering medications and only 2 patients required filtering surgery for steroid-related IOP



BCVA=best corrected visual acuity; DEX=dexamethasone; FA=fluocinolone acetonide.

Figure 3. Visual acuity changes in phase 3 DME studies of the dexamethasone implant in [A] phakic and [B] pseudophakic eyes; and [C] fluocinolone implants (includes phakic [65%] and pseudophakic eyes [35%]). Both steroid-eluting devices were associated with visual declines in phakic eyes due to cataract formation after approximately 18 to 24 months of treatment.^{11,12}

elevation.¹¹ Likewise, in the FAME fluocinolone implant trial, 38% of patients required IOP-lowering medications and 5% required filtering surgery.¹²

Although you cannot compare results from different trials directly, these studies suggest that 40% of patients are at risk for increased IOP with either the dexamethasone implant or the fluocinolone implant, but because the dexamethasone is released for only 3 months, the increase in IOP can almost always be controlled by medical management, whereas the persistent release of fluocinolone for 36 months results in glaucoma that cannot be controlled by medical management in 5% of patients. Further support of this observation comes from the fluocinolone trials for noninfectious posterior uveitis.^{13,14} These trials evaluated sewn-in fluocinolone implants that released a higher dose (0.59-2.1 $\mu\text{m/d}$) than that released from the injected fluocinolone implants (0.2-0.5 $\mu\text{m/d}$). The majority (75%) of eyes required IOP-lowering medications and 37% required filtering surgery. It is reasonable to assume that we can identify the majority of patients who will have uncontrolled glaucoma after a fluocinolone implant by first giving 2 or 3 injections of a dexamethasone implant. If a patient does not experience a substantial increase in IOP after 2 sequential injections of a dexamethasone implant 3 months apart, then he or she is unlikely to have severe glaucoma after injection of a fluocinolone implant.

CASE STUDY, Part 4

Despite treatment with the dexamethasone implant, repeated twice at 3-month intervals, Mr Williams has shown little to no improvement. His visual acuity has, in fact, gotten worse. In hopes of a response to a more potent steroid, the fluocinolone implant is injected, again with minimal effect. Now, more than a year after his first visit, his acuity is 20/60 and his CRT has increased to 410 μm . He feels that his vision loss is affecting his performance at work, and he is growing both frustrated and apprehensive about the future.

IS THERE A ROLE FOR SURGERY IN DIABETIC MACULAR EDEMA MANAGEMENT?

Dr Boyer: Are there any patients for whom you would consider surgery for DME?

Dr Ho: Surgery can be effective in select cases, but with our expanding drug options, it is becoming less commonly performed for DME. The ideal surgical candidate would have an eye(s) with evident mechanical forces contributing to the edema, such as vitreomacular traction or an epiretinal membrane.^{15,16} Historically, we have considered surgery to be a last resort in these patients and that is even more true in an era with expanding pharmacologic options for DME.

Dr Campochiaro: If there is vitreomacular traction or epiretinal membrane, as Dr Ho mentioned, then it is worthwhile to consider surgery. In patients with uncomplicated DME, there is no value in vitrectomy and removal of the internal limiting membrane.

CASE STUDY, Part 5

After a frank discussion with Mr Williams about the refractory nature of his disease, surgical options are

discussed. Reluctantly, he and his doctor agree to proceed with vitrectomy and internal limiting membrane peeling. Three months later, his visual acuity has improved slightly to 20/50 and his OCT reveals CRT of 350 μm .

