Intravitreal Angiogenesis Inhibitors for Retinal Vascular Conditions

Description

Angiogenesis inhibitors (e.g., ranibizumab, bevacizumab, pegaptanib) are being evaluated for the treatment of disorders of retinal circulation. Ophthalmic disorders affecting the retinal circulation include proliferative diabetic retinopathy, diabetic macular edema, central or branch retinal vein occlusion and retinopathy of prematurity.

Background

Vascular endothelial growth factor (VEGF) has been implicated in the pathogenesis of a variety of ocular vascular conditions characterized by neovascularization and macular edema. The macula, with the fovea at its center, has the highest photoreceptor concentration and is where visual detail is discerned. The anti-VEGF agents ranibizumab (Lucentis™), bevacizumab (Avastin®), pegaptanib (Macugen®) and aflibercept (Eylea™) are used to treat choroidal neovascularization associated with age-related macular degeneration (AMD) and are being evaluated for the treatment of disorders of retinal circulation (e.g., diabetic retinopathy, retinal vein occlusion, and retinopathy of prematurity).

For the treatment of ocular disorders, these agents are given by intravitreal injection every 1 to 2 months. Pegaptanib and ranibizumab bind extracellular VEGF to inhibit the angiogenesis pathway. Pegaptanib binds to the VEGF-165 isomer of VEGF-A while ranibizumab is an antibody fragment directed at all isoforms of VEGF-A. Bevacizumab is derived from the same murine monoclonal antibody precursor as ranibizumab, which binds to all isoforms of VEGF-A. Aflibercept (previously called VEGF Trap-Eye) is a recombinant fusion protein consisting of the VEGF binding domains of human VEGF receptors 1 and 2 fused to the Fc domain of human immunoglobulin-G1. Aflibercept binds VEGF-A and placental growth factor, another angiogenic growth factor.

Diabetic Retinopathy

Diabetic retinopathy is a common microvascular complication of diabetes and a leading cause of blindness in adults. The two most serious complications for vision are diabetic macular edema and proliferative diabetic retinopathy. At its earliest stage (nonproliferative retinopathy), microaneurysms occur. With disruption of the blood-retinal barrier, macular retinal vessels become permeable, leading
to exudation of serous fluid and lipids into the macula (macular edema). As the disease progresses, blood vessels that provide nourishment to the retina are blocked, triggering the growth of new and fragile blood vessels (proliferative retinopathy). Severe vision loss with proliferative retinopathy arises from vitreous hemorrhage. Moderate vision loss can also arise from macular edema (fluid accumulating in the center of the macula) during the proliferative or nonproliferative stages of the disease. Although proliferative disease is the main blinding complication of diabetic retinopathy, macular edema is more frequent and is the leading cause of moderate vision loss in people with diabetes.

Tight glycemic and blood pressure control is the first line of treatment to control diabetic retinopathy, followed by laser photocoagulation for patients whose retinopathy is approaching the high-risk stage. Although laser photocoagulation is effective at slowing the progression of retinopathy and reducing visual loss, it results in collateral damage to the retina and does not restore lost vision. Focal macular edema (characterized by leakage from discrete microaneurysms on fluorescein angiography) may be treated with focal laser photocoagulation, while diffuse macular edema (characterized by generalized macular edema on fluorescein angiography) may be treated with grid laser photocoagulation. Corticosteroids may reduce vascular permeability and inhibit vascular endothelial growth factor (VEGF) production but are associated with serious adverse effects including cataracts and glaucoma with damage to the optic nerve. Corticosteroids can also worsen diabetes control. VEGF inhibitors (e.g., ranibizumab, bevacizumab, and pegaptanib), which reduce permeability and block the pathway leading to new blood vessel formation (angiogenesis) are being evaluated for the treatment of diabetic macular edema and proliferative diabetic retinopathy. For diabetic macular edema, outcomes of interest are macular thickness and visual acuity. For proliferative diabetic retinopathy, outcomes of interest are operative and perioperative outcomes and visual acuity.

Central and Branch Retinal Vein Occlusions

Retinal vein occlusions are classified by whether there is a central retinal vein occlusion (CRVO) or branch retinal vein occlusion (BRVO). CRVO is also categorized as ischemic or non-ischemic. Ischemic CRVO is associated with a poor visual prognosis, with macular edema and permanent macular dysfunction occurring in virtually all patients. Non-ischemic CRVO has a better visual prognosis, but many patients will have macular edema, and it may convert to the ischemic type within 3 years. Most of the vision loss associated with CRVO results from the main complications, macular edema and intraocular neovascularization. BRVO is a common retinal vascular disorder in adults between 60 and 70 years of age and occurs approximately 3 times more commonly than CRVOs. Macular edema is the most significant cause of central visual loss in BRVO.

Retinal vein occlusions are associated with increased venous and capillary pressure and diminished blood flow in the affected area, with a reduced supply of oxygen and nutrients. The increased pressure causes water flux into the tissue while the hypoxia stimulates the production of inflammatory mediators such as VEGF, which increases vessel permeability and induces new vessel growth. Intravitreal corticosteroid injections or implants have been used to treat the macular edema associated with retinal vein occlusions, with a modest beneficial effect on visual acuity. However, cataracts are a common side effect, and steroid-related pressure elevation occurs in about one-third of patients, with some requiring filtration surgery. Macular grid photocoagulation has also been used to improve vision
in BRVO but is not recommended for CRVO. The serious adverse effects of available treatments have stimulated the evaluation of new treatments, including intravitreal injection of VEGF inhibitors. Outcomes of interest for retinal vein occlusions are macular thickness and visual acuity.

*Retinopathy of Prematurity*

Retinopathy of prematurity is a neovascular retinal disorder that primarily affects premature infants of low birth weight. It is one of the most common causes of childhood blindness in the United States. Typically, retinal vascularization begins at the optic nerve when the eye begins to develop (16 weeks’ gestation) and reaches the edge of the retina at 40 weeks’ gestation. If an infant is born prematurely, normal vessel growth may stop, followed by neovascularization at the interface between the vascular and avascular retinal areas. Stages of retinopathy of prematurity are defined by vessel appearance and the level of retinal detachment, ranging from mild (stage 1) to severe (stage 5). Stage I or stage II retinopathy of prematurity may resolve on its own. The optimal time for treatment is stage III, when a ridge with neovascularization extends into the vitreous gel. The neovascularization may progress and form fibrous scar tissue that causes partial (stage 4) or total retinal detachment (stage 5), accompanied by loss of vision. Both cryotherapy and laser therapy have been used to slow or reverse the abnormal growth of blood vessels in the peripheral areas of the retina. While successful in about 50% of cases, these treatments can cause myopia and permanent loss of the peripheral visual field. Vitrectomy may be needed when cryotherapy or laser therapy fail to induce regression.

*Other*

Other retinal vascular conditions that are being evaluated for treatment with VEGF inhibitors are cystoid macular edema resulting from vasculitis, Coats disease, Eales disease, idiopathic macular telangiectasia type II, neovascularization of the iris/neovascularization of the angle/neovascular glaucoma, pseudoxanthoma elasticum, radiation retinopathy, retinal neovascularization, rubeosis, Von Hippel- Lindau, and vitreous hemorrhage secondary to retinal neovascularization.

*Regulatory Status*

Pegaptanib (Macugen®, Eyetech and Pfizer), ranibizumab (Lucentis™) and aflibercept (EYLEA™, Regeneron Pharmaceuticals) are presently the only angiostatic drugs approved by the U.S. Food and Drug Administration (FDA) for use in the eye. Macugen® was the first VEGF antagonist to be approved by the FDA for use in wet AMD.

Ranibizumab (Genentech) was first approved for the treatment of patients with neovascular AMD. In 2010, Ranibizumab was approved by the FDA for the treatment of macular edema following retinal vein occlusion. In 2012, ranibizumab was approved for the treatment of diabetic macular edema and in 2015 it was approved for the treatment of proliferative diabetic retinopathy in patients with diabetic macular edema. (1)

Aflibercept was approved by the FDA in 2011 for the treatment of wet (neovascular) age-related macular degeneration and is administered by intravitreous injections every 4 or 8 weeks. In 2012, aflibercept was approved for the treatment of macular edema following central retinal vein occlusion.
(2) FDA approved the use of aflibercept (EYLEA™) to treat proliferative diabetic retinopathy on March 25, 2015. (3) Bevacizumab (Avastin®) Bevacizumab has been developed and approved for use in oncology but has not been licensed for use in the eye.

Related Policies

9.03.08 Photodynamic Therapy for Choroidal Neovascularization
9.03.13 Retinal Telescreening for Diabetic Retinopathy
9.03.23 Intravitreal Corticosteroid Implants

Policy

*This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.

Intravitreal injection of ranibizumab, bevacizumab, or aflibercept may be considered medically necessary for the treatment of the following retinal vascular conditions:

- Diabetic macular edema*
- Proliferative diabetic retinopathy*
- Macular edema following retinal vein occlusion*
- Retinopathy of prematurity
- Neovascular glaucoma
- Rubeosis (neovascularization of the iris)

Intravitreal injection of ranibizumab, bevacizumab, or aflibercept is considered investigational for the treatment of all other retinal vascular disorders.

Intravitreal injection of pegaptanib is considered investigational for treatment of retinal vascular disorders, including proliferative diabetic retinopathy, diabetic macular edema, and central or branch retinal vein occlusion.

* FDA approved indication Lucentis and Eylea.

Rationale

Diabetic Macular Edema

The available evidence on VEGF inhibitors for the treatment of diabetic macular edema consists of numerous RCTs, some of which are large, and systematic reviews of the published trials.

