

# An Update on FDA Approved Treatments for Diabetic Macular Edema [TPA]

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Diabetic retinopathy causes vision loss secondary to diabetic macular edema (DME), vitreous hemorrhage, tractional retinal detachment and/or macular ischemia.<sup>1,2,3</sup>

DME can occur in all stages of diabetic retinopathy and is a leading cause of visual impairment in diabetics. The risk for developing DME increases with the duration of the diabetes.<sup>2-4</sup> The prevalence of DME is 5% within the first five years after diagnosis of diabetes and 15% at 15 years.<sup>4</sup>

The pathogenesis of diabetic macular edema includes breakdown of the inner blood-retinal barrier. This leads to accumulation of intraretinal fluid and plasma constituents and is driven by hypoxia and hyperglycemia. Inflammatory factors including VEGF are expressed in DME. These factors affect the endothelial tight junctions leading to increased retinal permeability.<sup>5</sup> If the intraretinal edema persists, it can lead to irreversible damage to the photoreceptors.<sup>6,7</sup> Therefore, the diagnosis of DME and prompt treatment is important to prevent permanent vision loss.

The Early Treatment Diabetic Retinopathy Study (ETDRS) defined the criteria for clinically significant macular edema (CSME) and demonstrated that patients benefited from focal argon laser treatment.<sup>1</sup> This landmark study was considered the standard of care until recently when the Federal Drug Administration (FDA) approved new therapies. In 2013, an estimated 90% of retinal specialists in the United States reported treating vision loss from diabetic macular edema with anti-vascular endothelial growth factor (VEGF) therapy.<sup>8</sup>

## **Diabetic macular edema (DME)**

ETDRS defined diabetic macular edema as retinal thickening within 1 disc diameter of the center of the macula or definite hard exudates in this region. The ETDRS recommended that DME be followed every 4 to 6 months and treated when the CSME criteria is met.<sup>1</sup> The RIDE and RISE studies defined DME as macular edema with a central subfield thickness  $\geq 275$  microns on time-domain optical coherence tomography (TD-OCT) with a corresponding Snellen visual acuity decrease of 20/40-20/320.

## **Clinically significant macular edema (CSME)**

ETDRS Report 1 answered the question of whether photocoagulation is effective in the treatment of diabetic macular edema. The study defined CSME as any of the following characteristics:

- Thickening of the retina at or within 500 microns of the center of the macula
- Hard exudates at or within 500 microns of the center of the macula, if associated with thickening of adjacent retina (not residual hard exudates remaining after disappearance of residual thickening)
- A zone or zones of retinal thickening 1 disc area or larger, any part of which is within 1 disc diameter of the center of the macula

A patient may present with DME without qualifying for the criteria of CSME. The ETDRS assessed retinal thickening by stereo contact lens biomicroscopy or stereo photography. Fluorescein angiography leakage without retinal thickening did not meet the definition of CSME.<sup>1</sup> In clinical practice, providers do not routinely use stereo contact lens biomicroscopy. Student clinicians are trained to evaluate the fundus with slit-lamp biomicroscopy with non-contact 60-diopter, 78-diopter or 90-diopter lenses. Non-contact fundus biomicroscopy has been found to be slightly less sensitive than contact fundus biomicroscopy at detecting retinal thickening.<sup>9</sup>

With the advent of optical coherence tomography (OCT), the role of OCT in assessing DME in the management of diabetic retinopathy is increasing. The RIDE and RISE clinical trials did not use the CSME criteria defined by the ETDRS as their definition of DME. Instead, the study based their definition of DME on time-domain OCT findings and reduced visual acuity.<sup>5</sup> The precision and ability to detect retinal edema make OCT increasingly recognized as a new reference standard assessment for DME. Subclinical DME is easily detected with OCT and has been found to increase the risk for developing visually significant CSME.<sup>9,10</sup>

### **Laser Photocoagulation**

The ETDRS reported that eyes assigned to immediate focal laser treatment with argon blue-green or green-only photocoagulation were about half as likely to lose 15 or more letters on the ETDRS eye chart compared with eyes assigned to deferral. The study also found very few adverse effects of focal photocoagulation with only minor effects on central visual fields and no color vision changes. The study recommended all eyes with CSME be considered for focal photocoagulation even if visual acuity is not yet reduced.<sup>1</sup> FDA approved focal photocoagulation as treatment for diabetic macular edema based on the results of the ETDRS and has been the standard of care for many years.

