

ACHIEVING IMPROVED OUTCOMES THROUGH PARTNERSHIPS BETWEEN OPTOMETRISTS AND RETINA SPECIALISTS

CONSIDERATIONS IN THE TREATMENT OF DIABETIC RETINOPATHY AND DIABETIC MACULAR EDEMA

Chairs

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Consensus Panel Members

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Disclosure: The authors are paid consultants to and have ongoing relationships with Regeneron Pharmaceuticals, Inc. and/or its affiliates. This consensus panel was convened by Regeneron Pharmaceuticals to discuss and determine consensus on referrals and potential treatment.

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Introduction

More than 34 million adults in the United States have diabetes, and an estimated 88 million more have prediabetes.¹ Although diabetes is associated with sequelae across multiple organ systems,¹⁻³ the potential for vision loss represents a particularly devastating concern for patients and their families.⁴

This concern is well founded, as the Centers for Disease Control and Prevention (CDC) estimates that diabetic retinopathy (DR) affects almost 1 in 3 adults aged >40 years with diabetes and represents the most substantial cause of blindness among working-age adults in the United States.^{5,6} Diabetic macular edema (DME) is a complication of DR that can occur anytime and is a common cause of vision loss in patients with diabetes.⁷ Increased DR severity at baseline is significantly associated with the incidence of DME. In a study including 135,324 eyes, the cumulative incidence of DME development over 4 years was 27.1% in mild nonproliferative diabetic retinopathy (NPDR), 51.2% in moderate NPDR, and 60.6% in severe NPDR⁸; however, recent evidence suggests that with appropriate early management, patients with moderately severe to severe NPDR may be able to delay progression to vision-threatening complications (VTCs), defined as progression to proliferative diabetic retinopathy (PDR) or anterior segment neovascularization (ASNV), or the development of central-involved DME (CI-DME).⁹

Despite the availability of effective treatment options, DR and DME can still result in substantial vision loss, as many patients with diabetes go untreated. The reasons for this are multifactorial and may be overcome with multidisciplinary management.

In an attempt to better understand the causes of suboptimal treatment and to generate potential solutions, Regeneron hosted an advisory roundtable discussion of leaders in the fields of retina and optometry (Table 1). In an effort to evolve the current standard of care toward a

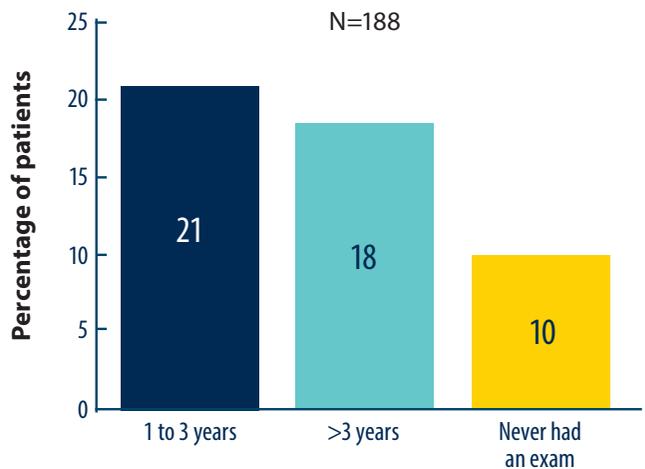
Table 1: Consensus panel members

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scientifically supported model of early and appropriate referral and treatment for patients, the panel discussed current unmet needs in the referral and management of DR (with or without DME), the role of current treatment options, the relationship between optometrists and retina specialists, and what the future may hold for eye care professionals in the management of DR. Following the panel's discussion, it was decided to develop a series of supplements to describe the consensus that were reached during discussions.

This supplement (the first in this series) describes the benefits of joint management of patients with DR by optometrists and retina specialists and discusses the importance of early identification and timely referral. This supplement has been published concurrently in *Optometry Times* and *Ophthalmology Times*.

Figure 1: Time since last eye exam



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Current landscape and unmet needs

The treatment landscape of DR with and without DME has evolved substantially, and although treatment is widely available, the panel recommends that practice guidelines, continuing education, and the understanding of treatment options in the eye care professional community should be adjusted to account for these advances. Eye care professionals should consider working together to improve patient care and ensure that more patients can take advantage of the treatment options available, when applicable. This often involves careful monitoring and attention of patients with diabetes by optometrists who are ready to refer patients earlier to retina specialists while continuing to address their patients' primary eye care needs, even after referral. With availability of a treatment that can help prevent vision-threatening complications in DR and further vision loss in DME, the need for proper screening and monitoring of these patients has increased.

Screening and diagnosis

A study on the adherence to DR screening guidelines found that approximately half of patients with diabetes do not receive an annual eye exam, with 28% not receiving an exam within 3 years (Figure 1), which could result in DR

“Every diabetic patient should have an annual dilated eye exam.”