In 2012, there were two technology assessments published that evaluated the efficacy of anti-growth factors as a group. In the first of these reports, the Institute for Clinical and Economic Review published a technology assessment on the comparative effectiveness of anti-growth factor therapies for diabetic macular edema for the Medicare Evidence Development and Coverage Advisory Committee (MEDCAC). (4,54) The assessment evaluated data from 15 randomized controlled trials and 8 observational studies of anti-VEGF drugs. Improvement in visual acuity was consistently seen for all
anti-VEGF agents, ranging from 6-9 letters greater than controls (laser or sham injection) for ranibizumab, bevacizumab, and aflibercept, and 4-5 letters greater than controls for pegaptanib. Meta-analysis of data on the mean change in best corrected visual acuity (BCVA) and percentage of patients gaining 10 or more letters indicated no significant differences in clinical performance between anti-VEGF agents. Serious adverse events were rare, and there was no conclusive evidence that rates of systemic events differed substantially between treatment and control arms. The greatest area of uncertainty was the systemic side effect profile of bevacizumab relative to other anti-VEGF agents, because the quality of the evidence on adverse events for bevacizumab was lower than for other agents. The assessment concluded that anti-VEGF therapy improves vision (approximately 2-3 times more than laser photocoagulation or sham injection) and provides other clinical benefits in patients with diabetic macular edema.

Another technology assessment, published in 2012, was from the American Academy of Ophthalmology (AAO). This report found 5 studies that provided level I evidence for the efficacy of intravitreal ranibizumab, alone or in combination with other treatments, as a treatment for diabetic macular edema. (6) The AAO also identified a level I study on pegaptanib for diabetic macular edema. Nine additional studies were rated as level II evidence. Evidence was limited for long-term results (i.e., more than 2 years of follow-up) or for the comparative efficacy of different anti-VEGF agents.

Also published in 2012 was a Cochrane review of VEGF inhibitors for diabetic macular edema. (7) This review was updated in 2014, and included 18 studies with a total of over 1000 patients for the 4 comparisons of interest. (8) Meta-analysis found that patients treated with ranibizumab, bevacizumab, or aflibercept were more likely to gain 3 or more lines of vision (risk ratio [RR], 3.6, 95% confidence interval [CI], 2.7 to 4.8) and less likely to lose 3 or more lines of vision (RR, 0.11, 95% CI, 0.05 to 0.24) than patients treated with grid laser photocoagulation. The overall quality of the body of evidence was considered to be high. It was estimated that 28 of 100 patients treated with VEGF inhibitors would gain 3 or more lines of visual acuity compared with 8 of 100 using photocoagulation. No significant differences were found between ranibizumab, bevacizumab, and aflibercept, although it was noted that this subanalysis was underpowered.

In 2015, the Diabetic Retinopathy Clinical Research Network (DRCRN) published results from a National Institutes of Health (NIH)-sponsored double-masked RCT with head-to-head comparison of aflibercept, bevacizumab, and ranibizumab. (9) A total of 660 patients with vision loss from DME were randomized to 1 of the 3 agents. The study drugs were administered at an interval as frequent as every 4 weeks, based on a prespecified algorithm. The median number of intravitreal injections was 9 in the aflibercept group, 10 in the bevacizumab group, and 10 in the ranibizumab group (p=0.045). At 1 year, visual acuity had improved significantly more with aflibercept (13.3 letters) compared with either bevacizumab (9.7 letters, p<0.001) or ranibizumab (11.2 letters, p=0.03), although this difference was not considered to be clinically meaningful. The advantage with aflibercept was driven primarily by patients with worse vision (20/50 or worse), where the mean improvement was 18.9 letters with aflibercept, compared to 11.8 with bevacizumab (p<0.001), and 14.2 with ranibizumab (p=0.003). This is a high quality trial with low risk of bias. There were no significant differences among the groups in the rates of serious adverse events.

The clinical trial evidence for individual agents is discussed below.
Diabetic Macular Edema: Ranibizumab (Lucentis™)

A number of large randomized controlled trials (RCTs) have evaluated ranibizumab for the treatment of diabetic macular edema. Two studies were sham-controlled trials with rescue laser photocoagulation as needed that evaluated efficacy versus placebo. Three studies compared ranibizumab to laser photocoagulation, evaluating the comparative efficacy of the two procedures.

Ranibizumab Compared to Sham Injection

The RESOLVE study is a 12-month multicenter randomized controlled trial (RCT) from Europe that compared ranibizumab (0.3 or 0.5 mg) with sham injection. (10) Included in the study were 151 eyes with type 1 or 2 diabetes, central retinal thickness ≥300 microns, and best corrected visual acuity (BCVA) of 73-39 letters (20/40 to 20/160), with the decrease in vision attributed to foveal thickening from diabetic macular edema. The treatment schedule comprised 3 monthly injections, after which treatment could be stopped or reinitiated, with an opportunity for rescue laser photocoagulation according to protocol-defined criteria. There were more discontinuations in the sham arm than the ranibizumab arm (18.4% vs. 9.8%). Dose doubling was allowed after the first month, and a total of 86% of patients in the pooled ranibizumab arm received a dose of 0.5 mg or higher. At 12 months, BCVA improved 10.3 letters in the pooled ranibizumab group and declined by 1.4 letters in the sham group. A gain of >10 letters BCVA occurred in 60.8% of ranibizumab and 18.4% of sham treated eyes. Mean central retinal thickness was reduced by 194 microns with ranibizumab (from 455 to 261) and 48 microns (from 448 to 400) with sham treatment.

In 2012, Nguyen and colleagues reported 24-month results from 2 identical FDA-regulated Phase III multicenter, double-masked, randomized sham-controlled trials named RISE and RIDE. (11) An additional publication in 2013 reported follow-up to 36 months. (12) A total of 759 patients with decreased vision from diabetic macular edema (central subfield thickness ≥275 microns) were randomized to 0.3 mg ranibizumab, 0.5 mg ranibizumab, or sham injections. All patients received 3 monthly injections and then were evaluated monthly for the need for macular laser according to protocol-specified criteria. The median number of ranibizumab injections was 24, and ranibizumab-treated patients underwent significantly fewer rescue laser procedures (mean of 1.8 and 1.6 laser procedures over 24 months in the sham groups vs. 0.8 in ranibizumab groups). Both trials found that significantly more ranibizumab-treated patients gained ≥15 letters. In RISE, 18.1% of sham patients gained ≥15 letters compared with 44.8% of 0.3 mg and 39.2% of 0.5 mg treated patients. In RIDE, 12.3% of sham-treated patients gained ≥15 letters compared with 33.6% of the 0.3 mg and 45.7% of the 0.5 mg group. Macular edema was also improved with ranibizumab; there was a mean change in central foveal thickness of 125-133 microns in the 2 control groups and over 250 microns in the 4 ranibizumab groups. Gains in visual acuity in the ranibizumab arms were maintained at 36 months.

In the 3rd year patients in the sham arm were allowed to cross over to treatment with 0.5 mg ranibizumab. These cross-over patients achieved lower gains in visual acuity compared to patients treated with ranibizumab in the first year of the study.
Ranibizumab Compared to Laser Photocoagulation

RESTORE was an industry-sponsored randomized double-masked comparative trial conducted at 73 centers outside of the U.S. (13-15) A total of 345 patients with diabetic macular edema were randomized to receive ranibizumab injection plus active laser, ranibizumab injection plus sham laser, or sham injection plus active laser. Patients were treated monthly for 3 months and then given additional treatment as required until month 12. Ranibizumab alone and ranibizumab combined with laser improved the mean average change in BCVA letter score to a greater degree than laser monotherapy. Mean changes in BCVA (mean for all monthly assessments from month 1 to month 12) were 6.1 for the ranibizumab group, 5.9 for the ranibizumab + laser group, and 0.8 for laser alone. The proportion of patients who had a BCVA gain of 5 letters or more was 65.2% for ranibizumab, 63.6% for ranibizumab and laser, and 33.6% for laser alone. Quality of life, measured with the National Eye Institute Visual Functioning Questionnaire-25 (NEI VFQ-25), showed significantly greater improvements for the ranibizumab groups in the overall composite score (5.0 and 5.4 more than laser alone) and in subscores for general vision, near vision activities, and distance activities for the ranibizumab groups. All patients were eligible to receive ranibizumab 0.5 mg PRN from month 12 to month 36. (14, 15) Two hundred and eight patients (86.7%) of 240 enrolled completed the 2-year extension study. The improvements in visual acuity and central retinal thickness achieved during the initial 12 months of ranibizumab were maintained at 36 months with a mean of 6.8 injections (prior ranibizumab) and 6.0 injections (prior ranibizumab + laser). The prior laser group achieved a progressive improvement in visual acuity over the 2 year extension period with a final gain of +6.0 letters, which was comparable to the visual acuity achieved in the prior ranibizumab arms (+6.7 and +8.0 letters).

