Vascular Endothelial Growth Factor Inhibitors for Ocular Indications

Number: 0701

Policy

*Please see amendment for Pennsylvania Medicaid at the end of this CPB.*

Aetna considers pegaptanib sodium injection (Macugen) medically necessary for the treatment of individuals with neovascular (wet) age-related macular degeneration (AMD) and diabetic macular edema.

Aetna considers pegaptanib sodium injection experimental and investigational for the treatment of the following indications (not an all-inclusive list) because its effectiveness for these indications has not been established:

- Cystoid macular degeneration,
- Ocular von Hippel Lindau disease lesions

Aetna considers intravitreal ranibizumab (Lucentis) or bevacizumab (Avastin) injections medically necessary for the treatment of the following indications:

- Diabetic macular edema
- Diabetic retinopathy

Policy History

Last Review: 08/01/2017
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Review History

Definitions

Additional Information

Clinical Policy Bulletin Notes
- Macular edema following retinal vein occlusion (RVO)
- Neovascular (wet) AMD
- Neovascular glaucoma
- Pseudoxanthoma elasticum
- Rare causes of choroidal neovascularization (angioid streaks, choroiditis [including choroiditis secondary to ocular histoplasmosis], idiopathic degenerative myopia, retinal dystrophies, rubeosis iridis, and trauma)
- Retinopathy of prematurity

Aetna considers intravitreal ranibizumab and bevacizumab injections experimental and investigational for treatment of the following indications (not an all-inclusive list) because their effectiveness for these indications has not been established.

- Amblyopia
- Central serous retinopathy
- Choroidal hemorrhage not related to a medically necessary indication
- Choroidal melanoma
- Coat's disease (Coates' disease, also known as exudative retinitis or retinal telangiectasis)
- Cystoid macular edema
- Glaucoma surgery, control of wound healing
- Primary pterygium (including as adjunctive therapy for primary pterygium surgery)
- Radiation retinopathy
- Retinal angioma
- Vitreous hemorrhage not related to a medically necessary indication

Aetna considers topical administration, subconjunctival or intrastromal injections of ranibizumab or bevacizumab for the treatment of corneal neovascularization experimental and investigational because their effectiveness for this indication has not been established.

Aetna considers intravitreal aflibercept (Eylea) injections medically necessary for the treatment of neovascular (wet) AMD,
diabetic macular edema (including diabetic retinopathy in persons with macular edema), and macular edema following retinal vein occlusion (RVO) (including central retinal vein occlusion (CRVO) and branch retinal vein occlusion (BRVO)).

Aetna considers aflibercept experimental and investigational for the treatment of colorectal, ovarian, and prostate cancers, and all other indications (e.g., myopic choroid neovascularization, neovascular glaucoma, and uterine leiomyosarcomas) because its effectiveness for these indications has not been established.

VEGF inhibitors for ocular indications are contraindicated and considered not medically necessary for persons with endophthalmitis or with ocular or periocular infections.

Concurrent use of more than one VEGF inhibitor in the same eye is considered experimental and investigational because the safety and effectiveness of combinational use of VEGF inhibitors for ocular indications has not been established.

See also CPB 0594 - Visudyne (Verteporfin) Photodynamic Therapy (../500_599/0594.html); CPB 0685 - Bevacizumab (Avastin) (../600_699/0685.html); CPB 0706 - Anecortave Acetate (Retaane) (0706.html), and CPB 0842 - Ziv-Aflibercept (Zaltrap) (../800_899/0842.html).

Background

Age-related macular degeneration:

VEGF is a naturally occurring substance in the body responsible for the growth of new blood vessels (neovascularization). In the retina however, VEGF may stimulate growth of abnormally fragile vessels prone to leakage. This leakage causes scarring in the macula and eventually leads to loss of central vision.

Age-related macular degeneration (AMD), characterized as a progressive degenerative disease of the macula, is the leading cause of blindness in developed countries afflicting approximately 15 million people in the United States. Age-related macular degeneration (AMD) is a major cause of painless central vision
loss and is a leading cause of blindness in people over 60.