—Mark T. Dunbar, OD

going unnoticed¹⁰; however, simply having any eye exam is not sufficient, as patients with diabetes should receive a dilated eye exam to assess for

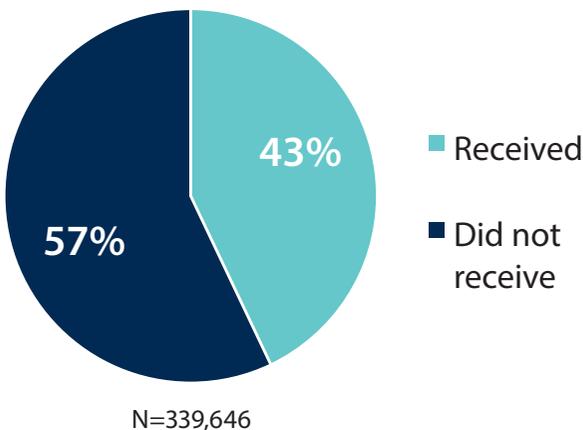
the presence of diabetes-related changes to the retina. Despite this need, large-scale claims data of 339,646 patients with diabetes show that 57% did not receive a dilated eye exam over a 2-year period (Figure 2).¹¹

The most commonly cited reason patients with diabetes give for not receiving an annual eye exam is that they feel there is no need for one.¹² In fact, only 26.1% of participants with DR (without DME) in the National Health and Nutrition Examination Survey reported that they had been informed by a doctor that diabetes had affected their eyes or that they had retinopathy.¹³

The educational need for patients starts with their primary care provider (PCP), who must create a sense of urgency to seek appropriate eye care soon after their initial diabetes diagnosis and annually thereafter.¹⁴ Creating this urgency is challenging, as PCPs lack the time to describe the dilated eye exam in a way that stresses its importance.¹¹ This panel believes optometrists and ophthalmologists alike should ask every patient scheduled for a routine refractive examination if they have ever been given a diagnosis of diabetes or prediabetes to ensure those patients receive a dilated eye examination.

In our discussion, the panel agreed that all patients with diabetes require a dilated eye exam and that it is the responsibility of any eye care professional who sees a patient to ensure that this is completed either by the individual provider or through referral. Optometrists should not assume that a patient with diabetes will

Figure 2: Percentage of patients with diabetes who received or did not receive a dilated eye exam over 2 years



“I tell my patients it’s easier to fix a problem early, before it starts to affect your vision, rather than after you already have vision loss.”

—Steven G. Ferrucci, OD

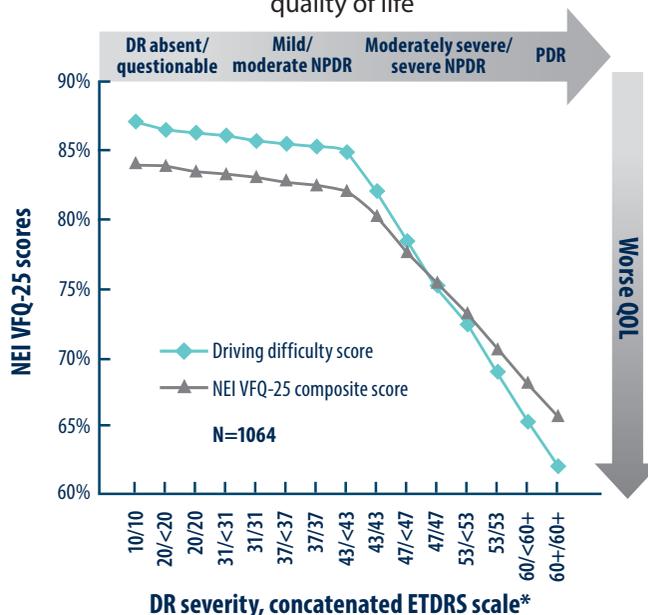
receive a dilated eye exam from another provider and should encourage a full eye exam, even if the patient’s appointment is for a routine vision exam.

Untreated patients are at risk for poor outcomes

According to the American Optometric Association (AOA), optometrists may be the first healthcare professionals to identify undiagnosed diabetes and DR.¹⁴ In 2018, optometrists found >301,000 patients with diabetes-related eye manifestations who did not know they had prediabetes or diabetes.¹⁵ Earlier and accurate detection of DR can reduce the risk of serious vision loss.