UNMET MEDICAL NEED IN DIABETIC MACULAR EDEMA THERAPY: DESIGNING THE IDEAL DRUG

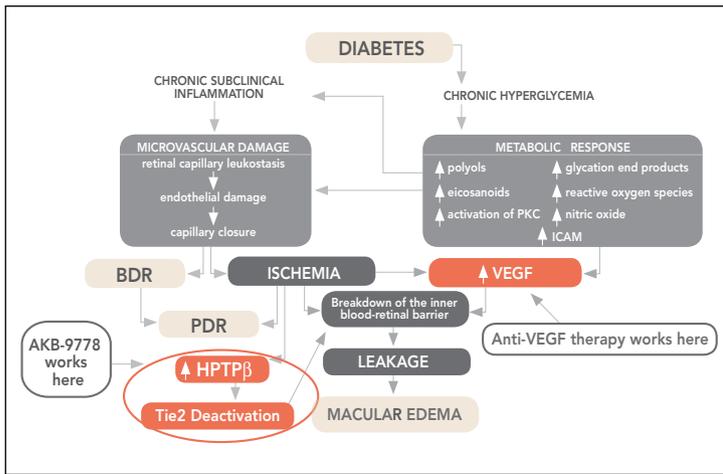
Dr Boyer: Throughout our discussion, we have identified a number of examples of unmet medical need in the DME therapeutic arena. Anti-VEGF therapy has had a tremendous effect on DME outcomes, but not every patient derives benefit. In the RISE/RIDE and VIVID/VISTA trials, approximately 2 of 3 patients gained fewer than 3 lines of vision.^{3,4} New steroid formulations offer a second line of treatment when anti-VEGF therapy alone is inadequate, but steroids come with additional safety issues. There remains a significant need for further innovation in DME therapy.

What are some features of a novel DME therapy that would be valuable for patients?

Dr Gonzalez: An ideal treatment would address the current burden of therapy. Patients with diabetes often have other serious comorbidities and may be visiting their various doctors as frequently as once or twice a month. When they develop DME, our current first-line therapy adds up to an additional 12 visits per year. This frequency of visits, testing, and treatment is expensive and time consuming. It is difficult for some patients, and impossible for others. I hope that our next treatment option has a substantially longer duration of action to minimize the frequency of visits. Ideally, we also could identify a route of administration other than via intravitreal injection to make the treatments less unpleasant for patients.

Dr Ho: Duration is an important consideration. Do we need another anti-VEGF agent? If it is longer-acting or has greater efficacy to improve vision in the two-thirds of patients who currently do not gain 3 or more lines with existing anti-VEGF agents, then yes. But VEGF is only one of the molecular signals driving the DME process. There would be great value in developing a therapy to target a different proangiogenesis factor or mediator of inflammation. This novel approach might be more effective and more durable than current anti-VEGF therapies or it might be complementary to anti-VEGF therapy, either in combination or in sequence.

Dr Campochiaro: A drug that works via a new pathway is attractive for an additional reason. One limitation of anti-VEGF therapy is that there are systemic safety concerns. We cannot safely administer anti-VEGF therapy systemically for DME—it has to be delivered by intravitreal injection. As Dr Gonzalez suggested, there would be great value in a drug that could be administered without the need for injections into the eye. If we had a drug that could be administered systemically, we could simultaneously treat both eyes of patients with bilateral disease. In patients with systemic microvascular disease related to diabetes, such a drug may have added benefits as well. If, as with insulin, the drug could be self-administered by patients, that would be ideal in reducing office visits and treatment burden.



BDR=background diabetic retinopathy; HPTP=human protein tyrosine phosphatase; ICAM=intercellular adhesion molecule; PDR=peripheral diabetic retinopathy; PKC=protein kinase C; VEGF=vascular endothelial growth factor.

Figure 4. Overview of the pathophysiology of DME.

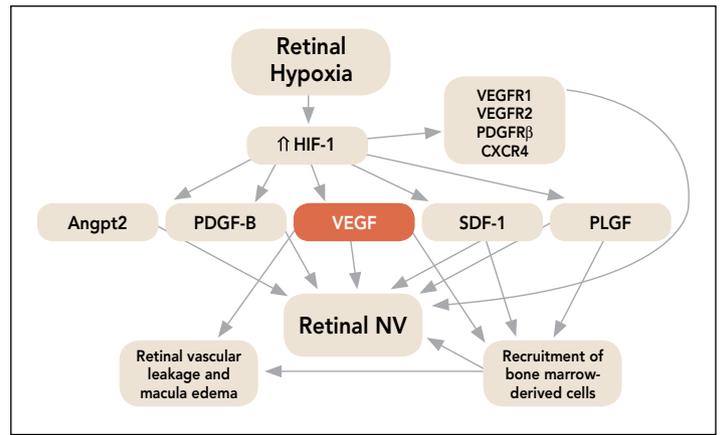
THE FUTURE OF DIABETIC MACULAR EDEMA THERAPY

Dr Boyer: Many of the features and attributes we have discussed as ideal for future DME therapy may soon become realities. Many novel therapeutics are in development for the treatment of DME. (See Sidebar 2: **Agents in Clinical Trials for Diabetic Macular Edema**, page 9.) These agents target familiar components of DME pathophysiology, such as angiogenesis, inflammation, and stabilization of the blood-retinal barrier (Figure 4). The routes of administration can also vary from local to systemic: oral, subcutaneous, and intravenous. Most are in early phase 1 and 2 testing, and little data have emerged to date. One promising future therapy targets a little-known proangiogenesis pathway: the Tie2 pathway. Two drugs are currently under development to target this pathway.