The ETDRS identified that eyes with diffuse leakage with or without grid pattern photocoagulation had a worse prognosis.<sup>1</sup> Focal laser photocoagulation increased the chance of visual improvement but many eyes still did not have significant improvement in vision even after treatment. The outcome of the study demonstrated that vision loss could be prevented, but not necessarily improved.<sup>1</sup> In comparison to the results of the ETDRS, the Diabetic Retinopathy Clinical Research Network (DRCR.net) evaluated steroid treatment compared to laser treatment for diabetic macular edema and found that 18% of DME patients treated with laser gain 15 or more letters of vision at three years.<sup>11</sup>

### **Anti-Vascular Endothelial Growth Factor**

Diabetic macular edema results from leakage due to increased retinal vascular permeability of the inner retinal blood brain barrier<sup>1,3</sup>. VEGF has been identified as the primary cytokine mediating this increase. Anti-VEGF therapy first approved by the FDA for the treatment of exudative age-related macular degeneration, has expanded its role and is now approved for the treatment of DME.<sup>12-13</sup>

More recently, the FDA expanded the approved use of Lucentis and Eylea to treat diabetic retinopathy in patients with macular edema. These anti-VEGF therapies have been shown to significantly reduce diabetic retinopathy progression as well as increase the likelihood of diabetic retinopathy regression.<sup>14</sup>

*Lucentis (Ranibizumab)*

Ranibizumab is an anti-VEGF antibody fragment designed for intraocular use due to its size and ability to neutralize all known forms of VEGF-A.<sup>15</sup> The FDA approved Ranibizumab 0.3-mg dose on August 10, 2012 for the treatment of diabetic macular edema. This was the first treatment option to be FDA approved for diabetic macular edema since focal photocoagulation in 1985.<sup>6</sup> The FDA approval came after the results of the RISE and RIDE phase III clinical trials. The RESTORE study demonstrated that ranibizumab 0.5-mg monotherapy was superior to laser treatment.<sup>16</sup>

#### RISE and RIDE

The RISE and RIDE clinical trials evaluated patients with diabetic macular edema. The trials defined macular edema with central subfield thickness  $\geq 275$  microns on TD-OCT with a corresponding Snellen visual acuity decrease of 20/40-20/320. Patients were treated monthly with 0.3-mg, 0.5-mg ranibizumab or sham injections. Starting at month 3, patients in all groups could also receive rescue macular laser photocoagulation if needed. The study demonstrated that within seven days, ranibizumab rapidly improved macular edema and vision. Patients receiving ranibizumab also had sustainably improved vision by gaining  $\geq 15$  letters or 3 lines on the ETDRS chart. The treatment also reduced the risk for further vision loss and improved DME with low rates of adverse events. The efficacy for the 0.3-mg and 0.5-mg of ranibizumab was similar over 36 months. The FDA approved the use of 0.3-mg in 2012 because it may reduce risks potentially related to systemic VEGF suppression while still maintaining optimal efficacy.<sup>6</sup>