Six month, 2-year and 3-year outcomes from the North American READ-2 study were reported in 2009 and 2010. (16-18) READ-2 was a randomized multicenter trial comparing ranibizumab (0.5 mg at baseline and months 1, 3, and 5) versus focal or grid laser photocoagulation (baseline and month 3 if needed), or combined ranibizumab and photocoagulation (baseline and month 3), with 42 patients per group. After the primary endpoint was reached at month 6, all subjects could be treated with ranibizumab. For the primary endpoint at month 6, the mean gain in best corrected visual acuity (BCVA) was significantly greater for 3 injections of ranibizumab (+7.2 letters) compared to photocoagulation (-0.4 letters), or the combined photocoagulation plus 2 injection treatment (+3.8 letters). Improvement of 3 lines or more occurred in 8 of 37 (22%) of the ranibizumab group, 0 of 38 (0%) of the photocoagulation group, and 3 of 40 (8%) of the combined group (91% follow-up out of 126). Excess foveal thickness (>212 microns) at baseline was 199 microns, 228 microns, and 262 microns for the 3 groups. Foveal thickness was reduced by 50%, 33%, and 45%, respectively. After the primary endpoint, most patients in all groups were treated with ranibizumab; the mean number of injections during the 18 months’ follow-up period was 5.3, 4.4, and 2.9, respectively. With approximately 80% follow-up for the 3 groups, the mean improvement in BCVA at 24 months was 7.7, 5.1, and 6.8 letters. At 36 months, BCVA in the prior ranibizumab only group increased slightly to 10.3 letters, while visual acuity in the other 2 groups was not significantly changed. The percentage of patients with a center subfield thickness of 250 microns or less at 24 months was 36%, 47%, and 68%, respectively. For all 3 groups, the percentage of patients with a foveal thickness of 250 microns or less increased between months 24 and 36.
The Diabetic Retinopathy Clinical Research Network published 1- and 2-year results of a sham controlled multicenter RCT that evaluated ranibizumab (with prompt or deferred laser) or triamcinolone plus prompt laser. (19, 20) A total of 854 eyes (691 participants) with visual acuity of 20/32 to 20/320 and diabetic macular edema involving the fovea were randomized to sham injection + prompt laser (n=293), ranibizumab + prompt laser (n=187), ranibizumab + deferred laser (n=188) or triamcinolone + prompt laser (n=186). The study drug or sham injection treatments were performed every 4 weeks through 12 weeks. Beginning at week 16, study drug or sham injections were performed according to a retreatment algorithm. Participants in the 3 prompt laser groups were masked through the 1-year primary outcome evaluation, with planned 5 years of follow-up. Analysis was based on intention-to-treat, with the last observation carried forward for missing data at 1 year. At 1-year follow-up, the sham + prompt laser group showed a 3 letter gain in BCVA. BCVA for both ranibizumab groups was significantly greater than sham (+9 letters for either the prompt or deferred laser), but the triamcinolone plus laser group was not significantly different from sham (+4 letters). The percentage of eyes meeting criteria for success (visual acuity letter score >84 [approx 20/20] or central subfield <250 microns) at 1 year was 32% for the sham + prompt laser, 64% for the ranibizumab + prompt laser, 52% for the ranibizumab + deferred laser, and 56% for the triamcinolone + prompt laser group. The reduction in macular thickness was similar in all 3 injection groups (median of 241, 256, and 247 microns) and was greater than the laser only group (307 microns).

Two-year data were available for 642 eyes of 526 patients and were not available for 212 eyes (25%) of 165 participants. (20) The major reason that patients were not available for follow-up (n=99) was a protocol change in which participants not originally assigned to ranibizumab could choose to receive ranibizumab. Most eyes assigned to ranibizumab received at least 1 additional injection because of recurrence of diabetic macular edema between the 1- and 2-year visits. Patients in the sham plus laser group gained an average of 3 letters, while patients in the ranibizumab + prompt laser group gained an average of 7 letters, and patients in the ranibizumab + deferred laser group gained an average of 9 letters. The percentage of patients who gained >15 letters was 29% and 28% in the ranibizumab groups compared with 18% in the laser group. The percentage of patients who lost >15 letters was 4% and 2% in the ranibizumab groups and 10% in the laser group. There were a greater proportion of patients who had retinal thickness less than 250 microns (54% and 56% vs. 39%) but no significant difference between groups in the mean change in retinal thickness from baseline.

**Diabetic Macular Edema: Bevacizumab (Avastin®)**

A number of smaller RCTs from Asia have been published that assessed the efficacy of bevacizumab for diabetic macular edema.

In 2008, Ahmadieh et al. reported the efficacy of 3 injections of bevacizumab (1.25 mg every 6 weeks) either alone or in combination with triamcinolone in 115 eyes (101 patients) with macular edema that was unresponsive to macular laser photocoagulation. (4) Patients were randomized to 1 of 3 study arms (3 injections of bevacizumab, combined triamcinolone and bevacizumab, or sham injection). Improvement in BCVA was observed earlier in the combined group (6 weeks) than the bevacizumab only group (12 weeks). At 24 weeks, BCVA was similar in the 2 treatment groups, (-0.18 and -0.21 logMAR [logarithm of the minimum angle of resolution]), vs. -0.3 logMAR for the sham group. The change in central macular thickness was -95.7 microns in the bevacizumab arm, -92.1 microns in the
combined group, and +34.9 microns in the control group. Elevation of intraocular pressure occurred in 3 eyes (8.1%) of the combined treatment group.

In 2009 and 2012, Soheilian et al. reported an RCT of intravitreal bevacizumab (1.25 mg alone or combined with triamcinolone) versus macular photocoagulation in 150 treatment-naive eyes (129 patients). (21, 22) Sham laser and sham injections were performed, and evaluators were blinded to the treatment condition. Evaluations were performed through 9 months in the 2009 report and through 24 months in the follow-up study. At 9 months, BCVA changes were -0.28 for bevacizumab alone, -0.04 for bevacizumab and triamcinolone, and +0.01 logMAR for photocoagulation. BCVA improvement greater than 2 Snellen lines was detected in 37%, 25%, and 14.8% of patients in the bevacizumab alone, bevacizumab and triamcinolone, and photocoagulation groups, respectively. Central macular thickness changes were not different between the groups. Throughout the follow-up, eyes with significant macular edema were retreated with the assigned intervention at 12-week intervals. The mean number of treatments for each arm of the study was 3.1 for bevacizumab, 2.6 for bevacizumab/triamcinolone, and 1.0 for photocoagulation. At 24-month follow-up, there was no significant difference in visual or anatomic outcomes between the 3 groups, suggesting that the superiority of bevacizumab may diminish over time when administered at this interval.

Michaelides and colleagues reported 12-month results from the BOLT study, an RCT that compared multiple intravitreal injections of bevacizumab (1.25 mg) with photocoagulation in 2010. (23) A total of 80 eyes of 80 patients who had diabetic macular edema and at least 1 prior macular laser therapy were randomized to bevacizumab every 6 weeks as needed (minimum of 3 and maximum of 9) or macular laser therapy (minimum of 1 and maximum of 4). The baseline BCVA was 55.7 in the bevacizumab group and 54.6 in the laser arm. With a median of 9 injections over the 12-month study, the bevacizumab group had gained a median of 8 letters while the laser group lost a median of 0.5 letters (61.3 vs. 50.1). The odds of gaining >10 letters was 5.1 times greater with bevacizumab. There was a trend toward a greater decrease in central macular thickness (from 507 to 378 microns in the bevacizumab group and from 481 to 413 microns in the laser group, p=0.06).

The results from these lower quality randomized controlled trials suggest that bevacizumab is effective for the treatment of diabetic macular edema, similar to results found for ranibizumab.

**Diabetic Macular Edema: Pegaptanib (Macugen®)**

A Phase II randomized double masked trial of pegaptanib patients (n=172) with diabetic macular edema was reported by the Macugen Diabetic Retinopathy Study Group in 2005. (24) Intravitreous pegaptanib (0.3, 1, or 3 mg) or sham injections were given at study entry, week 6, and week 12, with additional injections and/or focal photocoagulation as needed for another 18 weeks. Final assessments, conducted at week 36, showed BCVA improvement of >10 letters in 34% of the 0.3-mg group, 30% of the 1-mg group, 14% of the 3-mg group, and 10% of the sham group. Median BCVA was significantly better at week 36 only with the 0.3-mg dose (20/50), as compared to sham (20/63), with a larger proportion of those receiving 0.3 mg gaining >10 letters (34% vs. 10%) and >15 letters (18% vs. 7%). Mean changes in retinal thickness decreased were -68, -23, -5, and +4 microns, respectively. The reason for the greater efficacy of the lowest dose is not clear.
One-year and 2-year results from a Phase II/III multicenter RCT of pegaptanib for the treatment of diabetic macular edema were reported by the Macugen 1013 study group in 2011. (25) In year 1, a total of 288 patients were randomized to pegaptanib 0.3 mg or sham injections every 6 weeks, with supplemental focal or grid photocoagulation as needed. (The original protocol had included treatment groups of 0.003, 0.03, and 0.3 mg pegaptanib, but the 2 lower doses were eliminated from the study due to drug product instability issues.) In the second year, injections were provided as needed per prespecified criteria at up to 6-week intervals. At 1-year follow-up (n=230), more patients in the pegaptanib group had an increase >10 letters (36.8% vs. 19.7%), and fewer pegaptanib than sham-treated subjects received focal/grid laser treatment (23.3% vs. 41.7%). At 2-year follow-up (n=132), pegaptanib patients gained an average of 6.1 letters versus 1.3 letters for the sham group. The proportion of subjects with an improvement >10 letters was 38.3% for pegaptanib and 30.0% for sham (not significantly different). Eighty-three patients (29%) discontinued the study, and 53 patients (18%) had not yet reached the 2-year endpoint at the time of data analysis. In addition to the marginal efficacy of pegaptanib over sham observed at 2 years, these results are potentially biased by the high loss to follow-up and use of the last-observation-carried-forward method.