Dr Campochiaro, you have significant experience studying this pathway. Please give us an overview of the Tie2 pathway and its relevance to DME.

Dr Campochiaro: Tie2 is a tyrosine kinase receptor on endothelial cells that remains activated under normal circumstances because of constitutive release of its agonist, angiopoietin 1 (Ang1). This activation of Tie2 keeps blood vessels in a quiescent state in which they are unresponsive to VEGF and other proangiogenic/permeability factors. When the retina becomes hypoxic, there is release of angiopoietin 2 (Ang2), which binds to Tie2 and blocks its activation. Hypoxia also increases levels of vascular endothelial-protein tyrosine phosphatase (VE-PTP), which dephosphorylates Tie2. Therefore, Ang2 and VE-PTP work together to inactivate Tie2, making endothelial cells more responsive to a variety of other factors, including VEGF, that are increased by hypoxia, which promotes vascular leakage and angiogenesis (Figure 5).¹⁷ Inhibitors of both Ang2 and VE-PTP are in development—blocking either one of these should allow Ang1 to activate Tie2 and stabilize blood vessels.

The inhibitor of VE-PTP, AKB-9778 (See Sidebar 3: **Angiopoietin/Tie2 Pathway: Early Clinical Development**, page 9), has completed phase 1 safety evaluation, with



Angpt2=angiopoietin 2; CXCR=C-X-C chemokine receptor; HIF=hypoxia-inducible factor; NV=neovascularization; PDGF-B=platelet-derived growth factor B-chain; PDGFR=platelet-derived growth factor receptor; PLGF=placental growth factor; SDF-1=stromal cell-derived factor; VEGF=vascular endothelial growth factor.

Figure 5. Molecular pathogenesis of retinal neovascularization (NV).¹⁷ Reprinted with kind permission from Springer Science and Business Media.

promising exploratory efficacy results, and is now in phase 2 efficacy and safety testing. The only systemic safety signal in the small (24-patient) phase 1 trial was a reduction in blood pressure that was asymptomatic for most patients but led to a vasovagal effect in 2 subjects.¹⁸ This agent is delivered subcutaneously twice daily, and visual and anatomic benefits were not instantaneous, but occurred gradually over the course of the 28-day study.

Dr Boyer: Most of the patients enrolled in this study (71%) had shown suboptimal response to previous anti-VEGF treatment. This suggests that AKB-9778 may be helpful for the substantial number of patients for whom anti-VEGF therapy is inadequate.

Dr Campochiaro: The effect of this drug lasts much longer than its pharmacokinetic half-life would suggest, but we do not know the exact duration of effect. Furthermore, an advantage of giving systemic treatment in these patients is that it can potentially affect other microvascular beds. There may be benefit in terms of kidney disease as well as overall cardiac disease.

SUMMARY

Dr Boyer: We have summarized the current status and previewed the future of DME therapy. Anti-VEGF therapy has revolutionized our approach to this disease, is effective, and is generally well tolerated even though it is associated with a high treatment burden. New steroid formulations offer a potent second line of defense in eyes that respond inadequately to anti-VEGF therapy, but these drugs come with added risks, including cataract formation and glaucoma. In light of these therapeutic advances, surgery plays a minimal role in the routine management of DME. There remains an unmet medical need for further innovation in DME therapy. We would find value in an anti-VEGF drug with a longer duration of response or with greater efficacy. We are optimistic regarding the early-phase development of drugs targeting both familiar and novel pathways that allow alternate routes of administration—including the potential for patient self-administration—and that may be complementary to existing therapies.