#### RESTORE

The RESTORE clinical trial was a randomized, double-masked, multicenter, laser-controlled study to assess whether ranibizumab monotherapy or combined with laser was superior to laser alone in patients with DME. Three hundred and forty five patients were randomized 1:1:1 to intravitreal ranibizumab (0.5-mg) injection + sham laser, adjunctive administration of intravitreal ranibizumab (0.5-mg) injection + active laser, or laser treatment + sham injection. Patients received 3 initial consecutive monthly injections of ranibizumab followed by further treatment according to protocol-defined retreatment criteria. The number of ranibizumab/sham injections received was similar for all treatment groups. After 12 months, the study found that ranibizumab monotherapy and combined laser was superior to laser treatment in rapidly improving and sustaining VA in patients with DME. The study found that ranibizumab was superior to laser and there was no added benefit in combining laser with ranibizumab.<sup>16</sup>

#### *Eylea (Aflibercept)*

Aflibercept, also known as intravitreal aflibercept injection (IAI), VEGF Trap-Eye or IVT-AFL is composed of VEGF receptors 1 and 2 fused to the Fc domain of human immunoglobulin G1. It has approximately 100-fold greater binding affinity to VEGF-A than either bevacizumab or ranibizumab.<sup>17</sup> The approval of aflibercept in the treatment of DME was based on the one-year data from the phase III VISTA-DME and VIVID-DME studies. The recommended dose is 2-mg administered every 8 weeks following 5 initial monthly injections.<sup>18</sup>

#### VISTA and VIVID

The VISTA and VIVID clinical trials were 2 parallel, double-masked, randomized, phase III DME studies that included 862 patients. The trials compared aflibercept 2 mg given monthly to aflibercept 2 mg given every two months (after five initial monthly injections), to macular laser photocoagulation (at baseline and then as needed). The primary efficacy endpoint was the change from baseline in BCVA at week 52 with a secondary endpoint of proportion of eyes that gained  $\geq 15$  letters. At week 52, both aflibercept groups had similar efficacy and demonstrated to be superior in functional and anatomic endpoints over laser. The study demonstrated that aflibercept dosed at every 8 weeks (after 5 initial monthly doses) provided similar efficacy as monthly dosing. This dosing schedule would reduce the total number of injections and office visits.<sup>18</sup>

## **Intravitreal Implants**

### *Ozurdex (Dexamethasone)*

Ozurdex, an intravitreal dexamethasone (DEX) implant, was initially approved by the FDA in 2009 for the treatment of macular edema following retinal vein occlusion. The biodegradable implant delivers an extended release of the corticosteroid dexamethasone. In June 2014, FDA approved 0.7-mg Ozurdex for the treatment of DME in adult patients who were pseudophakic or scheduled for cataract surgery. Due to the results from the MEAD (Macular Edema: Assessment of Implantable Dexamethasone in Diabetes) clinical trial, the FDA approved the implant for use in all DME patients on September 2014.<sup>6</sup>

### MEAD

The MEAD study included two randomized, multi-centered, masked, sham-controlled, phase III clinical trials that evaluated two concentrations of DEX implant (0.3-mg and 0.7-mg) to sham treatment. The mean number of treatments received over 3 years was 4.1 and 4.4 in the 0.7-mg and 0.3-mg groups respectively. The primary endpoint was achievement of  $\geq 15$ -letters improvement in BCVA from baseline to the end of the study 3 years later. The percentage of patients with  $\geq 15$ -letter improvement in BCVA at the study end was greater with the DEX implant 0.7-mg (22.2%) compared to DEX implant 0.3-mg (18.4%) and sham (12.0%). Ocular adverse affects included cataracts and elevated intraocular pressures.<sup>6</sup>

### *Iluvien (Fluocinolone acetonide)*

Iluvien (fluocinolone acetonide intravitreal implant) 0.19-mg is an injectable, non-erodible, sustained release intravitreal implant. It received FDA approval in September 2014 for the treatment of DME in patients who have been previously treated with a course of corticosteroids and did not have a clinically significant rise in intraocular pressure. The implant is designed to release fluocinolone acetonide at an initial rate of 0.2  $\mu\text{g}/\text{day}$  and lasting 36 months.<sup>19</sup>