Patients with DR, either with or without DME, are at risk for disease progression as well as vision loss. Within 2 years, 33.7% and 44.1% of anti-vascular endothelial growth factor (VEGF)–naïve patients with moderate and severe NPDR, respectively, will develop DME. Between year 2 and year 4, the risk of conversion to PDR nearly doubles (20.9% and 46.8%, respectively).⁸ With increasing disease severity also comes increased risk of vision loss. In a retrospective analysis of the American Academy of Ophthalmology (AAO) Intelligent Research in Sight (IRIS®) Registry, patients with good visual acuity (VA) (20/40 or better) who were diagnosed with DR within 3 months were evaluated for risk factors associated with the development of sustained blindness. Patients with moderate and severe NPDR were 2.6 and 3.6 times more likely to develop sustained

Figure 3: The effect of DR severity on vision-related quality of life



ETDRS, Early Treatment Diabetic Retinopathy Study; NEI VFQ-25, National Eye Institute Visual Function Questionnaire 25; QOL, quality of life.
*The severity of DR for a participant denotes the severity in each eye.

blindness, respectively, than patients with mild NPDR.¹⁶ Further, the progression of DR past moderate NPDR in even 1 eye is associated with a steep decline in quality of life and driving ability (Figure 3).^{16, 17}

Despite the risks of disease progression, reduced VA, and poor quality of life, many patients with DR and DME do not receive treatment. Although DR and DME can result in substantial harm, there is potential to improve outcomes for patients. Clinical evidence supports that patients with DR and DME may benefit from earlier treatment, even in the nonproliferative stages of DR.^{9,18,19}

During our discussion, the panel reviewed pertinent guidelines from the AAO,²⁰ AOA,¹⁴ and the American Society of Retina Specialists (ASRS).¹⁹ The panel determined that the recommended patterns for referral and treatment

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“The key is empowering the frontline people to identify pathology and then refer before the onset of symptoms.”

—Charles C. Wykoff, MD, PhD

in those guidelines might be updated in future iterations to reflect recent data and clinical trial results. Here, the panel describes recent advancements in the field, as well as our suggestions as to how guidelines may evolve in the future to reflect a referral pattern that supports early intervention.

Referral

The decision as to when a patient with DR should be referred to a retina specialist may be viewed as complicated by some primary eye care professionals. Guidelines can be outdated and may require updates to align with currently available clinical evidence. Certainly, any patient with macular edema at any site—whether clinically significant or not—should be evaluated by a retina specialist within 1 month. In the absence of macular edema, the AOA guidelines recommend that patients with severe or very severe NPDR, as well as patients with non–high-risk PDR,

“Referring patients who might benefit from earlier treatment can improve outcomes.”

—A. Paul Chous, MA, OD

also should be seen by a retina specialist within 1 month. The AOA guidelines note the urgency of referral for patients with high-risk PDR and suggest retinal consultation within 2 days.¹⁴ The AOA guidelines do not recommend referring patients with mild or moderate NPDR to a retina specialist¹⁴; however, given the evidence of undergrading DR severity and the benefits of early treatment for patients with NPDR, referral to a retina specialist is reasonable.⁹

From the panel’s perspective, although communication with the PCP is important, it is not a substitute for communication between multidisciplinary eye care professionals. Primary eye care professionals and subspecialty eye care professionals should form relationships that facilitate a team-based approach to care and evidence-based referrals.

Shortly before the approval of the new AOA guidelines,¹⁴ additional evidence was presented to the US Food and Drug Administration (FDA) supporting the use of EYLEA® (aflibercept) Injection for intravitreal injection in the treatment of DR without DME, leading to its approval in this setting.²¹ Prior to this latest approval, EYLEA was approved for intravitreal injection in the treatment of DME in 2014.²² It is important to note that the approval in DR without DME was based on clinical trial results that specifically studied the safety and efficacy of EYLEA in patients with moderately severe to severe NPDR (Diabetic Retinopathy Severity Scale [DRSS] level 47 and 53).⁹ Given the availability and potential outcomes of treatment for this population, the panel believes it is reasonable to refer potentially treatable patients with less advanced disease for a retina evaluation so that retina specialists can make “decisions tailored to each patient’s clinical needs,” as proposed by new guidelines from the ASRS.¹⁹

INDICATIONS

EYLEA® (aflibercept) Injection 2 mg (0.05 mL) is indicated for the treatment of patients with Neovascular (Wet) Age-related Macular Degeneration (AMD), Macular Edema following Retinal Vein Occlusion (RVO), Diabetic Macular Edema (DME), and Diabetic Retinopathy (DR).

SELECT IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

EYLEA is contraindicated in patients with ocular or periocular infections, active intraocular inflammation, or known hypersensitivity to aflibercept or to any of the excipients in EYLEA.