Sidebar 1: Pharmacotherapy for Diabetic Macular Edema

The paradigm for the treatment of DME has shifted from laser therapy to pharmaceuticals. This major shift in treatment has been driven by expanding appreciation for the multifactorial pathophysiology of DME, with significant contributions from chronic inflammation and elevated VEGF levels (Figure 4). In the past 3 years, 4 drugs from 2 distinct classes have gained approval from the US Food and Drug Administration for the treatment of DME. An additional anti-VEGF agent and an additional steroid are also widely used off-label for the treatment of DME. All are delivered via intravitreal injection.

Anti-VEGF Agents

Anti-VEGF therapy was first shown to be effective and safe for the treatment of DME in the Protocol I study conducted by DRCR.net.² Additional phase 3 studies have further supported the benefits of ranibizumab and aflibercept for DME (Table 1).^{3,4,6,11,12} Most recently, the DRCRNet Protocol T study compared the clinical effectiveness of aflibercept, bevacizumab, and ranibizumab in the treatment of DME.⁶ All 3 agents were effective at improving vision in patients with DME. The primary end point, change in visual acuity at 1 year adjusted from baseline, was statistically better for aflibercept. However, the mean change of 2.1 letters was not considered clinically meaningful. Aflibercept appeared to be a better drying agent compared with other anti-VEGF agents. Safety end points, including endophthalmitis, inflammation, and hypertension, were similar among all 3 agents. Some secondary study end points have not yet been reported, including the 2-year follow-up and comparative efficacy of these anti-VEGF agents in regression of diabetic retinopathy. Additional data included in the initial Protocol T publication that were not part of the study design included a subset analysis by visual acuity (better vs worse) and cardiac/vascular disorders. Both analyses showed statistical significance, but the difference in cardiovascular disorders was discounted by the authors. The clinical relevance and nuances of the Protocol T results published to date are currently being debated.

Despite excellent efficacy and safety, anti-VEGF therapy does have limitations. Approximately 60% to 70% of patients in the phase 3 trials gained fewer than 3 lines of visual acuity with 8 to 12 injections a year for up to 3 years. In addition to the high injection burden—and the cumulative risk of injection-related adverse events such as endophthalmitis—there is a high burden of office visits associated with anti-VEGF therapy. Approaches such as treat-and-extend have been applied to anti-VEGF therapy for DME as a means of reducing both the visit and injection burdens. However, there remains little consensus on the optimal frequency of injections/visits, or what constitutes treatment failure. There is equally little consensus on the appropriate number of monthly treatments that should be administered before treatment failure is declared and alternate therapy is used.

Table 1. Efficacy and Safety Results of Phase 3 Trials of Agents Approved for the Treatment of DME

Trial	Treatments ^a	Primary End Point	Efficacy	Safety
RISE/ RIDE³	Ranibizumab 0.3 mg vs sham every mo	Gain >3 lines of vision at 24 mo	Ranibizumab: 34%-45% Sham: 12%-18%	Vitreous hemorrhage most common and occurred more in sham group; no systemic safety issues
VIVID/ VISTA⁴	Aflibercept 2 mg/ mo × 5 and then every 2 mo vs laser every 3 mo (at most)	Gain >3 lines of vision at 12 mo	Aflibercept: 31%-33% Laser: 8%-9%	Subconjunctival hemorrhage most common (25% for aflibercept vs 17% for laser); no systemic safety issues
Protocol T⁶	Aflibercept 2 mg/mo, ranibizumab 0.3 mg/mo, or bevacizumab 1.25 mg/mo until stable disease with 20/20 vision and no macular edema on OCT	Mean change in visual acuity at 12 mo	Aflibercept: 13.3 letters Ranibizumab: 11.2 letters Bevacizumab: 9.7 letters	No differences in adverse- event profiles—ocular or systemic
MEAD¹¹	Dexamethasone 0.7 mg implant every 6 mo (at most) vs sham	Gain >3 lines of vision at 36 mo	Dexa- methasone: 22% Sham: 12%	Cataract in 68% of dexamethasone vs 20% of sham eyes; 2 implant eyes and no sham eyes required filtering surgery
FAME¹²	Fluocinolone 0.2 mg/d implant every 12 mo (at most) vs sham	Gain >3 lines of vision at 36 mo	Fluocinolone: 29% Sham: 19%	Cataract surgery in 80% of implant eyes and in 27% of sham eyes; filtering surgery in 5% of implant eyes and in 0.5% of sham eyes

OCT=optical coherence tomography.
^aApproved dose and control arms, only.