### FAME

The FAME (Fluocinolone Acetonide for Diabetic Macular Edema) clinical trials were two randomized, sham injection-controlled, double-masked, multicenter clinical trials assessing the long-term efficacy and safety of intravitreal inserts releasing 0.2  $\mu\text{g}/\text{day}$  (low dose) or 0.5  $\mu\text{g}/\text{day}$  (high dose) fluocinolone in patients with DME. Subjects were randomized 1:2:2 to sham injection, low-dose insert or high-dose insert. After 6 weeks of initial treatment, patients could be eligible for rescue macular laser. At month 36, the percentage of patients who gained  $\geq 15$  letters that were still in the trial was 33.0%(low dose) and 31.9% (high dose) compared with 21.4% in the sham group. Ocular adverse side effects included cataracts and elevated intraocular pressure.<sup>19</sup>

### **Conclusion:**

Since the FDA approved laser photocoagulation in the 1980s for the treatment of CSME, many new treatment therapies have emerged. Retinal specialists now have the option of treating patients with FDA approved anti-VEGF therapies or intravitreal corticosteroid implants. These new therapies have proven to not only reduce the risk for vision loss, but also significantly improve vision in patients with diabetic macular edema.

### **Figure 1**

Definitions:

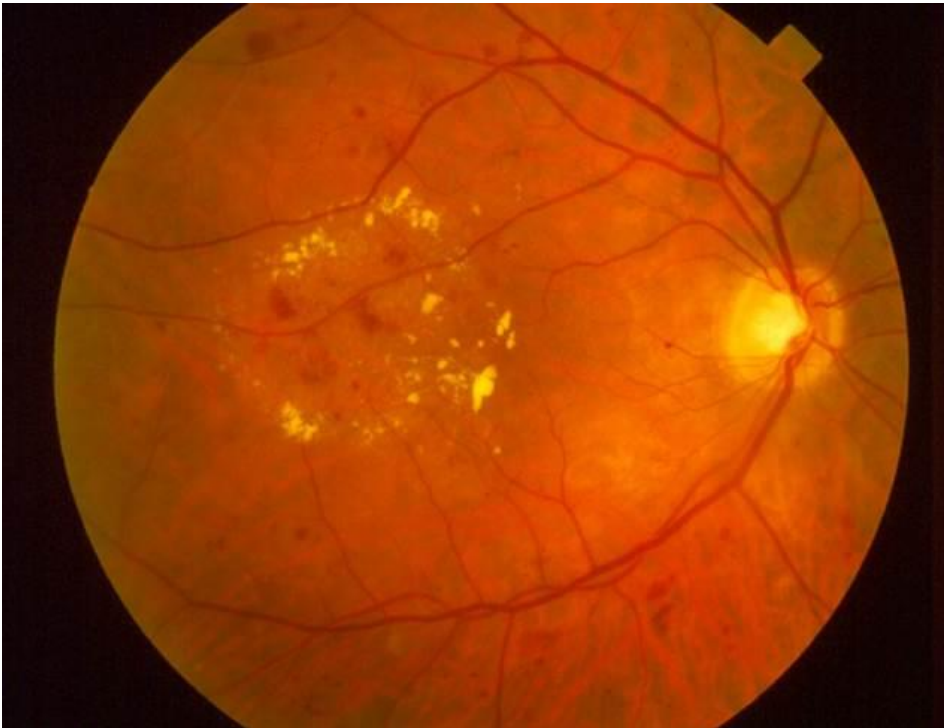
*Diabetic macular edema (DME):*

- ETDRS definition: retinal thickening within 1 disc diameter of the center of the macula or definite hard exudates in this region.
- RIDE and RIDE definition: macular edema and time-domain optical coherence tomography central subfield thickness  $\geq 275$  microns with a corresponding visual acuity decrease of 20/40-20/320.