There are 2 forms of AMD: (i) neovascular (wet) and (ii) non-neovascular (dry). The non-neovascular form of AMD is more common and leads to a slow deterioration of the macula with a gradual loss of vision over a period of years. Dry AMD is associated with atrophic cell death of the central retina or macula, which is required for fine vision used for activities such as reading, driving or recognizing faces. Approximately 10-20% of patients with dry AMD eventually progress to wet AMD.

The neovascular (wet) form of the disease is responsible for the majority of cases of severe vision loss and is due to proliferation of abnormal blood vessels behind the retina. These new blood vessels tend to be very fragile and often leak blood and fluid into the retina, that causes visual abnormalities, and cause scar tissue that destroys the central retina. The blood and fluid raise the macula from its normal place at the back of the eye. Damage to the macula occurs rapidly and results in a deterioration of sight over a period of months to years. The development of these abnormal blood vessels is due in part to the activity of vascular endothelial growth factor (VEGF), which induces angiogenesis, and increases vascular permeability and inflammation, all of which are thought to contribute to the progression of the neovascular (wet) form of AMD. Between 80% to 90% of AMD is dry, yet more than 80% of the visual loss attributable to AMD is caused by the wet form.

The natural history of AMD is variable, with clinical manifestations dependent on disease type, extent, and whether one or both eyes are affected. Principle risk factors include age, smoking, family history, Caucasian ethnicity, contralateral eye disease, diabetes, and cataract surgery. Genetics play a particularly strong role, with a single polymorphism estimated responsible for as much as 43% of disease occurrence. Treatment options for AMD include laser phototherapy and VEGF inhibitors.

**Central retinal vein occlusion**

Central retinal vein occlusion (CRVO) is a common retinal vascular
disorder. The exact etiology is unknown, however may be caused by arteriosclerotic changes in the central retinal artery or from a thrombotic occlusion of the central retinal vein.

Occlusion of the central retinal vein leads to backup of the blood in the retinal venous system and increases resistance to the venous blood flow. This increased resistance causes stagnation of the blood and ischemia to the retina. Ischemic damage to the retina stimulates increase production of vascular endothelial growth factor (VEGF), and increased levels of VEGF stimulate neovascularization of the posterior and anterior segment of the eye. Retinal Vein Occlusion can lead to Macular Edema or growth of fragile new blood vessels.

Treatment of CRVO includes aspirin, antiinflammatory agents, isovolemic hemodilution, plasmapheresis, systemic anticoagulation, fibrinolytic agents, systemic corticosteroids, local anticoagulation with intravitreal injections of alteplase, intravitreal injections of triamcinolone, intravitreal injections of bevacizumab.

There are two types of CRVO; ischemic and nonischemic.

- Nonischemic CRVO is the milder form of the disease and presents with good vision, few retinal hemorrhages and cotton-wool spots, and good perfusion to the retina. This type may resolve fully with good visual outcome or may progress to the ischemic type.
- Ischemic CRVO is the more severe form and presents with severe visual loss, extensive retinal hemorrhages, and cotton-wool spots. Poor perfusion of the retinal and patients may end up with neovascular glaucoma and painful blind eye.

In Branched retinal vein occlusion (BRVO) the blockage occurs in a smaller branch of the vessels that connect to the central retinal vein.

Both types of Retinal Vein Occlusion can lead to Macular Edema or growth of fragile new blood vessels.
**Diabetic Macular Edema**

Diabetic Macular Edema (DME) is the consequence of retinal microvascular changes from poorly controlled diabetes and diabetic retinopathy. DME is associated with thickening of the basement membrane and reduction of pericytes which are believed to increase permeability of the retinal vasculature. This compromises the blood-retinal barrier causing a leakage of plasma constituents and subsequent retinal edema and hypoxia, all of which stimulates the production of vascular endothelial growth factor (VEGF). DME damages the central retina, which impairs color and pinpoint vision, leading to blurry, washed-out vision. DME can be classified as either focal or diffuse types. In both cases, the predominant labeled treatment for DME is macular focal/grid laser photocoagulation (cauterization of ocular blood vessels). Intravitreal steroids and anti-VEGF agents are also used off-label. (Non-diabetic causes of macular edema include: AMD, uveitis, RVO, and certain genetic disorders.)