Steroids

Intravitreal triamcinolone has been used to treat DME since before the development of anti-VEGF therapy. More recently, 2 sustained-release steroid implants have been developed to extend the duration of action and to minimize the frequency of re-treatment (Table 1).^{3,4,6,11,12} The dexamethasone implant's duration of response is up to 6 months, whereas the fluocinolone implant lasts up to 36 months. Steroids are considered a second-line therapy for DME, however, based largely on their side-effect profile. Cataract development is common after treatment with either implant. Overall, 60% of dexamethasone-implanted phakic eyes and 80% of fluocinolone-implanted phakic eyes underwent cataract surgery by the end of the respective phase 3 trials. Elevated IOP also is a well-known side effect of steroid therapy. In the same trials, 42% of dexamethasone-implanted eyes required IOP-lowering medications, but <1% required a filtering procedure; the corresponding proportions for fluocinolone-implanted eyes were 38% and 5%, respectively.

Sidebar 2: Agents in Clinical Trials for Diabetic Macular Edema

In addition to AKB-9778, several other agents are in early-phase investigations for the treatment of DME (Table 2).¹⁹⁻²⁴ These potential therapies represent targeting of a variety of pathways known to play a role in the complex pathophysiology of DME and include novel anti-VEGF strategies, anti-inflammatory agents, and molecules that support the extracellular matrix and cell-cell adhesion to promote the health of the blood-retinal barrier. Routes of administration for these agents vary from intravitreal to oral to systemic dosing. These early-phase trials are designed to assess safety and begin to characterize efficacy, and most are designed as single-drug comparisons to established anti-VEGF therapy.

Table 2. Agents Under Investigation for DME Therapy

Drug/Pathway	Target	Mechanism of Action	Route of Administration	Investigational Status
AKB-9778 ¹⁹	VE-PTP	Angiogenesis	Subcutaneous	Randomized phase 2 in combination with ranibizumab
PF-04634817 ^{20*}	Chemokine receptor 2/5	Inflammation	Oral	Randomized phase 2 vs ranibizumab
Abicipar pegol ^{21†}	VEGF	Angiogenesis	Intravitreal	Randomized phase 2 vs ranibizumab
ASP8232 ^{22†}	Vascular adhesion protein-1 (VAP1)	Angiogenesis	Oral	Randomized phase 2 in combination with ranibizumab
Nesvacumab ²³	Angiopoietin 2 (Tie2 antagonist)	Angiogenesis	Intravitreal	Phase 1 in combination with aflibercept
Teprotumumab ²⁴	Insulin-like growth factor receptor	Angiogenesis	Intravenous	Phase 1

VEGF=vascular endothelial growth factor; VE-PTP=vascular endothelial protein tyrosine phosphatase.

* Also in clinical trials for diabetic nephropathy.

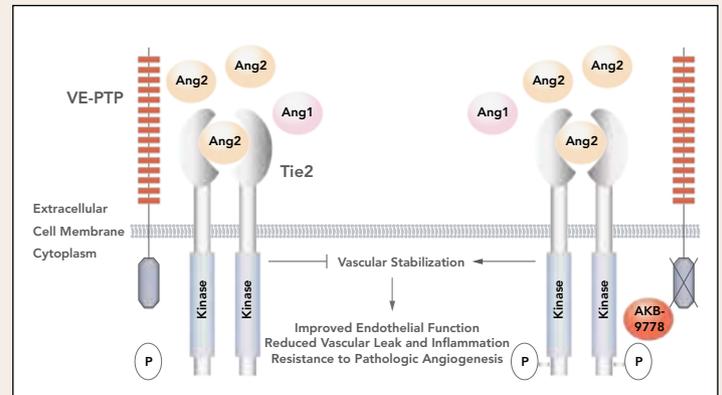
† Also in clinical trials for age-related macular edema.

Sidebar 3: Angiopoietin/TIE2 Pathway: Early Clinical Development

Anti-vascular endothelial growth factor therapy provides a safe and effective approach to the management of DME. But not all patients with DME have favorable responses to these agents. Furthermore, the burden of monthly therapy—while generally well accepted by older patients with AMD—can be prohibitive in younger people with DME who typically are active in the workforce. In addition, anti-VEGF therapy requires ongoing intravitreal injections; injection-related risks are rare, but the cumulative risk grows with years of monthly therapy. There remains unmet need for novel DME therapies that address these limitations of anti-VEGF therapy.