*Clinically significant macular edema (CSME):*

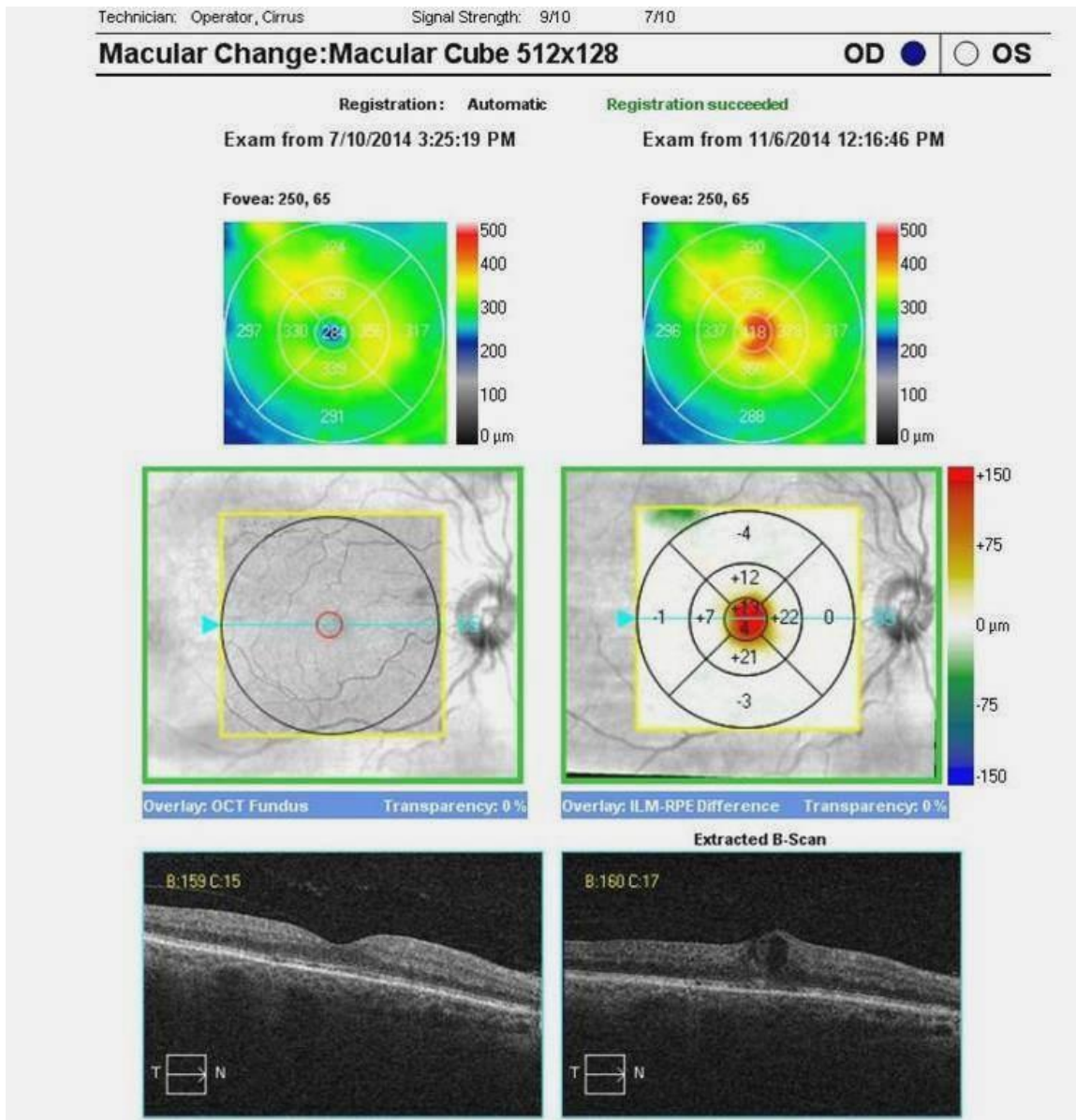
Defined by the ETDRS

- Thickening of the retina at or within 500 microns of the center of the macula
- Hard exudates at or within 500 microns of the center of the macula, if associated with thickening of adjacent retina (not residual hard exudates remaining after disappearance of residual thickening)
- A zone or zones of retinal thickening 1 disc area or larger, any part of which is within 1 disc diameter of the center of the macula



**Figure 2**

Color fundus photograph of a right eye with clinically significant macular edema. There are retinal hemorrhages with hard exudates and associated thickening.