Diabetic Macular Edema: Aflibercept (Eylea™)

In 2011, Do et al. reported 6-month results from the Phase II double-masked randomized, controlled multicenter (39 sites) DA VINCI trial of aflibercept (called “VEGF Trap-Eye” in the study) compared to laser photocoagulation. (26) A total of 221 patients with diabetic macular edema were randomized to 1 of 5 treatment regimens: 0.5 mg aflibercept every 4 weeks; 2 mg aflibercept every 4 weeks; 2 mg aflibercept for 3 initial monthly doses and then every 8 weeks; 2 mg aflibercept for 3 initial monthly doses and then on an as-needed (PRN) basis; or macular laser photocoagulation. Patients in the laser arm received sham injections at each visit, and patients in the aflibercept arms received sham injections during visits in which an active dose was not given. Sham laser was given to the aflibercept groups at week 1. Patients in the laser arm could be retreated no more often than every 16 weeks. A total of 200 patients (90%) completed the study, with a similar proportion of discontinuations among the treatment groups. Gains from baseline of >0, >10, and >15 letters were seen in 68%, 32%, and 21%, respectively, in the laser group. In the aflibercept groups, gains from baseline >0 letters ranged from 77% to 91%; >10 letters ranged from 43% to 64%, and >15 letters ranged from 17% to 34%. Outcomes tended to be worse for the 0.5 mg and the 8-week interval groups. A total of 200 patients (90%) completed the study, with a similar proportion of discontinuations among the treatment groups. Gains from baseline of >0, >10, and >15 letters were seen in 68%, 32%, and 21%, respectively, in the laser group. In the aflibercept groups, gains from baseline >0 letters ranged from 77% to 91%; >10 letters ranged from 43% to 64%, and >15 letters ranged from 17% to 34%. Outcomes tended to be worse for the 0.5 mg and the 8-week interval groups. No patients in the 2-mg aflibercept groups lost >15 letters compared with 9.1% of the laser group. Gains in visual acuity were significantly greater in the aflibercept groups (from 8.5 to 11.4 letters) compared with the laser group (2.5 letters). Mean reductions in central retinal thickness were significantly greater in the 4 aflibercept groups (ranging from -127.3 to -194.5 microns vs. -67.9 microns in the laser group). There was a 1-2% incidence of myocardial infarction, cerebrovascular accident, and death in patients who were treated with aflibercept compared with 0% in the laser group, but a history of cardiac disease was twice as common in the aflibercept groups compared with the laser group.

A Phase III trial is ongoing.
Diabetic Macular Edema: Section Summary

There is evidence that VEGF inhibitors (bevacizumab, ranibizumab, aflibercept) are efficacious agents for the treatment of DME when given by the intravitreal route. A large high-quality head-to-head comparison of aflibercept, bevacizumab, and ranibizumab by DRCRN demonstrated generally similar outcomes for the three agents, with some advantage of aflibercept in patients with worse visual acuity at baseline.

Additional evidence includes results from 2 sham-controlled trials and 3 controlled trials of ranibizumab versus laser photocoagulation. These studies report that ranibizumab is an efficacious agent for treating DME and consistently show superior outcomes compared with laser photocoagulation. Although for bevacizumab, the quality of the other RCTs is less, and for aflibercept there are fewer trials completed, the evidence from the DRCRN trial is sufficient to conclude that these agents are at least as effective as ranibizumab for the treatment of DME. Evidence remains insufficient to determine if pegaptanib is as effective as alternative treatments.

Proliferative Diabetic Retinopathy

VEGF inhibitors are being evaluated as adjunctive treatment to reduce bleeding, improve surgical outcomes, reduce edema, and improve visual acuity in patients with proliferative diabetic retinopathy. Typically, a single injection of a VEGF inhibitor is administered several days before photocoagulation or vitrectomy. In a 2011 Cochrane review, 4 RCTs of anti-VEGF for the prevention of postoperative vitreous cavity hemorrhage after vitrectomy were included, but due to methodologic issues, they were unable to conduct a meta-analysis. (27) Participants in the trials had to have proliferative diabetic retinopathy undergoing vitrectomy for the first time. Trials were excluded if participants had silicone oil used as a tamponade agent postoperatively. The authors concluded that results from one of the studies (28) supported the use of preoperative intravitreal bevacizumab to reduce the incidence of early vitreous cavity hemorrhage after vitrectomy, but due to methodologic issues in the remaining studies, definitive conclusions could not be reached.

Proliferative Diabetic Retinopathy: Ranibizumab (Lucentis™)

In 2013, the Diabetic Retinopathy Clinical Research Network reported a double-masked, randomized, 61 center Phase 3 trial with 261 patients that compared intravitreal injection at 0, 4, and 8 weeks of 0.5 mg ranibizumab or saline for the treatment of vitreous hemorrhage from proliferative diabetic retinopathy. (29) The cumulative probability of vitrectomy within 16 weeks was 12% with ranibizumab and 17% with saline, suggesting little likelihood of a clinically important difference in the short term. Secondary outcomes (complete panretinal photocoagulation, improvement in visual acuity, recurrent vitreous hemorrhage) showed a modest improvement with ranibizumab.

A 2015 study by Ip et al examined the effect of long-term use of ranibizumab on the development of proliferative diabetic retinopathy. (30) This was analysis of data from the RISE and RIDE trials previously described, and included 759 patients with DME, randomized to monthly 0.3 or 0.5 mg ranibizumab or sham injections for 2 years. (11) During the third year, patients in the sham arm could be treated with 0.5 -mg ranibizumab. The primary outcome for this analysis was a composite measure...
of progression to proliferative diabetic retinopathy based on photographic changes and clinical events. At the 36-month follow-up, a 3-step or greater improvement in the Early Treatment Diabetic Retinopathy Study severity scale was achieved by 3.3% of eyes in the sham/0.5 mg crossover arm, compared with 15.0% of eyes in the 0.3-mg arm and 13.2% of eyes in the 0.5-mg ranibizumab arm (p<0.000). By 36 months, proliferative diabetic retinopathy had developed in 39.1% of patients in the sham/0.5-mg group compared with 18.3% and 17.1% of eyes treated with 0.3 mg or 0.5 mg ranibizumab, respectively.

**Proliferative Diabetic Retinopathy: Bevacizumab (Avastin®)**

A number of smaller RCTs (<100 patients) have been identified that examined a single injection of bevacizumab as an adjunct to laser photocoagulation or vitrectomy.

One double-masked trial from 2010 (included in the Cochrane review above) randomized 68 eyes of 68 patients to a single injection of bevacizumab or sham injection 1 week before vitrectomy. (28) Eyes were included if indications for vitrectomy for complications of proliferative diabetic retinopathy existed such as nonclearing vitreous hemorrhage, tractional retinal detachment, and active progressive proliferative diabetic retinopathy. The primary outcome measure was the incidence of early postvitrectomy hemorrhage. Secondary outcome measures included changes in BCVA and adverse events. Nineteen eyes were omitted from the study because exclusion criteria were met during surgery (intraoperative use of long-acting gas or silicone oil). Resolution of vitreous hemorrhage was observed in 9 eyes (25.7%) after bevacizumab injection and 2 eyes (6.1%) in the control group, obviating the need for vitrectomy. Sixteen patients in the bevacizumab group and 18 patients in the control group completed the study according to the protocol. Intraoperative bleeding occurred in 63% of the bevacizumab group and 94% of the control group. Intraoperative endodiathermy for controlling the hemorrhage was reduced (mean of 1.90 vs. 2.47 times). Iatrogenic retinal breaks occurred in 2 eyes in the bevacizumab group and 1 eye in the control group. In both the intention-to-treat and per protocol analysis, the incidence of postvitrectomy hemorrhage 1 week and 1 month after surgery was significantly lower in the bevacizumab group compared with the control group. Mean BCVA (per protocol) improved from 1.88 to 0.91 logMAR in the bevacizumab group and from 1.88 to 1.46 logMAR in the control group. No bevacizumab-related complication was observed.

Another 2010 study randomized 40 eyes (40 patients) to a single 1.25 mg injection of bevacizumab 48 hours before vitrectomy or vitrectomy alone. (31) Inclusion criteria were presence of advanced proliferative diabetic retinopathy, presence of tractional retinal detachment threatening the macula area, and HbA1c <7. The effective vitrectomy time was significantly shorter in the bevacizumab group, taking 8.05 minutes versus 16.8 minutes for the control group. Mean total vitrectomy time was 62 minutes for the bevacizumab group and 98 minutes for the control group. There was also less intraoperative bleeding with bevacizumab. During 6 months of follow-up, the vitrectomy alone group showed no improvement in visual acuity, with values close to 2.0 logMAR. Visual acuity significantly improved in the bevacizumab group at follow-up of 1 week and 3 and 6 months. The mean final visual acuity at 6-month follow-up was 0.82 logMAR in the bevacizumab group versus 2.01 logMAR in the non-bevacizumab group. Persistent hemorrhage was observed in 4 eyes in the bevacizumab-treated group and 8 eyes in the control group. Transient ocular hypertension was observed in 3 eyes of the
bevacizumab group compared to none in the control group. There were no significant differences in
the incidence of complications between the 2 groups in this small study.