**Macugen**

Macugen (pegaptanib octasodium) is an aptamer, a pegylated modified oligonucleotide, that is a selective vascular endothelial growth factor (VEGF) antagonist, a type of signaltransduction inhibitor (STI) and angiogenesis inhibitor.

Pegaptanib octasodium has been approved by the U.S. Food and Drug Administration (FDA) for the treatment of age related macular degeneration, Neovascular (Wet).

Macugen (pegaptanib sodium injection) is an intravitreal injection developed for the treatment of neovascular (wet) AMD. Pegaptanib binds to VEGF and inhibits its binding to cellular receptors. Macugen’s anti-VEGF activity is expected to inhibit abnormal blood vessel proliferation and therefore decrease the vision loss associated with the proliferation of abnormal blood vessels.

Gragoudas et al (2004) reported the results of 2 concurrent, prospective, randomized, double-blind, multi-center, dose-
ranging, controlled clinical trials (n = 1,186) on the use of pegaptanib in the treatment of neovascular AMD. Intravitreous injection into 1 eye per patient of pegaptanib (at a dose of 0.3 mg, 1.0 mg, or 3.0 mg) or sham injections were administered every 6 weeks over a period of 48 weeks, for a total of 9 treatments. The primary end point was the proportion of patients who had lost fewer than 15 letters of visual acuity at 54 weeks.

In the combined analysis of the primary end point, efficacy was demonstrated, without a dose-response relationship, for all 3 doses of pegaptanib (p < 0.001 for the comparison of 0.3 mg with sham injection; p < 0.001 for the comparison of 1.0 mg with sham injection; and p = 0.03 for the comparison of 3.0 mg with sham injection). Verteporfin photodynamic therapy (PDT) usage was permitted at the discretion of the investigators in patients with predominantly classic lesions. Concomitant use of PDT overall was low. More sham treated patients (25 %) received PDT than Macugen 0.3 mg treated patients (20 %). In the group given pegaptanib at 0.3 mg, 70 % of patients lost fewer than 15 letters of visual acuity, as compared with 55 % among the controls (p < 0.001). The risk of severe loss of visual acuity (loss of 30 letters or more) was reduced from 22 % in the sham-injection group to 10 % in the group receiving 0.3 mg of pegaptanib (p < 0.001). More patients receiving pegaptanib (0.3 mg), as compared with sham injection, maintained their visual acuity or gained acuity (33 % versus 23 %; p = 0.003). As early as 6 weeks after beginning therapy with the study drug, and at all subsequent points, the mean visual acuity among patients receiving 0.3 mg of pegaptanib was better than in those receiving sham injections (p < 0.002). Dose levels above 0.3 mg did not demonstrate any additional benefit. On average, Macugen (0.3) mg treated patients and sham treated patients continued to experience vision loss. However, the rate of vision decline in the Macugen treated group was slower than the rate in the patients who received sham treatment. Among the adverse events that occurred, endophthalmitis (1.3 % of patients), traumatic injury to the lens (0.7 %), and retinal detachment (0.6 %) were the most serious and required vigilance. These events were associated with a severe loss of visual acuity in 0.1 % of patients. The
authors concluded that pegaptanib appears to be an effective therapy for neovascular AMD; however, its long-term safety is not known.

Prescribing information available on the Eyetech Pharmaceuticals, Inc. and Pfizer, Inc. website reports that at the end of the first year (week 54), approximately 1,050 patients were re-randomized to either continue the same treatment or to discontinue treatment through week 102. Macugen was shown to be less effective during the second year of the study than during the first year.

Pegaptanib octasodium is available as Intraocular Solution: 0.3 MG/0.09 ML. Macugen 0.3 mg should be administered once every 6 weeks by intravitreous injection into the eye to be treated. The safety and efficacy of Macugen therapy administered to both eyes concurrently have not been studied.