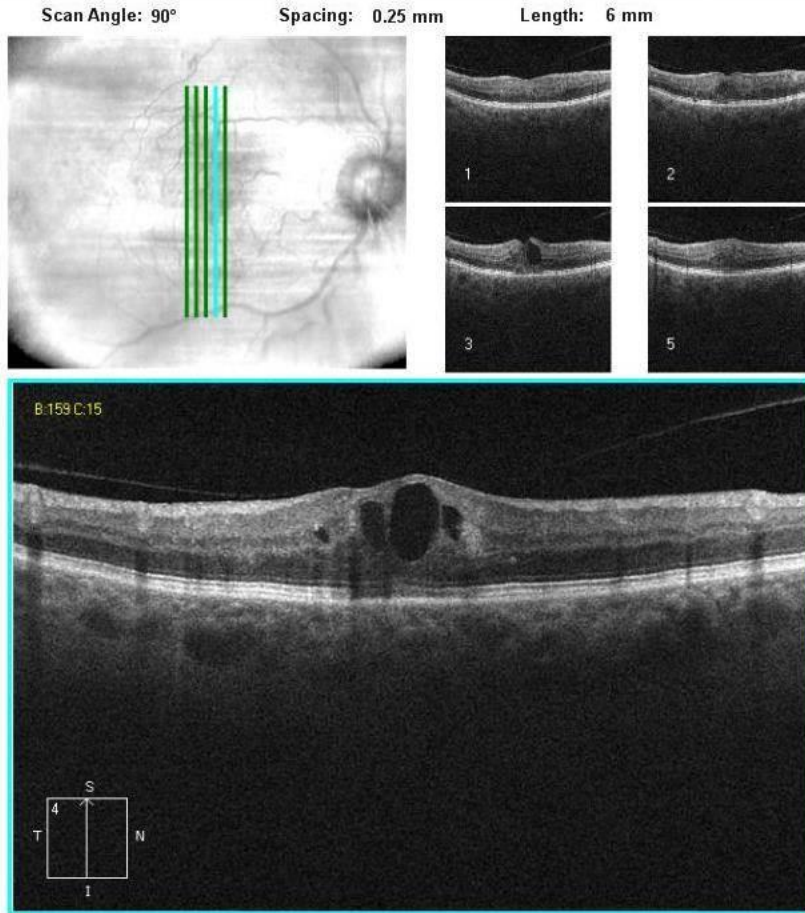


**Figure 3**

Cirrus SD-OCT macular change analysis over four months in a diabetic patient. The central subfield thickness at the initial visit on 07/10/14 was 284 microns. This increased to 418 microns at the follow up visit four months later on 11/06/14.

**High Definition Images: HD 5 Line Raster**

OD ● ○ OS



**Figure 4**

Cirrus SD-OCT HD 5-line raster scan revealing intraretinal edema and elevation in a patient with diabetic macular edema.