In 2010, Di Lauro and colleagues reported a block randomized study on 72 eyes of 68 patients with
severe proliferative diabetic retinopathy who were affected by vitreous hemorrhage and tractional
retinal detachment. (32) The patient groups were matched by vitreous hemorrhage, prior retinal laser-
photocoagulation, and morphologic type of retinal detachment. Outcome measures were the
intraoperative management, safety, and efficacy of bevacizumab at 7 or 20 days before vitrectomy. An
additional 3 patients were excluded from the study due to significant regression of the retinal
neovascularization and the complete clearing of vitreous hemorrhage after injection of bevacizumab.
In the group receiving sham injections, the mean surgical time was 84 minutes. Intraoperative
bleeding occurred in 79% of cases, use of endodiathermy in 54%, relaxing retinotomy in 4%, and
iatrogenic retinal breaks occurred in 17% of patients. In the group that received bevacizumab 7 days
before vitrectomy, the mean surgical time was 65 minutes. Intraoperative bleeding occurred in 8%,
and the use of endodiathery was necessary in 8%. No iatrogenic breaks occurred during the surgery.
In the group receiving bevacizumab 20 days before vitrectomy, the mean surgical time was 69
minutes. Intraoperative bleeding occurred in 13%, use of endodiathermy in 13%, and an iatrogenic
break in 4%. The best surgical results were achieved with bevacizumab administered 7 days
preoperatively. At 6-month follow-up, the mean BCVA had increased from 1.6 to 1.2 logMAR in the
sham-treated group, from 1.4 to 0.78 logMAR in the 7-day group, and from 1.6 to 0.9 logMAR in the
20-day bevacizumab group.

In a 2010 randomized study, a single injection of bevacizumab or triamcinolone was administered as
an adjunct to panretinal (scatter) photocoagulation to reduce the macular edema that can
develop/increase with this treatment. (33) Of 91 eyes (76 patients) with severe diabetic retinopathy, 46
eyes had clinically significant macular edema and 45 did not. Triamcinolone was administered 1 day
after the first session of photocoagulation while bevacizumab was given about 1 week before
photocoagulation. BCVA and central macular thickness at 1 and 3 months (after the final session of
photocoagulation) were compared with eyes that had been randomized to photocoagulation alone. At
baseline, the mean BCVA (logMAR) was 0.27 in the triamcinolone group, 0.28 in the bevacizumab
group, and 0.26 in the control group. The mean macular thickness was 344 microns in the
triamcinolone group, 328 microns in the bevacizumab group, and 326 microns in the control
(photocoagulation alone) group. In the photocoagulation alone group, there was significant worsening
of BCVA from 0.26 logMAR to 0.29 logMAR at both 1 and 3 months’ follow-up. In the triamcinolone
and bevacizumab groups, there were no significant changes in BCVA from baseline. In eyes without
macular edema at baseline, there was significant worsening of BCVA only in the control group
(photocoagulation alone). In eyes with macular edema at baseline, only the triamcinolone group had
an improvement in BCVA, and the proportion of eyes with a decrease in macular thickness was
greater with triamcinolone than with bevacizumab or photocoagulation alone. Triamcinolone resulted
in increased intraocular pressure in 4 eyes.

One double-masked trial with 40 patients used a single injection of bevacizumab on the first day of
laser treatment with a sham control procedure in the other (fellow) eye in patients with high-risk
diabetic retinopathy characteristics (identified by the area and location of neovascularization and/or
presence of hemorrhage). (34) All cases received standard laser treatment and focal or grid macular
photocoagulation for clinically significant macular edema. Panretinal laser photocoagulation was completed in 3 sessions, 1 week apart. Follow-up was performed on the first day, at weeks 1, 2, 3, and 6 and then monthly thereafter to monitor safety and efficacy. The primary outcome measure was regression, and the secondary outcome measure was recurrence from week 6 to week 16 of follow-up. A total of 87.5% of bevacizumab-treated eyes and 25% of control eyes showed complete regression at week 6. However, at week 16, proliferative diabetic retinopathy recurred in many of the bevacizumab-treated eyes, and the complete regression rate in the 2 groups was the same (25%). Partial regression rates were 70% versus 65%. The study concluded that repeat injections of bevacizumab may be needed.

In 2011, Schmidinger et al. reported the use of repeated intravitreal bevacizumab for the treatment of persistent new vessels after complete panretinal photocoagulation in a series of 10 patients (11 eyes). (35) Patients received bevacizumab at baseline and at each of the monthly follow-up visits when reappearance of retinal new vessels was documented. At the 1-week follow-up visit, 8 eyes (73%) showed complete regression of retinal neovascularizations. These 8 eyes had stable retinal findings until the 3-month follow-up visit. At the 3-month follow-up, 8 eyes (73%) were retreated with bevacizumab because of the reappearance of new vessels. At 6 months, 36% of the eyes were found to have reperfusion of retinal new vessels and were retreated. Over the course of the 6-month study, the mean retreatment rate was 1.9, with a mean interval to retreatment of 2.9 months. The mean leakage area decreased from 7.2 mm² at baseline to 1.2 mm² at the final follow-up. BCVA increased from 59.2 to 70.7 at the final visit.

Proliferative Diabetic Retinopathy: Pegaptanib (Macugen®)

Gonzalez et al. compared intravitreal pegaptanib versus panretinal photocoagulation in a randomized open-label study of 20 patients with active proliferative diabetic retinopathy. (36) Pegaptanib-treated eyes were scheduled to receive a total of 6 intravitreal injections at 6-week intervals, while photocoagulation was administered in 1 or 2 sessions. Two patients from each arm were discontinued from the study due to non-compliance. In 90% of the eyes randomized to pegaptanib, retinal neovascularization showed regression by week 3. By week 12, all pegaptanib-treated eyes showed complete regression of neovascularization, and this was maintained through week 36. In the laser-treated group, 2 eyes showed complete regression, 2 showed partial regression, and 4 showed active proliferative retinopathy. The mean change in visual acuity at 36 weeks was +5.8 letters in pegaptanib-treated eyes and -6.0 letters in laser-treated eyes (not statistically significant). Additional controlled studies with a larger number of subjects and longer follow-up are needed to evaluate the safety and efficacy of pegaptanib for this condition.

Proliferative Diabetic Retinopathy: Section Summary

For the treatment of proliferative diabetic retinopathy, evidence is available for ranibizumab, bevacizumab and pegaptanib. A number of smaller RCTs report superior outcomes for bevacizumab as a single agent or as an adjunct to vitrectomy. A single small RCT reported that pegaptanib was not significantly more effective than photocoagulation for patients with proliferative diabetic retinopathy. For the treatment of proliferative diabetic retinopathy, evidence is available for ranibizumab, bevacizumab and pegaptanib. A number of smaller RCTs report superior outcomes for bevacizumab.
as a single agent or as an adjunct to vitrectomy. A single small RCT reported that pegaptanib was not significantly more effective than photocoagulation for patients with proliferative diabetic retinopathy. Analysis of data from the RISE and RIDE trials found that treatment with ranibizumab over 3 years led to improvement in proliferative diabetic retinopathy in a significantly greater proportion of eyes than those treated with sham injections for the first 2 years. In February 2015, FDA approved Lucentis™ to treat diabetic retinopathy in patients with diabetic macular edema.

**Retinal Vein Occlusion**

A 2010 Cochrane review assessed the evidence on the use of anti-VEGF treatments for macular edema secondary to central retinal vein occlusion. (37) Included in the review were the CRUISE (ranibizumab) and CRVOSC (pegaptanib) studies, which are described in more detail below. (37, 38) Participants with ischemic central retinal vein occlusion (CRVO) were excluded in these trials. The primary outcome for the systematic review was BCVA of >15 letters (3 lines) on the Early Treatment in Diabetic Retinopathy Study (EDTRS) Chart with at least 6 months of follow-up. Secondary outcomes were the proportion of patients with a loss of 15 or more letters compared to baseline and objective assessment of macular edema regression, measured by mean change in central retinal thickness on ocular coherence tomography (OCT). In the study with ranibizumab, outcomes were significantly improved in both treatment groups compared to sham. (38) In the smaller Phase II study with pegaptanib, efficacy was demonstrated for some but not all outcomes. (39) The authors noted that numerous RCTs investigating anti-VEGF for the treatment of CRVO were in progress, and that, while anti-VEGF may improve outcomes at 6 months, effectiveness and safety over longer periods of follow-up had yet to be determined. In addition, there were no RCT data on their use in the treatment of ischemic CRVO, and the optimal timing of treatment had not yet been determined.

A 2013 Cochrane review assessed the evidence on the use of anti-VEGF treatments for macular edema secondary to branch retinal vein occlusion. (40) Included in the review was the BRAVO trial (RCT of ranibizumab versus placebo, described in more detail below) and a small quasi-randomized study of bevacizumab with 30 patients. (41, 42) A larger study with bevacizumab was excluded as it had follow-up only to 3 months. (3 The Cochrane review concluded that ranibizumab may improve clinical and visual outcomes at 6 and 12 months, but questions remain concerning the frequency of retreatment, the effect of prior or combined laser photocoagulation on outcomes, and long-term efficacy and safety.

**Retinal Vein Occlusion: Ranibizumab (Lucentis™)**

Ranibizumab has been evaluated for macular edema following central retinal vein occlusion (CRVO) and branch retinal vein occlusion (BRVO), with 6- and 12-month results available from 2 double-masked multicenter trials.

A Phase III trial of ranibizumab for macular edema following CRVO was reported by the CRUISE investigators in 2010 and 2011. (38, 44) A total of 392 patients with macular edema after CRVO were randomized to monthly injections of 0.3 or 0.5 mg ranibizumab or sham. Inclusion criteria were BCVA ≤20/40 or mean central subfield thickness ≥250 microns. Randomization was stratified by baseline BCVA letter score and study center. One eye was chosen as the study eye for each patient. The
intent-to-treat approach was used for efficacy analysis and included all patients as randomized; missing values were imputed using the last observation carried forward. The approximate BCVA at baseline was 20/100, and the central foveal thickness was more than 650 microns. The improvement in BCVA following ranibizumab treatment was rapid, with patients gaining an average of 9 letters 7 days after the first injection. Following treatment for 6 months, the mean change from baseline BCVA score was 12.7 and 14.9 letters in the 0.3-mg and 0.5-mg groups compared with 0.8 letters in the sham group. The percentage of patients who gained >15 letters was 46.2% (0.3 mg) and 47.7% (0.5 mg) in the ranibizumab groups and 16.9% in the sham group. The percentage of patients who achieved BCVA >20/40 was 43.9% (0.3 mg) and 46.9% (0.5 mg) compared with 20.8% in the sham group. Central foveal thickness decreased by a mean of 434 microns (0.3 mg) and 452 microns (0.5 mg) in the ranibizumab groups and 168 microns in the sham group. At month 6, the mean increase from baseline National Eye Institute Visual Functioning Questionnaire-25 (NEI VFQ-25) composite score was 7.1 points (0.3 mg) and 6.2 points (0.5 mg) in the ranibizumab-treatment groups compared with 2.8 points in the sham group.

