Intravitreal Angiogenesis Inhibitors for Retinal Vascular Conditions

Medical Policy

Section | Original Policy Date | Last Review Status/Date
---|---|---
Miscellaneous Policies | 12/2013 | Reviewed with literature search/12/2013

Issue
12/2013

Disclaimer

Our medical policies are designed for informational purposes only and are not an authorization, or an explanation of benefits, or a contract. Receipt of benefits is subject to satisfaction of all terms and conditions of the coverage. Medical technology is constantly changing, and we reserve the right to review and update our policies periodically.

Description

Angiogenesis inhibitors (e.g., ranibizumab, bevacizumab, pegaptanib, aflibercept) can be given via intraocular injections as a treatment for 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. Pegaptanib 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. Labeling indicates that patients should be treated monthly. The FDA has required a postmarketing safety and efficacy study on at least 150 patients who have received at least 7 doses of Lucentis™ and have been followed for at least 15 months. In 2012, ranibizumab was approved for the treatment of 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) As of 2012, a supplemental Biologics License Application (sBLA) was under review by the FDA for the treatment of patients with diabetic macular edema.

Bevacizumab has been developed and approved for use in oncology but has not been licensed for use in the eye.

Policy

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

- Diabetic macular edema*
- Proliferative diabetic retinopathy as an adjunctive treatment to vitrectomy or photocoagulation
- Macular edema following central retinal vein occlusion*
- Macular edema following branch retinal vein occlusion*
- Neovascular glaucoma
- Rubeosis (neovascularization of the iris)

Intravitreal injection of bevacizumab may be considered medically necessary for the treatment of retinopathy of prematurity.

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

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

- Diabetic macular edema
- Macular edema following central retinal vein occlusion**

Intravitreal injection of aflibercept is considered investigational for treatment of other retinal vascular disorders, including proliferative diabetic retinopathy and macular edema following branch retinal vein occlusion.

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)
**FDA approved indication (EYLEA)
Policy Guidelines

Rationale
This policy was created in 2011 and updated periodically with searches of the MEDLINE database. The most recent literature update was performed through November 2012. Following is a summary of key literature to date.

Diabetic Macular Edema

The available evidence on vascular endothelial growth factor (VEGF) inhibitors for the treatment of diabetic macular edema consists of numerous randomized controlled trials (RCTs), some of which are large, and systematic reviews of the published trials.

In 2012, two technology assessments were 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). (3, 4) The assessment evaluated data from 15 RCTs 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.

The second 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. (5) 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.

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

A number of large 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 RCT from Europe that compared ranibizumab (0.3 or 0.5 mg) with sham injection. (6) Included in the study were 151 eyes with type 1 or 2 diabetes, central retinal thickness ≥300 microns, and 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. (7) 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.

Ranibizumab Compared to Laser Photocoagulation

RESTORE was an industry-sponsored randomized double-masked comparative trial conducted at 73 centers outside of the U.S. (8) 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.

Six month and 2-year outcomes from the North American READ-2 study were reported in 2009 and 2010. (9, 10) 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 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. Mean foveal thickness at 24 months was 340 microns, 286 microns, and 258 microns for the 3 groups, respectively. The percentage of patients with a center subfield thickness of 250 microns or less was 36%, 47%, and 68%, respectively.

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. (11, 12) 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 [approximately 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. (12) 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 was 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. (3) 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-naïve eyes (129 patients). (13, 14) 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. (15) 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. (16) 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. (17) 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. (18) 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 (PRM) basis; or macular laser photocoagulation. Patients in the laser arm received sham injections at each visit, and patients in the aflibercept arm 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. 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: Conclusions**

There is evidence that VEGF inhibitors (bevacizumab, ranibizumab, aflibercept) are efficacious agents for the treatment of diabetic macular edema when given by the intravitreal route.

The largest amount of evidence is available for ranibizumab. Results from 2 sham controlled trials report that ranibizumab is an efficacious agent for treating diabetic macular edema. Results from 3 controlled trials of ranibizumab versus laser photocoagulation consistently show superior outcomes for patients treated with ranibizumab. For bevacizumab, the quality of the RCTs is less, and for aflibercept there are fewer trials completed. However, the available evidence does not suggest that there are major differences in efficacy between the 3 different agents. Evidence remains insufficient to determine if pegaptanib is as effective as alternative treatments. Therefore, it is considered investigational.

**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. (19) 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 (20) 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™)**

No RCTs were identified that evaluated intravitreal ranibizumab for the treatment of proliferative diabetic retinopathy.
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. (20) 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. (21) 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. (22) 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 endodiathermy 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. (23) 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). (24) 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). (25) 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. (26) 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: Conclusions**

For the treatment of proliferative diabetic retinopathy, evidence is available for 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.