Table 2: ETRS DRSS

Level	Severity	Definition
10	DR absent	Microaneurysms and other characteristics absent
14*	DR questionable	HE, SE, or IRMA definite; microaneurysms absent
15*	DR questionable	Hemorrhage(s) definite; microaneurysms absent
20	Microaneurysms only	Microaneurysms definite; other characteristics absent
35 [†]	Mild NPDR	One or more of the following: Venous loops \geq D/1; SE, IRMA, or VB = Q; retinal hemorrhages present; HE \geq D/1; SE \geq D/1
43	Moderate NPDR	H/Ma = M/4-5 – S/1 or IRMA = D/1-3 (not both)
47	Moderately severe NPDR	Both L43 characteristics and/or one (only) of the following: IRMA = D4-5; H/Ma = S/2-3; VB = D/1
53	Severe NPDR [†]	One or more of the following: \geq 2 of the 3 L47 characteristics; H/Ma \geq S/4-5; IRMA \geq M/1; VB \geq D/2-3
61	Mild PDR	FPD or FPE present with NVD and NVE absent; or NVE = D
65	Moderate PDR	Either of the following: (1) NVE \geq M/1 or NVD = D; and VH and PRH = A or Q; (2) VH or PRH = D and NVE < M/1 and NVD absent
71	High-risk PDR	Any of the following: (1) VH or PRH \geq M/1; (2) NVE \geq M/1 and VH or PRH \geq D/1; (3) NVD = 2 and VH or PRH \geq D/1; (4) NVD \geq M
75	High-risk PDR	NVD \geq M and VH or PRH \geq D/1
81	Advanced PDR: fundus partially obscured, center of macula attached	NVD = cannot grade, or NVD < D and NVE = cannot grade in \geq 1 field and absent in all others; and retinal detachment at center of macula < D
85	Advanced PDR: posterior fundus obscured, or center of macula detached	VH = VS in fields 1 and 2; or retinal detachment at center of macula = D
90	Cannot grade, even sufficiently of level 81 or 85	

A, absent; D, definitely present; FPD, fibrous proliferations disc; FPE, fibrous proliferations elsewhere; HE, hard exudates; H/Ma, hemorrhages/microaneurysms; IRMA, intraretinal microvascular abnormalities; M, moderate; NVD, new vessels disc (within 1 DD of disc margin); NVE, new vessels elsewhere (>1 DD from disc); PRH, preretinal hemorrhage; Q, questionable; S, severe; SE, soft exudates; VB, venous beading; VH, vitreous hemorrhage; VS, very severe.
^{*}Levels 14 and 15 are not considered separate steps in the scale but are pooled with level 10 or 20.
[†]NPDR levels 35 and above all require presence of microaneurysms.

Available evidence suggests that there is a high potential for underestimating the severity of DR, as well as some discrepancy between clinicians in their analysis. In a phase 3 clinical trial, approximately 30% of patients who were assessed as having mild NPDR or better by a retina specialist were determined to have a more severe degree of DR by an independent reading center.⁹

Appropriately grading DR for prompt referral

In clinical trials, the DRSS is used to measure the quality and progression of DR. The DRSS is a 13-step scale that stratifies DR from absent to severe PDR (Table 2).²³ This scale has been validated in clinical trials and is based on disease signs independent of macular edema.²⁴

Treatment is supported by clinical evidence as early as moderately severe NPDR (DRSS level 47).⁹ It is important to refer patients to retina specialists prior to the development of more severe DR so that individualized decisions regarding treatment can be made.¹⁹ Given the potential for underestimating severity,⁹ it may be reasonable for eye care professionals to collaborate and co-manage patients earlier in the course of the disease to ensure that treatment decisions are made in a timely manner. The members of this panel choose to refer or hope to receive patients who have moderate or worse NPDR (DRSS \geq 43) for collaborative management between optometrists and retina specialists.

The DRSS scale, while useful in clinical trials and in granularly establishing DR severity, may be cumbersome and complicated in clinical practice; therefore, the panel proposes a simplified checklist (Box 1) that describes patients with a DRSS of \geq 43 who should be referred to a retina specialist for further evaluation.¹⁹

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“Relationships with retina specialists are based on mutual respect and understanding each other’s strengths and weaknesses to provide the best possible patient care.”

—Steven G. Ferrucci, OD

Despite the possibility that a patient’s condition at the time of referral may not warrant treatment, there is still value for the patient in establishing a relationship with a retina specialist, as DR is a progressive disease and most anti-VEGF-naïve patients with moderate NPDR will develop DME.⁸

Box 1: NPDR characteristics that necessitate referral

- Moderate RH in 4 quadrants
- Severe RH in ≥ 1 quadrant
- Mild or worse IRMA in ≥ 1 quadrant
- Venous beading

IRMA, intraretinal microvascular abnormality; RH, retinal hemorrhage.

Maintaining communication

A critical postreferral consideration is the coordination between the primary eye care professional (optometrist or ophthalmologist) and the retina specialist. Patients with diabetes are at increased risk for nonretinal eye conditions that must be concurrently diagnosed and managed.^{25,26} Patients may not understand the different services offered by different eye care professionals and the various types of care that they might need with respect to both diabetes-related conditions and nondiabetic ocular conditions for which they are at risk. The optometrist is critical in coordinating all of this care, as well as providing direct treatment for other ocular conditions.

The referring optometrist or ophthalmologist will likely be the most informed member of the eye care team with respect to the patient’s overall condition, including other relevant nonocular disorders. They may choose to evaluate a patient with greater frequency than the retina specialist, which means that they may be the first to notice additional signs of disease progression. To complement the care primary eye care professionals provide to patients with diabetes, consulting retina specialists should

- Ensure that the referring optometrist/ophthalmologist is provided key information regarding interventions performed, progress notes, and diagnostic evaluations

SELECT IMPORTANT SAFETY INFORMATION (CONT’D) WARNINGS AND PRECAUTIONS

Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments. Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately. Intraocular inflammation has been reported with the use of EYLEA.

Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with VEGF inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately.

There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors, including EYLEA. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence of reported thromboembolic events in wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA compared with 1.5% (9 out of 595) in patients treated with ranibizumab; through 96 weeks, the incidence was 3.3% (60 out of 1824) in the EYLEA group compared with 3.2% (19 out of 595) in the ranibizumab group. The incidence in the DME studies from baseline to week 52 was 3.3% (19 out of 578) in the combined group of patients treated with EYLEA compared with 2.8% (8 out of 287) in the control group; from baseline to week 100, the incidence was 6.4% (37 out of 578) in the combined group of patients treated with EYLEA compared with 4.2% (12 out of 287) in the control group. There were no reported thromboembolic events in the patients treated with EYLEA in the first six months of the RVO studies.

“It is essential for the referring OD to be in the loop to help answer questions that patients may have.”
—Steven G. Ferrucci, OD

- Include PCPs on correspondence with the referring optometrist/ophthalmologist to engage the entire diabetes management team
- Establish a plan for how the patient will be monitored for DR/DME disease activity
- Understand diagnostic instrumentation (eg, optical coherence tomography/optical coherence tomography angiography wide-field retinal imaging, electrodiagnostics) and technological capabilities of referring optometrists to aid in the distribution of management responsibilities
- Counsel patients to maintain their scheduled optometry appointments and provide education regarding the importance of continued optometric management concurrent with retinal management
- Educate patients about potential treatments and which eye care professional administers them

Conclusions

Diabetes is a complex condition with a vast array of symptoms and pathology across multiple organs.¹⁻³ While it is well accepted that patients with diabetes benefit from a multidisciplinary care team on a high-level perspective—including PCPs, subspecialty physicians, nurse practitioners, physician assistants, nurses, dietitians, exercise specialists, pharmacists, dentists, podiatrists, and mental health professionals²⁷—less attention has been given to the specific and complementary roles that members of the eye care team can have in improving the health of this vulnerable population.

This working group, composed of optometrists and retina specialists, met to discuss how our disciplines could leverage our distinct skill sets and relationships with patients to evolve the current standard of care toward a

scientifically supported model of early and appropriate referral and treatment for patients with DR and DME. In this effort, the panel considered the current treatment environment, the need for patient education, recent advances in the treatment of DR and DME, and the relationships between optometrists and retina specialists to deliver optimal care for patients with diabetes. These topics will continue to be discussed in greater detail as this series is developed.

Current landscape and need for patient education

Some currently available guidelines suggest that referral to a retina specialist can wait until the patient has progressed to severe NPDR¹⁴; however, the members of this panel refer patients with moderate NPDR or worse so that they may be evaluated by a retina specialist, given the availability of therapy and the speed at which DR can progress.

Patients must also be educated regarding the potential for ocular complications secondary to diabetes, and the panel believes that optometrists and other primary eye care professionals hold a key role in these educational discussions. Patients must be informed of the value of systemic metabolic control (blood glucose, pressure, and lipids) as it relates to overall disease progression and promoting metabolic memory,²⁸ but they must also be informed of the potential for ocular complications before they suffer any vision declines or other ocular symptoms. Additionally, they should be informed that their risk of VTCs may be reduced with timely and appropriate treatment.

“Retina specialists near my practice have made the effort to visit, invite me to educational events, and otherwise educate me on clinical topics.”
—A. Paul Chous, MA, OD

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Relationships among eye care professionals

When we work together and complement each other's strengths, patients have the best opportunity for optimal outcomes. Optometrists and other eye care professionals are critical in ensuring that patients are referred to subspecialists promptly. They are also key influencers in ensuring adherence in the overall diabetes management plan. To be effective in their efforts, optometrists must be informed of the progress of each patient following referral. It is also critical that subspecialists, including retina specialists, remind their patients that their eye health involves a team of professionals who interface with the systemic disease management team through their optometrist or other primary eye care professional. The optometrist or other eye care professional takes a lead role in coordinating the eye health of patients with diabetes.

Treatment considerations

Although DR and DME can result in substantial harm, there is potential to improve outcomes for patients. A strong working relationship between optometrists and retina specialists can help ensure more patients take advantage of the treatment options available. Clinical evidence supports that patients with DR and DME can benefit from timely treatment, and anti-VEGF agents have been proven to have a positive impact on vision and anatomic outcomes in patients with DR and/or DME.^{9,18,19} Both optometrists and retina specialists should educate patients on the risks and benefits of treatment to ensure appropriate adherence to treatment.