After 6 months, all patients with BCVA <20/40 or mean central subfield thickness >250 microns could receive ranibizumab. Between months 6 and 12, the mean number of as-needed ranibizumab injections was 3.8, 3.3, and 3.7 in the 0.3-mg, 0.5-mg, and sham/0.5-mg groups, respectively. At 12-month follow-up, the mean change from baseline BCVA was maintained at 13.9 letters in both ranibizumab groups and improved to 7.3 letters in the sham/0.5 mg group. The percentage of patients who gained >15 letters was 47% and 50.8% for 0.3 mg and 0.5 mg ranibizumab and 33.2% for sham/0.5 mg. The reduction in central foveal thickness in the ranibizumab groups was maintained at 453 (0.3 mg) and 462 (0.5 mg) microns at month 12. There was a rapid reduction in average central foveal thickness in the sham/0.5-mg group after the first as-needed injection of ranibizumab; this was sustained through month 12 (427 micron reduction). The reduction in central foveal thickness did not differ significantly between the 3 groups. Treatment with ranibizumab as needed from months 6-11 maintained, on average, the increases in the NEI VFQ-25 (7.1 and 6.6 points) and resulted in an increase of 5 points from baseline in the sham/0.5-mg group. There was an increase in the incidence of cataract in the ranibizumab groups at 12 months (3.8% for 0.3 mg and 7.0% for 0.5 mg) compared with 0% for sham at 6-months.

Also published in 2010 and 2011 by the BRAVO investigators were results from a Phase III trial of ranibizumab for macular edema following BRVO. (41, 42) The study design was similar to the study on CRVO (above) and included 397 patients with macular edema who received monthly intracocular injections of 0.3 mg or 0.5 mg ranibizumab or sham injections. Rescue laser treatment was allowed for eyes meeting pre-specified criteria. The approximate BCVA at baseline was 20/80, and the central foveal thickness was greater than 475 microns. At 7 days after the first treatment, the ranibizumab groups had gained an average of 7.5 letters. After 6 months of treatment, the mean BCVA improvement was 16.6 and 18.3 letters for the 0.3-mg and 0.5-mg ranibizumab groups and 7.3 letters for the sham group. The percentage of patients who gained >15 letters was 55.2% (0.3 mg) and 61.1% (0.5 mg) in the ranibizumab groups compared with 28.8% in the sham group. The percentage of patients who achieved BCVA >20/40 was 67.9% (0.3 mg) and 64.9% (0.5 mg) compared with 41.7% in the sham group. Central foveal thickness decreased by a mean of 337 microns (0.3 mg) and 345 microns (0.5 mg) in the ranibizumab groups and 158 microns in the sham group. More patients in
the sham group (54.5%) received rescue grid laser compared with the 0.3-mg (18.7%) and 0.5-mg (19.8%) ranibizumab groups. No new safety events were identified in patients with BRVO.

After 6 months, all patients with BCVA <20/40 or mean central subfield thickness >250 microns could receive ranibizumab. Patients could also receive rescue laser treatment once during the observation period if criteria were met. The percentage of patients who received rescue laser treatment during the 6-month observation period was 30.6% (0.3 mg), 23.7% (0.5 mg), and 23.5% (sham/0.5 mg). Between months 6 and 12, the mean number of as-needed ranibizumab injections was 2.8, 2.7, and 3.6 in the 0.3-mg, 0.5-mg, and sham/0.5-mg groups, respectively. The percentage of patients who did not receive any injections during the observation period was 20.9%, 23.7%, and 12.9%, respectively. There was a decrease in BCVA in eyes that did not receive ranibizumab from month 6 to 7, but the mean change from baseline BCVA letter score at month 12 was maintained at 16.4 (0.3 mg) and 18.3 (0.5 mg) letters. Eyes in the sham/0.5-mg group gained 12.1 letters from baseline; this was significantly lower than both ranibizumab groups. The percentage of patients who gained >15 letters from baseline at month 12 was 56.0%, and 60.3% in the 0.3-mg and 0.5-mg groups and 43.9% in the sham/0.5-mg group. On average, the reduction in central foveal thickness was maintained in the ranibizumab groups (314 and 347 microns). There was a rapid reduction in central foveal thickness after the first as-needed injection in the sham/0.5-mg group, which was sustained through month 12 (273.7 microns); this was significantly less than both ranibizumab groups. No new ocular or nonocular safety events were identified, although the cataract rate was reported to be 4.5% and 6.2% in the 0.3-mg and 0.5-mg ranibizumab groups compared with 3.1% for sham at 6 months.

Vision-related function in the BRAVO and CRUISE trials was reported by Varma et al. in 2012. (45) Baseline scores on the NEI VFQ-25 were comparable between groups. Through the 6 month follow-up, visual function on the NEI VFQ-25 was statistically greater in the ranibizumab groups compared to sham. In BRAVO, the sham group improved by 5.4 points, the ranibizumab 0.3 mg group improved by 9.3 points, and the 0.5 mg group improved by 10.4 points. In CRUISE, the sham group improved by 2.8 points, the 0.3 mg group improved by 7.1 points, and the 0.5 mg group improved by 6.2 points. The proportion of patients who improved by a clinically meaningful amount (> 5 points on the NEI VFQ-25) was reported to be greater for ranibizumab than sham.

**Bevacizumab (Avastin®)**

Three RCTs from outside of the U.S. have been published on the use of bevacizumab for macular edema following retinal vein occlusion. Two of the trials were sham-controlled (1 CRVO and 1 BRVO), the third compared bevacizumab with triamcinolone in patients with BRVO.

In 2012, Epstein et al. reported a randomized, sham-controlled, double-masked trial in 60 patients with CRVO. (46, 47) Intracocular bevacizumab or sham injections were administered every 6 weeks for 6 months. For the next 6 months, all patients received bevacizumab every 6 weeks. Mean BCVA at baseline was 44.1 letters (Snellen equivalent of 20/125). At 6-month follow-up, mean BCVA improved by 14.1 letters in the bevacizumab group compared with a decrease of 2.0 letters in the control group. Sixty percent of patients in the bevacizumab group had gained 15 letters or more compared to 20% in the control group, and 6.7% of patients in the bevacizumab group lost more than 15 letters compared to 23.3% in the control group. The mean decrease in central retinal thickness was greater in the
bevacizumab group (426 microns) compared to controls (102 microns), and 86.7% of patients in the bevacizumab group had no residual edema (defined at central retinal thickness < 300 microns) compared to 20% in the control group. At 12-month follow-up, central retinal thickness decreased to a similar extent in the continued bevacizumab vs. delayed bevacizumab groups (435 microns vs. 404 microns). The percentage of patients who had gained 15 letters or more remained at 60% in the bevacizumab/bevacizumab group, while 33% of patients who received sham/bevacizumab gained 15 letters or more, suggesting that patients receiving delayed treatment may have limited visual improvement.

A 2011 publication reported a double-masked sham-controlled RCT in 81 eyes (81 patients) with branch retinal vein occlusion (BRVO). (43) Bevacizumab or sham injection was administered after baseline and week 6. The mean duration of symptoms was 7.5 weeks in the bevacizumab group and 4.9 weeks in the sham group. In the sham group, BCVA was 0.8 logMAR at baseline, 0.75 logMAR at week 6, and 0.66 logMAR at week 12. In the bevacizumab group, BCVA improved from 0.74 logMAR at baseline to 0.49 logMAR at week 6 and 0.42 logMAR at week 12. The difference between groups was statistically significant at week 6 and approached significance (p=0.064) at week 12. Central macular thickness at baseline was 471 microns for the control group and 575 microns for the bevacizumab group. At week 6, the central macular thickness was 462 microns for sham and 325 microns for bevacizumab. Central macular thickness at week 12 was 393 microns for sham versus 309 microns for bevacizumab. The difference in macular thickness was statistically different at both 6 and 12 weeks’ follow-up.

Another study with 52 patients compared triamcinolone (4 mg) or bevacizumab (1.25 mg) monotherapy versus combined therapy (2 mg triamcinolone and 1.25 mg bevacizumab) for macular edema due to BRVO. (48) Fifty-two eyes with BRVO, visual acuity of 20/40 or worse, and central macular thickness of 250 microns or greater were enrolled in the study. Nearly 90% of eyes received intravitreal injections as the primary treatment, the remainder had received grid laser photocoagulation at least 4 months before enrollment. Re-injections of triamcinolone or bevacizumab were done when macular edema recurred that was at least 1 month apart for bevacizumab monotherapy, 2 months for bevacizumab plus triamcinolone, and 3 months for triamcinolone monotherapy, and the mean number of injections within 6 months ranged from 1.4 to 1.6. Otherwise, grid laser photocoagulation was performed. Macular grid laser photocoagulation was applied within 3 months of injections in 47% of the triamcinolone monotherapy group, 50% of bevacizumab monotherapy, and 43% of the combined treatment group. All 3 groups showed significant reductions of central macular thickness and improvement in visual acuity 1 month after injection, but by 6 months, only the bevacizumab monotherapy group demonstrated significant improvement in visual acuity (from 0.9 to 0.4 logMAR). At 6 months, there was a significant reduction in central macular thickness for all 3 groups (follow-up was completed in 86-88% of patients in the monotherapy groups but only 48% of the combined therapy group). The average intraocular pressure change from baseline (+1.4) was significantly higher in the triamcinolone monotherapy group. Cataract progression was noted in 36% of phakic eyes in the triamcinolone monotherapy group, 8% of the bevacizumab monotherapy group, and 10% of eyes in the combined treatment group.