**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. (27) Included in the review were the CRUISE (ranibizumab) and CRVOSC (pegaptanib) studies, which are described in more detail below. (28, 29) 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 (ETDRS) 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. (28) In the smaller Phase II study with pegaptanib, efficacy was demonstrated for some but not all outcomes. (29) 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.
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. (28, 30) 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 approximate BCVA at baseline was 20/100, and the mean 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 change from baseline 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. (31, 32) The study design was similar to the study on CRVO (above) and included 397 patients with macular edema who received monthly intraocular 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. (33) 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. (34, 35) Intraocular 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 as 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). (36) 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. (37) 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. (38) 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. (39) 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 increase 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 bevacizumab and to evaluate durability of treatment over longer periods of follow-up. Comparison with grid photoagulation 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). (29) 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 2-mg aflibercept or sham administered every 4 weeks. 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).

**Retinal Vein Occlusion: Conclusions**

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. (40) 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 (ROP) in one or both eyes requiring retreatment before 54 weeks’ postmenstrual age. ROP 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. (41) 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: Conclusions

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.

Ongoing Clinical Trials

A search of the online site ClinicalTrials.gov in November 2012 identified a number of clinical trials with anti-VEGF therapy for retinal vascular conditions. Of particular note are the following:

- Ranibizumab for ischemic retinal vein occlusions is currently in Phase I trials. (Available online at: http://www.clinicaltrials.gov/ct2/results?term=retinal+vein+occlusion+VEGF)

- A comparison of bevacizumab and ranibizumab for the treatment of macular edema from retinal vein occlusion (CRAVE; NCT01428388). The study has an estimated enrollment of 150 subjects with completion expected in 2013.

- An industry-sponsored Phase III study of monthly injection of aflibercept (VEGF Trap-Eye) vs. laser treatment in subjects with macular edema secondary to BRVO (NCT01521559). A total of 180 subjects are expected to be enrolled, with an estimated study completion date of April 2014.

- An industry-sponsored Phase III study of aflibercept (VEGF Trap-Eye) vs. laser photocoagulation in subjects with diabetic macular edema (VIVID-DME; NCT01331681). The primary outcome is the change from baseline of BCVA ETDRS (early treatment diabetic retinopathy) letter score at 52 weeks. A total of 375 subjects are expected to be enrolled, with the primary outcome measure completed by May 2013 and a study completion date of March 2015.

- The Diabetic Retinopathy Research Network is conducting a comparative effectiveness study of aflibercept, bevacizumab, and ranibizumab for the treatment of diabetic macular edema (NCT01627249). This is a randomized trial that is funded by the National Eye Institute, Genentech, and Regeneron Pharmaceuticals. The study has an estimated enrollment of 660 patients with completion expected in January 2016.
Clinical Input Received through Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

2011

In response to requests, input was received from 1 physician specialty society and 3 academic medical centers while this policy was under review in 2011. The input supported the use of ranibizumab and bevacizumab for diabetic retinopathy (diabetic macular edema and proliferative diabetic retinopathy) and for central or branch retinal vein occlusions. Reviewers suggested additional indications for VEGF inhibitors including 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, retinopathy of prematurity, rubeosis, Von Hippel-Lindau, and vitreous hemorrhage secondary to retinal neovascularization.

2013

In response to requests, input was received from 2 physician specialty societies and 1 academic medical center while this policy was under review in 2013. Input agreed with the medically necessary indications, but also recommended use of bevacizumab for earlier stages of retinopathy of prematurity. Input supported use of intravitreal VEGF inhibitors for neovascular glaucoma and rubeosis (neovascularization of the iris). Input was mixed on the medical necessity of VEGF inhibitors for cystoid macular edema resulting from vasculitis, Coats disease, Eales disease, idiopathic macular telangiectasia type II, neovascularization of the angle, pseudoxanthoma elasticum, radiation retinopathy, retinal neovascularization, Von Hippel-Lindau, and vitreous hemorrhage secondary to retinal neovascularization.

Summary

Evidence on vascular endothelial growth factor (VEGF) antagonists for retinal vascular disorders consists of several large randomized controlled trials, with supporting evidence provided from smaller randomized controlled trials. When evaluated in combination with clinical input, the available evidence is considered sufficient to conclude that ranibizumab and bevacizumab may be medically necessary for the following conditions:

- Diabetic macular edema
- Proliferative diabetic retinopathy as an adjunctive treatment to vitrectomy or photocoagulation
- Macular edema secondary to central retinal vein occlusion
- Macular edema secondary to branch retinal vein occlusion
- Neovascular glaucoma
- Rubeosis (neovascularization of the iris)
Ranibizumab and bevacizumab have been shown to lead to improved visual acuity for the above conditions, compared to standard treatment without these agents. For diabetic proliferative retinopathy, these drugs also lead to reduced vitreous hemorrhage, and for macular edema, reduced macular thickness.

Bevacizumab has been shown in a well-conducted multicenter randomized trial to be superior to laser therapy for the treatment of stage 3+ retinopathy of prematurity in zone 1 and at least as effective as laser therapy for the treatment of zone 2, and may be considered medically necessary for this indication. Clinical input indicates that treatment of retinopathy of prematurity should also be offered for stages less than 3+.