SUMMARY OF FINDINGS

- Perform a dilated eye exam on all patients with diabetes
- Refer in a timely manner due to availability of therapy and possible progression
- Educate patients at time of referral
- Coordinate care between retina specialists and optometrists to improve patient outcomes
- Treat patients with DR and DME earlier to help prevent progression

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SELECT IMPORTANT SAFETY INFORMATION (CONT'D) ADVERSE REACTIONS

Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment.

The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and intraocular pressure increased.

Patients may experience temporary visual disturbances after an intravitreal injection with EYLEA and the associated eye examinations. Advise patients not to drive or use machinery until visual function has recovered sufficiently.

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Please see Important Safety Information throughout and Brief Summary of full Prescribing Information at the end of this article.

Supplement 1



BRIEF SUMMARY—Please see the EYLEA full Prescribing Information available on HCP.EYLEA.US for additional product information.

1 INDICATIONS AND USAGE

EYLEA is a vascular endothelial growth factor (VEGF) inhibitor indicated for the treatment of patients with:

Neovascular (Wet) Age-Related Macular Degeneration (AMD), Macular Edema Following Retinal Vein Occlusion (RVO), Diabetic Macular Edema (DME), Diabetic Retinopathy (DR).

4 CONTRAINDICATIONS

4.1 Ocular or Periorcular Infections

EYLEA is contraindicated in patients with ocular or periorcular infections.

4.2 Active Intraocular Inflammation

EYLEA is contraindicated in patients with active intraocular inflammation.

4.3 Hypersensitivity

EYLEA is contraindicated in patients with known hypersensitivity to afibercept or any of the excipients in EYLEA. Hypersensitivity reactions may manifest as rash, pruritus, urticaria, severe anaphylactic/anaphylactoid reactions, or severe intraocular inflammation.

5 WARNINGS AND PRECAUTIONS

5.1 Endophthalmitis and Retinal Detachments

Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments [see *Adverse Reactions* (6.J)]. Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately [see *Patient Counseling Information* (17)].

5.2 Increase in Intraocular Pressure

Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA [see *Adverse Reactions* (6.J)]. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with vascular endothelial growth factor (VEGF) inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately.

5.3 Thromboembolic Events

There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors, including EYLEA. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence of reported thromboembolic events in wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA compared with 1.5% (9 out of 595) in patients treated with ranibizumab; through 96 weeks, the incidence was 3.3% (60 out of 1824) in the EYLEA group compared with 3.2% (19 out of 595) in the ranibizumab group. The incidence in the DME studies from baseline to week 52 was 3.3% (19 out of 578) in the combined group of patients treated with EYLEA compared with 2.8% (8 out of 287) in the control group; from baseline to week 100, the incidence was 6.4% (37 out of 578) in the combined group of patients treated with EYLEA compared with 4.2% (12 out of 287) in the control group. There were no reported thromboembolic events in the patients treated with EYLEA in the first six months of the RVO studies.

6 ADVERSE REACTIONS

The following potentially serious adverse reactions are described elsewhere in the labeling:

- Hypersensitivity [see *Contraindications* (4.3)]
- Endophthalmitis and retinal detachments [see *Warnings and Precautions* (5.1)]
- Increase in intraocular pressure [see *Warnings and Precautions* (5.2)]
- Thromboembolic events [see *Warnings and Precautions* (5.3)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in other clinical trials of the same or another drug and may not reflect the rates observed in practice.

A total of 2980 patients treated with EYLEA constituted the safety population in eight phase 3 studies. Among those, 2379 patients were treated with the recommended dose of 2 mg. Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment. The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and intraocular pressure increased.

Neovascular (Wet) Age-Related Macular Degeneration (AMD). The data described below reflect exposure to EYLEA in 1824 patients with wet AMD, including 1223 patients treated with the 2-mg dose, in 2 double-masked, controlled clinical studies (VIEW1 and VIEW2) for 24 months (with active control in year 1).

Safety data observed in the EYLEA group in a 52-week, double-masked, Phase 2 study were consistent with these results.

Table 1: Most Common Adverse Reactions (≥1% in Wet AMD Studies)

Adverse Reactions	Baseline to Week 52		Baseline to Week 96	
	EYLEA (N=1824)	Active Control (ranibizumab) (N=595)	EYLEA (N=1824)	Control (ranibizumab) (N=595)
Conjunctival hemorrhage	25%	28%	27%	30%
Eye pain	9%	9%	10%	10%
Cataract	7%	7%	13%	10%
Vitreous detachment	6%	6%	8%	8%
Vitreous floaters	6%	7%	8%	10%
Intraocular pressure increased	5%	7%	7%	11%
Ocular hyperemia	4%	8%	5%	10%
Corneal epithelium defect	4%	5%	5%	6%
Detachment of the retinal pigment epithelium	3%	3%	5%	5%
Injection site pain	3%	3%	3%	4%
Foreign body sensation in eyes	3%	4%	4%	4%
Lacrimation increased	3%	1%	4%	2%
Vision blurred	2%	2%	4%	3%
Intraocular inflammation	2%	3%	3%	4%
Retinal pigment epithelium tear	2%	1%	2%	2%
Injection site hemorrhage	1%	2%	2%	2%
Eyelid edema	1%	2%	2%	3%
Corneal edema	1%	1%	1%	1%
Retinal detachment	<1%	<1%	1%	1%

Less common serious adverse reactions reported in <1% of the patients treated with EYLEA were hypersensitivity, retinal tear, and endophthalmitis.