Macugen should not be used in the following:

- Hypersensitivity to pegaptanib octasodium or any component of the product, may manifest as severe intraocular inflammation
- Patients with ocular or periocular infection.

In a short-term phase II clinical trial, Cunningham et al (2005) assessed the safety and effectiveness of pegaptanib sodium injection (pegaptanib) in the treatment of diabetic macular edema (DME). Subjects were individuals with a best-corrected visual acuity (VA) between 20/50 and 20/320 in the study eye and DME involving the center of the macula for whom the investigator judged photocoagulation could be safely withheld for 16 weeks. Intravitreous pegaptanib (0.3 mg, 1 mg, 3 mg) or sham injections were administered at study entry, week 6, and week 12 with additional injections and/or focal photocoagulation as needed for another 18 weeks. Final assessments were conducted at week 36. Main outcome measures include best-corrected VA, central retinal thickness at the center point of the central subfield as assessed by optical coherence tomography measurement, and additional therapy with photocoagulation between weeks 12 and
36. A total of 172 patients appeared balanced for baseline demographic and ocular characteristics. Median VA was better at week 36 with 0.3 mg (20/50), as compared with sham (20/63) (p = 0.04). A larger proportion of those receiving 0.3 mg gained VAs of greater than or equal to 10 letters (approximately 2 lines) (34 % versus 10 %, p = 0.003) and greater than or equal to 5 letters (18 % versus 7 %, p = 0.12). Mean central retinal thickness decreased by 68 micron with 0.3 mg, versus an increase of 4 micron with sham (p = 0.02). Larger proportions of those receiving 0.3 mg had an absolute decrease of both greater than or equal to 100 micron (42 % versus 16 %, p = 0.02) and greater than or equal to 75 micron (49 % versus 19 %, p = 0.008). Photocoagulation was deemed necessary in fewer subjects in each pegaptanib arm (0.3 mg versus sham, 25 % versus 48 %; p = 0.04). All pegaptanib doses were well-tolerated. Endophthalmitis occurred in 1 of 652 injections (0.15 %/injection; i.e., 1/130 [0.8 %] pegaptanib subjects) and was not associated with severe visual loss. Subjects assigned to pegaptanib had better VA outcomes, were more likely to show reduction in central retinal thickness, and were deemed less likely to need additional therapy with photocoagulation at follow-up. These investigators noted that confirmation of these preliminary results across a broad spectrum of patients with DME in sufficiently powered prospective clinical trials is being planned.

A 2-year phase III study demonstrated that pegaptanib sodium improved vision in persons with diabetic macular edema (Pfizer, 2010). The study included 260 subjects who received 0.3 mg pegaptanib sodium or a sham procedure consisting of anesthesia and a simulated injection in the eye every 6 weeks for a total of 9 injections in year 1. In year 2, subjects received injections as often as every 6 weeks based on pre-specified criteria. Up to 3 focal or grid laser treatments per year were permitted beginning at week 18, at the investigator’s discretion. The primary outcome measure of the study was the proportion of subjects who, after 1 year, experienced an improvement in vision from baseline of 2 lines, or 10 letters, on the Early Treatment Diabetic Retinopathy Study (ETDRS) eye chart. The investigators reported that 37 % of subjects treated with pegaptanib sodium gained 2 lines, or 10 letters, of vision on the ETDRS eye chart at 54 weeks, versus 20 % of subjects who received the sham procedure (p = 0.0047).
average, subjects treated with pegaptanib sodium gained 5.2 letters of vision at year 1 compared to 1.2 letters for subjects receiving sham (p < 0.05). At the end of year 2, subjects receiving pegaptanib sodium had gained on average 6.1 letters of vision compared to 1.3 letters for subjects in the sham arm of the study (p < 0.01). The investigators reported that adverse events were consistent with those observed in clinical trials of pegaptanib sodium in persons with neovascular age-related macular degeneration and similar to clinical experience with pegaptanib sodium.