Yasuda et al. reported rebound of macular edema (>110% of baseline thickness) in 7 of 65 eyes (10.8%) after treatment of BRVO with bevacizumab. (49) This retrospective study examined the
records of all patients who had received an intravitreal injection of bevacizumab, had received no other treatment for BRVO, and had at least 6 months of follow-up. Patients were evaluated monthly for BCVA and foveal thickness by OCT. The mean interval between the onset of symptoms and intravitreal bevacizumab was 10 weeks (range, 2 to 52 weeks). Bevacizumab was found to be not effective in 3 eyes (4.6%), effective without recurrence in 21 eyes (32.3%), effective with a recurrence <110% of baseline thickness in 34 eyes (52.3%), and effective with a recurrence ≥110% of baseline thickness in 7 eyes (10.8%). Retreatment was performed as needed. Multivariate logistic regression and subgroup analyses showed that a thinner pretreatment fovea and a shorter interval between symptom onset to the initiation of the intravitreal bevacizumab were significantly associated with a rebound of macular edema. The interval from symptom onset to the initiation of treatment was less than 8 weeks in all 7 eyes with a rebound macular edema.

Another retrospective study from 2011 evaluated factors predictive for improvement of visual acuity and central retinal thickness following treatment with bevacizumab. (50) A total of 205 eyes (204 patients) with macular edema secondary to BRVO from 6 sites were included. Measurement of BCVA and retinal thickness was measured every 12 weeks with results at 24 weeks used for analysis of predictive factors. The mean follow-up was 36.8 weeks (range, 18 to 54 weeks). During the follow-up period, retreatments were performed in 85% of eyes, with a median of 3 injections (range, 1 to 10). Although both non-ischemic and ischemic eyes showed a median 2-line improvement of BCVA, the final median BCVA was significantly worse in eyes with ischemic macular edema compared to non-ischemic macular edema (0.6 logMAR vs. 0.3 logMAR). Eyes with a duration of macular edema less than 3 months had a median 2.5-line improvement of BCVA, while eyes with a duration of macular edema between 3 and 12 months had a median 2-line increase in BCVA, and eyes with a duration >12 months had a 0.5-line increase in median BCVA. Other factors identified were absence of previous treatments of macular edema, age younger than 60 years, and low baseline BCVA.

Additional studies are needed to determine the appropriate candidates and timing of anti-VEGF treatment and to evaluate durability of treatment over longer periods of follow-up. Comparison with grid photocoagulation for BRVO is also needed.

Retinal Vein Occlusion: Pegaptanib (Macugen®)

In 2009, the Central Retinal Vein Occlusion Study Group published results from their Phase II multicenter double-masked randomized trial (CRVOSC). (39) Ninety-eight subjects were randomized to receive 0.3 mg or 1 mg pegaptanib or sham injections every 6 weeks for 24 weeks. For the primary outcome measure (the percentage of subjects showing a gain of 15 or more letters at week 30), there was no significant difference between the groups treated with pegaptanib 0.3 mg and 1 mg (36% and 39%, respectively) and the control group (28%). For the secondary outcome measures, fewer subjects treated with pegaptanib lost 15 or more letters (9% and 6%) compared with sham-treated eyes (31%) and showed greater improvement in mean visual acuity (+7.1 and +9.9 vs. -3.2 letters with sham). However, there was no difference in the percentage of subjects with visual acuity of 20/50 or better at week 30 (33% for both pegaptanib doses and 34% for sham). By week 30, the difference in mean reduction in retinal thickness between the 0.3-mg dose and sham was 95 microns, while the difference between the 1-mg group and sham was 31 microns.
Retinal Vein Occlusion: Aflibercept (Eylea™)

Safety and efficacy of aflibercept were assessed in two pivotal randomized, multi-center, double-masked, sham-controlled studies (COPERNICUS and GALILEO) in patients with macular edema following CRVO. (2) A total of 358 patients were randomized in a 3:2 ratio to 2mg aflibercept or sham administered every 4 weeks. Between 24 and 48 weeks patients were treated PRN. At 24 weeks, the proportion of patients who gained at least 15 letters in BCVA following treatment with aflibercept was 56% and 60% (COPERNICUS and GALILEO, respectively). For the 2 control groups, 12% and 22% of patients gained at least 15 letters. The mean change in BCVA was 17.3 and 18.0 letters for aflibercept compared to -4.0 and +3.3 for controls (all respectively).

The 6-, 18- and 24-month results of the COPERNICUS and GALILEO trials were published in 2013 and 2014. (51-54) At 52 weeks in the GALILEO trial, the percentage of patients gaining 15 or more letters was 60.2% in the aflibercept group and 32.4% in the sham group, and at 76 weeks, the proportion of patients gaining at least 15 letters was 57.3% and 29.4%, respectively. At 100 weeks in the COPERNICUS trial, the proportion of patients who gained at least 15 letters was 49.1% in the aflibercept groups and 23.3% with sham. All differences were statistically significant. Treatment with aflibercept also led to a greater reduction in central retinal thickness compared with sham treatment.

Retinal Vein Occlusion: Section Summary

RCTs on the treatment of retinal vein occlusion are available for all four agents (ranibizumab, bevacizumab, pegaptanib, and aflibercept). These trials are consistent in reporting that ranibizumab, bevacizumab, and aflibercept are efficacious agents in preserving visual acuity and reducing retinal thickness. The largest amount of evidence is available for ranibizumab and bevacizumab, but there is no evidence that one agent is superior to the others for this indication.

Retinopathy of Prematurity

Retinopathy of Prematurity: Bevacizumab (Avastin®)

The BEAT-ROP cooperative study group reported a multicenter randomized trial of a single injection of bevacizumab versus conventional laser therapy in 2011. (55) One hundred and fifty infants (300 eyes with stage 3+ disease in zone I or zone II) were randomized to receive intravitreal bevacizumab or conventional laser therapy. (Zone I is a circle whose radius extends from the optic disk and is twice the distance between the center of the disk and the center of the macula, while zone II encircles zone I with a radius that is 3 times the distance between the center of the disk and the center of the macula.) The study was not masked, due to the marks made by laser therapy. However, photographs taken at 54 weeks were assessed post hoc by 6 independent experts at the reading center who were masked to treatment by cropping the photographs. The primary outcome was recurrence of retinopathy of prematurity in one or both eyes requiring retreatment before 54 weeks’ postmenstrual age. Retinopathy of prematurity was found to recur in 4 infants (4%) in the bevacizumab group compared to 19 infants (22%) in the laser-therapy group. The mean time for recurrence was 16.0 weeks for 6 eyes after bevacizumab compared with 6.2 weeks for 32 eyes after laser therapy. When divided by zone, a significant treatment effect was found for zone I disease but not for zone II. For
zone I disease, recurrences were observed in 6% of infants treated with bevacizumab compared to 42% of infants treated with laser therapy. For zone II disease, the rate of recurrence was 5% in infants treated with bevacizumab and 12% in infants treated with laser therapy. The study appears to have been underpowered to detect the smaller difference between the groups in zone II, since there is less recurrence following laser therapy in zone II (12%) than zone I (42%), and the study did not achieve the target enrollment of 50 infants per group with zone II disease. Notably, intravitreal bevacizumab was found to allow vessel growth into the peripheral retina while conventional laser therapy resulted in permanent destruction of vessels in the peripheral retina. Thus, bevacizumab was more effective than laser for zone I disease and at least as effective as laser for zone II disease without the ocular adverse effects of laser therapy, which can include significant loss of visual field.

Retinopathy of Prematurity: Pegaptanib (Macugen®)

In 2012, Autrata et al. reported a randomized study of intravitreal pegaptanib combined with laser therapy in 152 eyes (76 premature babies) with stage 3+ ROP in zone I and posterior zone II. (56) Controls were treated with laser alone or laser plus cryotherapy. The authors did not report the method of randomization or whether the treatment condition was masked. The rationale for using pegaptanib was that the more selective VEGF-165 inhibitor might be a safer option for ROP treatment than bevacizumab. The primary outcome of treatment success was defined as absence of recurrence of stage 3+ ROP in one or both eyes by 55 weeks postmenstrual age. This outcome was observed in 85.4% of eyes in the pegaptanib group and 50% of eyes in the control group. Treatment failure, defined as the recurrence of neovascularization, was observed in 11.7% of infants in the pegaptanib groups and 38% of infants in the laser control group. At about 20 months follow-up, 89.7% of eyes in the pegaptanib group and 60.8% of eyes in the laser control group had a favorable anatomic outcome and stable regression of ROP.

Retinopathy of Prematurity: Section Summary

The evidence on the benefit of VEGF treatment for retinopathy of prematurity is limited. However, at least two RCTS, one using bevacizumab and a more problematic study using pegaptanib, report that recurrence of retinopathy is reduced compared to laser treatment alone. This evidence suggests that bevacizumab improves outcomes for infants with retinopathy of prematurity when given by the intravitreal route.