Macular Edema Following Retinal Vein Occlusion (RVO). The data described below reflect 6 months exposure to EYLEA with a monthly 2 mg dose in 218 patients following central retinal vein occlusion (CRVO) in 2 clinical studies (COPERNICUS and GALILEO) and 91 patients following branch retinal vein occlusion (BRVO) in one clinical study (VIBRANT).

REGENERON

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Based on the August 2019 EYLEA® (afibercept) Injection full Prescribing Information.

EYL.20.09.0052

Table 2: Most Common Adverse Reactions (≥1% in RVO Studies)

Adverse Reactions	CRVO		BRVO	
	EYLEA (N=218)	Control (N=142)	EYLEA (N=91)	Control (N=92)
Eye pain	15%	5%	4%	5%
Conjunctival hemorrhage	12%	11%	20%	4%
Intraocular pressure increased	8%	6%	2%	0%
Corneal epithelium defect	5%	4%	2%	0%
Vitreous floaters	5%	1%	1%	0%
Ocular hyperemia	5%	3%	2%	2%
Foreign body sensation in eyes	3%	5%	3%	0%
Vitreous detachment	3%	4%	2%	0%
Lacrimation increased	3%	4%	3%	0%
Injection site pain	3%	1%	1%	0%
Vision blurred	1%	<1%	1%	1%
Intraocular inflammation	1%	1%	0%	0%
Cataract	<1%	1%	5%	0%
Eyelid edema	<1%	1%	1%	0%

Less common adverse reactions reported in <1% of the patients treated with EYLEA in the CRVO studies were corneal edema, retinal tear, hypersensitivity, and endophthalmitis.

Diabetic Macular Edema (DME) and Diabetic Retinopathy (DR). The data described below reflect exposure to EYLEA in 578 patients with DME treated with the 2-mg dose in 2 double-masked, controlled clinical studies (VIVID and VISTA) from baseline to week 52 and from baseline to week 100.

Table 3: Most Common Adverse Reactions (≥1% in DME Studies)

Adverse Reactions	Baseline to Week 52		Baseline to Week 100	
	EYLEA (N=578)	Control (N=287)	EYLEA (N=578)	Control (N=287)
Conjunctival hemorrhage	28%	17%	31%	21%
Eye pain	9%	6%	11%	9%
Cataract	8%	9%	19%	17%
Vitreous floaters	6%	3%	8%	6%
Corneal epithelium defect	5%	3%	7%	5%
Intraocular pressure increased	5%	3%	9%	5%
Ocular hyperemia	5%	6%	5%	6%
Vitreous detachment	3%	3%	8%	6%
Foreign body sensation in eyes	3%	3%	3%	3%
Lacrimation increased	3%	2%	4%	2%
Vision blurred	2%	2%	3%	4%
Intraocular inflammation	2%	<1%	3%	1%
Injection site pain	2%	<1%	2%	<1%
Eyelid edema	<1%	1%	2%	1%

Less common adverse reactions reported in <1% of the patients treated with EYLEA were hypersensitivity, retinal detachment, retinal tear, corneal edema, and injection site hemorrhage. Safety data observed in 269 patients with nonproliferative diabetic retinopathy (NPDR) through week 52 in the PANORAMA trial were consistent with those seen in the phase 3 VIVID and VISTA trials (see Table 3 above).

6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for an immune response in patients treated with EYLEA. The immunogenicity of EYLEA was evaluated in serum samples. The immunogenicity data reflect the percentage of patients whose test results were considered positive for antibodies to EYLEA in immunosays. The detection of an immune response is highly dependent on the sensitivity and specificity of the assays used, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to EYLEA with the incidence of antibodies to other products may be misleading.

In the wet AMD, RVO, and DME studies, the pre-treatment incidence of immunoreactivity to EYLEA was approximately 1% to 3% across treatment groups. After dosing with EYLEA for 24-100 weeks, antibodies to EYLEA were detected in a similar percentage range of patients. There were no differences in efficacy or safety between patients with or without immunoreactivity.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Adequate and well-controlled studies with EYLEA have not been conducted in pregnant women. Afibercept produced adverse embryofetal effects in rabbits, including external, visceral, and skeletal malformations. A fetal No Observed Adverse Effect Level (NOAEL) was not identified. At the lowest dose shown to produce adverse embryofetal effects, systemic exposures (based on AUC for free afibercept) were approximately 6 times higher than AUC values observed in humans after a single intravitreal treatment at the recommended clinical dose [see *Animal Data*].