VEGF is not the only signaling protein to be upregulated in response to hypoxia, and the VEGF receptor is not the only receptor to mediate hypoxic response (Figure 5).¹⁷ In recent years, there has been growing interest and increasing research into an alternate pathway linking ischemia to neovascularization and vascular permeability: the Tie2 pathway (Figure 4).

The Tie2 receptor is similar to the VEGF receptor and has 2 important ligands. Ang 1 is a Tie2 receptor agonist and Ang 2 is a Tie2 receptor antagonist. When Ang1 binds to Tie2, endothelial cell survival is promoted and responsiveness to VEGF is dampened. In contrast, when Ang2 is elevated and binds antagonistically to Tie2, this blocks the vessel-stabilizing effect of Tie2 and leads to greater responsiveness of endothelial cells to VEGF (Figure 6).



Ang=angiopoietin; P=phosphate; VE-PTP=vascular endothelial protein tyrosine phosphatase.

Figure 6. Role of the Ang2/Tie2 pathway in vascular stabilization.

Animal models support a role for this pathway in ocular ischemic disease. In a mouse model of oxygen-induced ischemic retinopathy, normal mice will develop moderate neovascularization. Mice genetically engineered to overexpress Ang2 get a greater amount of neovascularization, whereas mice engineered to overexpress Ang1 have little neovascularization. Taking it a step further, mice engineered to overexpress VEGF get severe leakage and exudative retinal detachments, whereas the same mice engineered to overexpress both VEGF and Ang1 demonstrate no leakage or detachment.

Tie2 is also regulated by VE-PTP. As are VEGF and Ang2, VE-PTP is upregulated by hypoxia and promotes leakage and neovascularization. Inhibition of VE-PTP could be beneficial in hypoxic eyes.

AKB-9778 is an investigational compound designed to inhibit VE-PTP and thus activate the Tie2 pathway, even in the presence of high levels of Ang2. The drug is delivered by subcutaneous injection and achieves excellent intraocular concentration. AKB-9778 was evaluated in a phase 1b/2a clinical trial in which 24 patients with DME were treated with twice-daily subcutaneous injections of 5 mg, 15 mg, 22.5 mg, or 30 mg of AKB-9778 for 28 days.¹⁸ All doses were well tolerated, with no injection-site issues or systemic laboratory abnormalities. Some transient hemodynamic effects were observed, including asymptomatic reduction in blood pressure and 2 vasovagal episodes within 2 hours of dosing (1 each in the 2 high-dose groups), prompting withdrawal from the study. This was primarily a safety and dose determination study, but efficacy end points were evaluated in an exploratory fashion. Overall, 13 of the 18 participants receiving ≥ 15 -mg doses gained ≥ 5

ETDRS (Early Treatment of Diabetic Retinopathy Study) letters of visual acuity, including 1 who gained between 10 and 15 letters and 2 who gained ≥ 15 letters. In these same 18 patients, central subfield thickness (CST) by OCT decreased by ≥ 100 μm in 5 patients and by 50 to 100 μm in 2 other patients, with a significant correlation between CST and visual acuity gains. A randomized phase 2 trial in patients with DME is under way comparing AKB-9778 vs ranibizumab vs combination therapy with both agents. The primary end point of this study is the mean change from baseline in CST measured by spectral-domain OCT, and its secondary end point is mean change from baseline in ETDRS visual acuity, both assessed at 3 months. If this trial demonstrates efficacy, testing of this drug may extend to other retinal and choroidal vascular diseases.