**TABLE 1**

**FDA APPROVED TREATMENT FOR DIABETIC MACULAR EDEMA**

**MEDICATION**

<b>TRADE NAME</b>	<b>GENERIC NAME</b>	<b>DOSAGE</b>	<b>STUDY</b>
LUCENTIS	RANIBIZUMAB	0.3-MG MONTHLY	RISE/RIDE
		2-MG EVERY 8 WKS AFTER 5 INITIAL	
EYLEA	AFLIBERCEPT	MONTHLY INJECTIONS	VISTA/VIVID
OZURDEX	DEXAMETHASONE	0.7-MG; RETREATMENT AFTER ≥ 6 MONTHS FROM PREVIOUS TX	MEAD

(DEX IMPLANT)

ILUVIEN	FLUOCINOLONE ACETONIDE	0.19-MG LAST UP TO 36 MONTHS	FAME
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**CE@Home May/June Questions**  
**An Update on FDA Approved Treatments**  
**for Diabetic Macular Edema [TPA]**

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By: Lee Vien, OD, FAAO

Answer the following 10 questions to the best of your ability. To receive CE credit, please fax in your answers to 916-448-1423 or mail them to **California Optometric Association, Attn: CE, 2415 K Street, Sacramento, CA 95816**. Answers are due July 15, 2015. Test submissions are entered every Friday; transcripts are available every Saturday morning.

- 1) Which of the following causes vision loss in diabetic retinopathy?
  - a. Diabetic macular edema
  - b. Vitreous hemorrhage
  - c. Tractional retinal detachment
  - d. All of the above
- 2) What was the recommended follow up by the ETDRS for patients with diabetic macular edema (DME) without clinically significant macular edema (CSME)?
  - a. 1-3 months
  - b. 4-6 months
  - c. 7-9 months
  - d. >12 months
- 3) What was the definition of diabetic macular edema (DME) in the RISE and RIDE clinical trials?
  - a. Retinal thickening within 2 disc diameters
  - b. A zone or zones of retinal thickening 1 disc area or larger, any part of which is within 1 disc diameter of the center of the macula
  - c. Macular edema and time-domain optical coherence tomography central subfield thickness  $\geq 275$  microns with a corresponding visual acuity decrease of 20/40-20/320.
  - d. Hard exudates at or within 500 microns of the center of the macula, if associated with thickening of adjacent retina
- 4) Which of the following characteristics is not part of the definition of clinically significant macular edema (CSME)?
  - a. Thickening of the retina at or within 500 microns of the center of the macula
  - b. Hard exudates at or within 500 microns of the center of the macula, if associated with thickening of adjacent retina (not residual hard exudates remaining after disappearance of residual thickening)
  - c. A zone or zones of retinal thickening 1 disc area or larger, any part of which is within 1 disc diameter of the center of the macula
  - d. Optical coherence tomography central subfield thickness  $\geq 300$  microns
- 5) Which of the following method(s) was used to assess retinal thickening for clinically significant macular edema (CSME) in the ETDRS?
  - a. Stereo contact lens biomicroscopy
  - b. Stereo photography
  - c. Spectral domain optical coherence tomography (SD-OCT)
  - d. Fluorescein angiography
  - e. A and B
- 6) Focal photocoagulation was the first FDA approved treatment for clinically significant macular edema.
  - a. True
  - b. False
- 7) Which of the following is an anti-vascular endothelial growth factor (VEGF) agent(s)?
  - a. Lucentis (Ranibizumab)
  - b. Ozurdex (Dexamethasone)
  - c. Eylea (Aflibercept)
  - d. Iluvien (Fluocinolone acetonide)
  - e. A and C
- 8) What is the FDA approved dosage for ranibizumab in the treatment of diabetic macular edema (DME)?
  - a. 0.5-mg monthly injection
  - b. 0.5-mg PRN
  - c. 0.3-mg monthly injection
  - d. 0.3-mg PRN
- 9) What is the FDA approved dosage for aflibercept in the treatment of diabetic macular edema (DME)?
  - a. 2-mg every 8 weeks after 5 initial monthly injections
  - b. 2-mg every 8 weeks after 3 initial monthly injections
  - c. 4-mg every 4 weeks
  - d. 4-mg every 8 weeks
- 10) Which clinical trial did not evaluate the treatment of diabetic macular edema?
  - a. RISE and RIDE
  - b. VISTA and VIVID
  - c. MEAD
  - d. BRAVO
  - e. FAME