A Phase II randomized controlled trial has shown greater gains in visual acuity in the aflibercept groups compared with the laser group in patients with diabetic macular edema. Efficacy of aflibercept has also been demonstrated in two pivotal randomized, multi-center, double-masked, sham-controlled studies in patients with macular edema following central vein occlusion (CRVO). Therefore, aflibercept may be considered medically necessary for these indications. No studies have been identified on use of aflibercept in patients with branch retinal vein occlusion (BRVO).

Trials with pegaptanib for diabetic macular edema 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 retinopathy of prematurity (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.

**Practice Guidelines and Position Statements**

In a final appraisal determination from July 15, 2011, the National Institute for Health and Clinical Excellence (NICE) does not recommend ranibizumab (Lucentis) for the treatment of diabetic macular edema. (42) 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. An update of this guidance is expected in 2013. (Available online at: http://guidance.nice.org.uk/TA/Wave23/41.)

In development by NICE is guidance on the use of ranibizumab for macular edema caused by retinal vein occlusion. (Available online at: http://guidance.nice.org.uk/TA/Wave23/26.)

2012 Guidelines on diabetic retinopathy from the American Academy of Ophthalmology (AAO) Retina Panel indicate that anti-vascular endothelial growth factor agents (off-label use except ranibizumab) may be considered as adjunctive treatments to focal and/or grid laser. (43) 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.
In a 2012 technology assessment, the AAO concluded that intravitreal injection of anti-VEGF agents is a safe and effective treatment for diabetic macular edema through 2 years; further study is needed to evaluate long-term safety and efficacy. (5)

Medicare National Coverage

In March 2012, Centers for Medicare and Medicaid Services (CMS) held a Medicare Evidence Development and Coverage Advisory Committee (MEDCAC) meeting on use of anti-VEGF agents for the treatment of diabetic macular edema. The panel voted that they had moderately high confidence that there is adequate evidence to evaluate whether diabetic macular edema management using intravitreal targeted anti-VEGF treatment improves patient health outcomes compared to DME management without targeted anti-VEGF treatment. CMS concluded that repeated eye injections of anti-VEGF medications may help to manage diabetic macular edema, preventing visual loss and promoting recovery. CMS does not have a national coverage determination for the use of anti-VEGF treatments in diabetic macular edema.

References:


<table>
<thead>
<tr>
<th>Codes</th>
<th>Number</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT</td>
<td>67028</td>
<td>Intravitreal injection of a pharmacologic agent (separate procedure)</td>
</tr>
<tr>
<td>ICD-9 Procedure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICD-9 Diagnosis</td>
<td>250.50-250.53</td>
<td>Diabetes with ophthalmic manifestations, code range</td>
</tr>
<tr>
<td></td>
<td>362.02</td>
<td>Proliferative diabetic retinopathy</td>
</tr>
<tr>
<td></td>
<td>362.07</td>
<td>Diabetic macular edema</td>
</tr>
<tr>
<td>Code</td>
<td>Description</td>
<td></td>
</tr>
<tr>
<td>--------</td>
<td>-----------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>362.83</td>
<td>Retinal edema</td>
<td></td>
</tr>
<tr>
<td>C9257</td>
<td>Injection, bevacizumab, 0.25 mg (new code 1/1/10)</td>
<td></td>
</tr>
<tr>
<td>C9291</td>
<td>Injection, aflibercept, 2 mg vial (new code effective 4/1/12)</td>
<td></td>
</tr>
<tr>
<td>J2503</td>
<td>Injection, pegaptanib sodium, 0.3 mg</td>
<td></td>
</tr>
<tr>
<td>J2778</td>
<td>Injection, ranibizumab, 0.1 mg</td>
<td></td>
</tr>
<tr>
<td>Q2046</td>
<td>Injection, aflibercept, 1 mg (code deleted 12/31/12)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Codes (effective 10/1/14)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>E10.311, E10.321, E10.331, E10.341, E10.351</td>
<td>Type 1 diabetes mellitus with ophthalmic complications, codes for macular edema</td>
</tr>
<tr>
<td>E10.359</td>
<td>Type 1 diabetes mellitus with ophthalmic complications, proliferative diabetic retinopathy without macular edema</td>
</tr>
<tr>
<td>E11.359</td>
<td>Type 2 diabetes mellitus with ophthalmic complications, proliferative diabetic retinopathy without macular edema</td>
</tr>
<tr>
<td>H35.81</td>
<td>Retinal edema</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Codes (effective 10/1/14)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>3E0C3GC</td>
<td>Administration, physiological systems and anatomical regions, introduction, eye, percutaneous, therapeutic substance</td>
</tr>
</tbody>
</table>

Index

- Diabetic Retinopathy
- Macular Edema
- Retinal Vein Occlusion