Animal reproduction studies are not always predictive of human response, and it is not known whether EYLEA can cause fetal harm when administered to a pregnant woman. Based on the anti-VEGF mechanism of action for afibercept, treatment with EYLEA may pose a risk to human embryofetal development. EYLEA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

In two embryofetal development studies, afibercept produced adverse embryofetal effects when administered every three days during organogenesis to pregnant rabbits at intravenous doses ≥3 mg per kg, or every six days during organogenesis at subcutaneous doses ≥0.1 mg per kg.

Adverse embryofetal effects included increased incidences of postimplantation loss and fetal malformations, including anasarca, umbilical hernia, diaphragmatic hernia, gastroschisis, cleft palate, ectrodactyly, intestinal atresia, spina bifida, encephalomenocele, heart and major vessel defects, and skeletal malformations (fused vertebrae, sternbrae, and ribs; supernumerary vertebral arches and ribs; and incomplete ossification). The maternal No Observed Adverse Effect Level (NOAEL) in these studies was 3 mg per kg. Afibercept produced fetal malformations at all doses assessed in rabbits and the fetal NOAEL was not identified. At the lowest dose shown to produce adverse embryofetal effects in rabbits (0.1 mg per kg), systemic exposure (AUC) of free afibercept was approximately 6 times higher than systemic exposure (AUC) observed in humans after a single intravitreal dose of 2 mg.

8.2 Lactation

Risk Summary

There is no information regarding the presence of afibercept in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production/excretion. Because many drugs are excreted in human milk, and because the potential for absorption and harm to infant growth and development exists, EYLEA is not recommended during breastfeeding.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for EYLEA and any potential adverse effects on the breastfed child from EYLEA.

8.3 Females and Males of Reproductive Potential

Contraception

Females of reproductive potential are advised to use effective contraception prior to the initial dose, during treatment, and for at least 3 months after the last intravitreal injection of EYLEA.

Infertility

There are no data regarding the effects of EYLEA on human fertility. Afibercept adversely affected female and male reproductive systems in cynomolgus monkeys when administered by intravenous injection at a dose approximately 1500 times higher than the systemic level observed in humans with an intravitreal dose of 2 mg. A No Observed Adverse Effect Level (NOAEL) was not identified. These findings were reversible within 20 weeks after cessation of treatment.

8.4 Pediatric Use

The safety and effectiveness of EYLEA in pediatric patients have not been established.

8.5 Geriatric Use

In the clinical studies, approximately 76% (2049/2701) of patients randomized to treatment with EYLEA were ≥65 years of age and approximately 46% (1250/2701) were ≥75 years of age. No significant differences in efficacy or safety were seen with increasing age in these studies.

17 PATIENT COUNSELING INFORMATION

In the days following EYLEA administration, patients are at risk of developing endophthalmitis or retinal detachment. If the eye becomes red, sensitive to light, painful, or develops a change in vision, advise patients to seek immediate care from an ophthalmologist [see *Warnings and Precautions* (5.J)].

Patients may experience temporary visual disturbances after an intravitreal injection with EYLEA and the associated eye examinations [see *Adverse Reactions* (6)]. Advise patients not to drive or use machinery until visual function has recovered sufficiently.

IMPORTANT SAFETY INFORMATION AND INDICATIONS

CONTRAINDICATIONS

- EYLEA is contraindicated in patients with ocular or periocular infections, active intraocular inflammation, or known hypersensitivity to aflibercept or to any of the excipients in EYLEA.

WARNINGS AND PRECAUTIONS

- Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments. Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately. Intraocular inflammation has been reported with the use of EYLEA.
- Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with VEGF inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately.
- There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors, including EYLEA. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence of reported thromboembolic events in wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA compared with 1.5% (9 out of 595) in patients treated with ranibizumab; through 96 weeks, the incidence was 3.3% (60 out of 1824) in the EYLEA group compared with 3.2% (19 out of 595) in the ranibizumab group. The incidence in the DME studies from baseline to week 52 was 3.3% (19 out of 578) in the combined group of patients treated with EYLEA compared with 2.8% (8 out of 287) in the control group; from baseline to week 100, the incidence was 6.4% (37 out of 578) in the combined group of patients treated with EYLEA compared with 4.2% (12 out of 287) in the control group. There were no reported thromboembolic events in the patients treated with EYLEA in the first six months of the RVO studies.

ADVERSE REACTIONS

- Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment.
- The most common adverse reactions ($\geq 5\%$) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and intraocular pressure increased.
- Patients may experience temporary visual disturbances after an intravitreal injection with EYLEA and the associated eye examinations. Advise patients not to drive or use machinery until visual function has recovered sufficiently.

INDICATIONS

EYLEA® (aflibercept) Injection 2 mg (0.05 mL) is indicated for the treatment of patients with Neovascular (Wet) Age-related Macular Degeneration (AMD), Macular Edema following Retinal Vein Occlusion (RVO), Diabetic Macular Edema (DME), and Diabetic Retinopathy (DR).

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