Trial Abbreviations Used

FAME Fingolimod-Associated Macular Edema

MEAD Macular Edema: Assessment of Implantable Dexamethasone in Diabetes

READ1/2 Prospective, randomized, interventional, multicenter clinical trials of long-term effects of ranibizumab for edema of the macula in diabetes 2

RIDE/RISE A study of ranibizumab injection in subjects with clinically significant macular edema with center involvement secondary to diabetes mellitus

VISTA/VIVID A study of intravitreal administration of aflibercept in patients with diabetic macular edema

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1. What is the preferred first-line treatment for center-involved DME?
 - a. Steroids
 - b. Laser
 - c. Anti-VEGF therapy
 - d. Anti-VEGF therapy + Laser
2. Which of the following results did the DRCR.net Protocol T study comparing the clinical effectiveness of aflibercept, bevacizumab, and ranibizumab in the treatment of DME show?
 - a. All 3 agents were statistically and clinically equivalent at improving vision
 - b. Aflibercept was more effective in eyes with poor vision than in eyes with good vision
 - c. Ranibizumab was more effective in pseudophakic eyes
 - d. The safety profiles of all 3 agents were similar
3. Which of the following is a consideration for monitoring response to therapy with anti-VEGF agents?
 - a. Recognizing that visual gains plateau more quickly in DME than they do in AMD
 - b. Combining anti-VEGF with laser if response is suboptimal after the first injection
 - c. Switching to another anti-VEGF therapy if response is suboptimal after 3 months
 - d. Monitoring for signs of cataract
4. Why do some cases of DME respond poorly to anti-VEGF therapy?
 - a. At the recommended doses, anti-VEGF agents might not neutralize 100% of VEGF
 - b. High IOP might be the primary driver of disease
 - c. Both VEGF and non-VEGF permeability factors are driving disease
 - d. Presence of inflammation inactivates anti-VEGF agents
5. Which of the following factors does not increase the risk for elevated IOP following steroid treatment?
 - a. Genetic predisposition to a steroid response
 - b. Choice of steroid
 - c. Patient age
 - d. Route of administration
6. Factors that support a role for vitrectomy for DME include:
 - a. Presence of a cataract
 - b. Poor response to anti-VEGF therapy
 - c. Poor vision
 - d. Vitreomacular traction
7. Which of the following is NOT a desired feature of potential new treatments for patients with DME that does not respond to anti-VEGF or who have bilateral disease?
 - a. Systemic administration
 - b. Non-VEGF pathway drug target
 - c. Shorter duration of response
 - d. Fewer office visits
8. Potential therapies in clinical development for DME target all the following pathologic features of the disease, except:
 - a. Inflammation
 - b. VEGF overexpression
 - c. Ischemia
 - d. Cell-cell adhesion
9. Which of the following mechanisms explains how Tie2 activation overcomes the effects of hypoxia in eyes with DME?
 - a. Stabilizes the vasculature
 - b. Downregulates expression of VEGF
 - c. Protects endothelial cells from VEGF
 - d. Upregulates expression of ANG1
10. Which of the following statements regarding the early clinical development of agents targeting the Tie2 pathway is true?
 - a. Subcutaneous route resulted in good intraocular drug concentration
 - b. Response was gradual over the 28-day study period
 - c. Safety signals included symptomatic blood pressure reduction
 - d. No responses were seen in patients previously treated with anti-VEGF

ACTIVITY EVALUATION /CREDIT REQUEST

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OVERALL ACTIVITY EVALUATION

Rate the extent to which:	Very High	High	Moderate	Low	Very Low
1. Learning Objectives of this activity were met					
<i>Upon completion of this activity, I am better able to discuss current treatments for patients with DME</i>	<input type="radio"/>				
<i>Upon completion of this activity, I am better able to review the pathophysiology of DME</i>	<input type="radio"/>				
<i>Upon completion of this activity, I am better able to describe the mechanism behind Tie2 activation for treating DME</i>	<input type="radio"/>				
<i>Upon completion of this activity, I am better able to examine the potential role of Tie2 activation in the treatment of DME</i>	<input type="radio"/>				
2. You were satisfied with the overall quality of this activity	<input type="radio"/>				
3. Content was relevant to your practice	<input type="radio"/>				
4. Participation in this activity will change your knowledge/attitudes	<input type="radio"/>				
5. You will make a change in your practice as a result of participation in this activity	<input type="radio"/>				
6. The activity presented scientifically rigorous, unbiased, and balanced information	<input type="radio"/>				
7. Individual faculty comments were free of commercial bias	<input type="radio"/>				
8. In the event that you believe a faculty participant introduced commercial bias, please describe the specifics below:					
9. Topic/Content was appropriate for your needs	<input type="radio"/>				
Was there a particular discussion that you felt had the most impact?					
What are some of the take-aways/changes that you will implement in your practice as a result of participating in this activity?					
Comments/Suggestions for Future Topics					