Neovascular Glaucoma

A 2013 Cochrane review found no RCTs that met the review’s inclusion criteria; 2 RCTS of anti-VEGF agents for treating neovascular glaucoma were not included in the review due to heterogeneity and uncontrolled adjunct treatments. (57)

Clinical Trials

A search of the online site ClinicalTrials.gov in February 2015 identified a number of clinical trials with anti-VEGF therapy for retinal vascular conditions. Of particular note are the following:
• NCT01428388: A comparison of bevacizumab and ranibizumab for the treatment of macular edema from retinal vein occlusion (CRAVE). The study has an estimated enrollment of 150 subjects with completion expected in May 2014.

• NCT01635790: A randomized comparison of effectiveness and cost of bevacizumab and ranibizumab in patients with diabetic macular edema (BRDME). A total of 246 patients are expected to be enrolled. The expected study completion date is June 2016.

• NCT01331681: An industry-sponsored Phase III study of aflibercept (VEGF Trap-Eye) vs. laser photocoagulation in subjects with diabetic macular edema (VIVID-DME). The primary outcome is the change from baseline of BCVA ETDRS (early treatment diabetic retinopathy) letter score at 52 weeks. A total of 404 subjects are expected to be enrolled, with the primary outcome measure completed by May 2013 and a study completion date of April 2015. This study has results.

• NCT01783886: An industry-sponsored randomized, double-masked Phase III comparison of VEGF-Trap Eye vs laser photocoagulation for treatment of diabetic macular edema. The study has an estimated enrollment of 375 patients with completion expected July 2015.

• NCT01908816: An industry-sponsored open-label extended clinical protocol of ranibizumab to evaluate safety and efficacy in rare VEGF-driven ocular diseases (ECLIPSE). The study has an estimated enrollment of 350 patients with completion expected in September 2017.

Practice Guidelines and Position Statements

In a final appraisal determination from July 15, 2011, the United Kingdom’s National Institute for Health and Clinical Excellence (NICE) does not recommend ranibizumab (Lucentis) for the treatment of diabetic macular edema. (58) The independent Appraisal Committee found that the manufacturer's model underestimated the incremental cost-effectiveness ratio (ICER) for ranibizumab monotherapy compared with the current standard treatment for people with diabetic macular edema, laser photocoagulation. It concluded that a model that relied on a combined set of plausible assumptions would be certain to produce an ICER that substantially exceeded the range that NICE considers represents an effective use of National Health Service (NHS) resources. Therefore, ranibizumab could not be recommended as a treatment for people with diabetic macular edema. In 2013 NICE issued a Technology Assessment (TA) 274 that stated that ranibizumab is recommended as an option for the treatment of macular edema only if the eye to be treated has a central retinal thickness of 400 micrometers or more at the start of treatment and the agreed upon manufacturer discount is in place. (59)

In 2013 NICE issued TA283 which recommended the use of ranibizumab as a treatment option for macular edema following central retinal vein occlusion or branch retinal vein occlusion only if treatment with laser photocoagulation has not been beneficial or is not possible due to macular hemorrhage. It is also only recommended if the agreed upon manufacturer discount is in place. (60) The 2014 Preferred Practice Pattern for Diabetic Retinopathy and the 2014 Benchmark Summary from the American Academy of Ophthalmology state that multiple studies have demonstrated the benefit of anti-VEGF therapy in cases of center-involving diabetic edema. The guideline also states that at the present time, anti-VEGF is the initial treatment of choice for center-involving macular edema with
possible subsequent or deferred focal laser treatment. This recommendation is derived from data from the Diabetic Retinopathy Clinical Research Network in 2011 that demonstrated that, at 2 years of follow-up, intravitreal ranibizumab with prompt or deferred laser resulted in greater visual acuity gain in pseudophakic eyes compared with laser alone. Adverse effects and complications of intravitreal injections include infectious endophthalmitis, transient sterile inflammatory reactions, and a possible systemic effect.

**U.S. Preventive Services Task Force Recommendations**

Not applicable

**Summary**

There is evidence that vascular endothelial growth factor (VEGF) inhibitors (bevacizumab, ranibizumab, aflibercept) are efficacious agents for the treatment of diabetic macular edema (DME) when given by the intravitreal route. A high-quality randomized controlled trial (RCT) with head-to-head comparison of aflibercept, bevacizumab, and ranibizumab was performed by the Diabetic Retinopathy Clinical Research Network (DRCRN). This trial demonstrated generally similar outcomes for the 3 agents, with some advantage of aflibercept in patients with worse visual acuity at baseline.

Additional evidence includes 2 sham-controlled trials and 3 trials that compared ranibizumab versus laser photocoagulation. These trials consistently show that ranibizumab is an efficacious agent for treating DME and results in superior outcomes compared with laser photocoagulation. Although for bevacizumab, the quality of the other RCTs is less, and for aflibercept, there are fewer trials completed, the evidence from the DRCRN trial is sufficient to conclude that the these agents are at least as effective as ranibizumab for the treatment of DME. Evidence remains insufficient to determine if pegaptanib is as effective as alternative treatments.

For the treatment of proliferative diabetic retinopathy, evidence is available for ranibizumab, bevacizumab and pegaptanib. A single small RCT reported that pegaptanib was not significantly more effective than photocoagulation for patients with proliferative diabetic retinopathy. Analysis of data from the RISE and RIDE trials found that treatment with ranibizumab over 3 years led to improvement in proliferative diabetic retinopathy in a significantly greater proportion of eyes than those treated with sham injections for the first 2 years. In February 2015, the U.S. Food and Drug Administration approved Lucentis™ to treat diabetic retinopathy in patients with DME. A number of smaller RCTs report superior outcomes for bevacizumab as a single agent or as an adjunct to vitrectomy.

RCTs on the treatment of retinal vein occlusion are available for all 4 agents (ranibizumab, bevacizumab, pegaptanib, aflibercept). These trials are consistent in reporting that ranibizumab, bevacizumab, and aflibercept are efficacious agents in preserving visual acuity and reducing retinal thickness. The largest amount of evidence is available for ranibizumab and bevacizumab, but there is no evidence that either agent is superior to the others for this indication.

The evidence on the benefit of VEGF treatment for retinopathy of prematurity (ROP) is limited. However, at least 2 RCTS, one high-quality trial using bevacizumab and a more problematic study
using pegaptanib, report that recurrence of retinopathy is reduced compared with laser treatment alone. This evidence suggests that bevacizumab improves outcomes for infants with ROP when given by the intravitreal route.

Given the similarity in efficacy of aflibercept, bevacizumab, and ranibizumab, these 3 VEGF inhibitors may be considered medically necessary for the treatment of DME and proliferative retinopathy, retinal vein occlusion, and ROP. Based on clinical input, aflibercept, bevacizumab, and ranibizumab may be considered medically necessary for the treatment of neovascular glaucoma and rubeosis (neovascularization of the iris).

Trials with pegaptanib for DME and retinal vein occlusion do not conclusively demonstrate a gain in visual acuity with this treatment. Pegaptanib was reported to be superior to laser therapy in a large trial of infants with ROP, although this study did not describe the method of randomization or whether the treatment condition was masked. Therefore, intravitreal injection of pegaptanib for retinal vascular conditions is considered investigational.

References


Section: Other
Effective Date: July 15, 2015
Subsection: Vision
Original Policy Date: September 13, 2011
Subject: Intravitreal Angiogenesis Inhibitors for Retinal Vascular Conditions
Page: 24 of 29


Intravitreal Angiogenesis Inhibitors for Retinal Vascular Conditions

Policy History

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Reason</th>
</tr>
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<tbody>
<tr>
<td>September 2011</td>
<td>New Policy</td>
<td>Literature search update. References 7, 10 and 33 added.</td>
</tr>
<tr>
<td>September 2012</td>
<td>Replace Policy</td>
<td>Aflibercept considered medically necessary for diabetic macular edema; bevacizumab considered medically necessary for stage 3+ retinopathy of prematurity.</td>
</tr>
<tr>
<td>June 2013</td>
<td>Update Policy</td>
<td>Policy updated with literature review; references added and reordered; Policy statements Ranibizumab and bevacizumab considered medically necessary for neovascular glaucoma and rubeosis; stage 3+ removed from treatment of retinopathy of prematurity; aflibercept may be considered medically necessary for macular edema following central retinal vein occlusion.</td>
</tr>
<tr>
<td>June 2014</td>
<td>Update Policy</td>
<td>Policy updated with literature review through February 23, 2014; references 6, 9, 11-12, 15, 26, 36, 47-48, 53-54, and 56 added and reordered; policy statements unchanged</td>
</tr>
<tr>
<td>June 2015</td>
<td>Update Policy</td>
<td>Policy updated with literature review through January 30, 2015; references 7-8, 29, 52-53 added, and references 1-2, 60-61 updated. Treatment of proliferative diabetic retinopathy considered medically necessary; ranibizumab, bevacizumab, and aflibercept considered equivalent and policy statements combined.</td>
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Keywords

Diabetic Retinopathy
Macular Edema
Retinal Vein Occlusion
Anti-VEGF
Bevacizumab, Avastin
Branch Retinal Vein Occlusion, BRVO

Central Retinal Vein Occlusion, CRVO
Diabetic Retinopathy
Aflibercept, EYLEA
Ranibizumab, Lucentis
Pegaptanib, Macugen

This policy was approved by the FEP Pharmacy and Medical Policy Committee on June 19, 2015 and is effective July 15, 2015.

Signature on file

Deborah M. Smith, MD, MPH