In a pilot study, Dahr et al (2007) examined the safety and effectiveness of pegaptanib for patients with juxtapapillary or large peripheral angiomas secondary to von Hippel-Lindau (VHL) disease. A total of 5 patients with severe ocular VHL lesions received intravitreal injections of pegaptanib (3 mg/100 microL), given every 6 weeks for minimum of 6 injections. The primary outcome of this study was a change of greater than or equal to 15 letters (3 lines) in best-corrected VA by 1 year. Secondary outcomes included changes in macular thickness, as determined by optical coherence tomography, and changes in fluorescein leakage. Two of 5 patients completed the course of treatment and 1 year of follow-up. These 2 patients had progressive decrease in retinal hard exudate and reduction in central retinal thickness measured by optical coherence tomography. One of these 2 patients had improvement in VA of 3 lines. No significant change in fluorescein leakage or tumor size was detected in either patient. Lesions in the other 3 patients continued to progress despite treatment, and these patients did not complete the entire treatment course. One patient developed a tractional retinal detachment. Additional serious adverse events included transient post-injection hypotony in 2 eyes. The authors concluded that intravitreal injections of pegaptanib may decrease retinal thickening minimally and reduce retinal hard exudates in some patients with advanced VHL angiomas. This finding may be related to a reduction in vasopermeability, because there was no apparent effect of treatment on the size of the primary retinal angiomas in this small pilot study.

Lucentis
Lucentis (ranibizumab) is a recombinant monoclonal antibody, ophthalmic Vascular Endothelial Growth Factor (VEGF) Inhibitor. Lucentis (ranibizumab) binds to and inhibits vascular endothelial growth factor (VEGF-A) from promoting growth of new blood vessels beneath the retina, by intravitreal injection.

Ranibizumab has been approved by the FDA for the treatment of Exudative (wet) Age-related Macular Degeneration (AMD), Macular Edema following Retinal Vein Occlusion (RVO), Diabetic Macular Edema (DME), and Diabetic Retinopathy in patients with DME.

On June 30, 2006, the United States Food and Drug Administration (FDA) approved Lucentis (ranibizumab injection, Genentech Inc., South San Francisco, CA) for the treatment of patients with neovascular AMD. Lucentis is designed to block new blood vessel growth and leakiness, and is the first treatment which, when given monthly, can maintain the vision of more than 90% of patients with this type of AMD. In contrast to pegaptanib (Macugen), ranibizumab is a recombinant humanized monoclonal antibody fragment with specificity for all isoforms of human VEGF. Ranibizumab exhibits high affinity for human VEGF and exerts its neutralizing effects by inhibiting the VEGF-receptor interaction. Unlike the larger whole antibody, ranibizumab can penetrate the internal limiting membrane and reach the sub-retinal space following intravitreal injection (van Wijngaarden et al, 2005).

The FDA approval of Lucentis is based on data from 2 phase III clinical studies (MARINA and ANCHOR). In these studies, nearly all patients (about 95%) treated with Lucentis (0.5 mg) maintained (defined as the loss of less than 15 letters in VA) and up to 40% improved (defined as the gain of 15 letters or more in VA) vision at 1-year, as measured on the Early Treatment of Diabetic Retinopathy eye chart. On average, patients treated with Lucentis in the MARINA study experienced an improvement from baseline of 6.6 letters at 2-year compared to a loss of 14.9 letters in the sham group. In the ANCHOR study, patients treated with Lucentis, on average, experienced an 11.3 letter gain from baseline at 1-year compared to a loss of 9.5 letters in the
Visudyne photodynamic therapy control group. Up to 40% of patients treated with Lucentis achieved vision of 20/40 or better.

In addition to data from the 2 phase III clinical trials, data from phase I/II studies were also included in the FDA review. In an open-label, 2-center, uncontrolled, randomized, phase I clinical trial, Rosenfeld and colleagues (2006) examined if multiple intravitreal doses of up to 2 mg of ranibizumab can be tolerated and are biologically active when injected using a dose-escalating strategy in eyes of patients with neovascular AMD. A total of 32 patients with primary or recurrent sub-foveal choroidal neovascularization secondary to AMD were enrolled. Baseline best-corrected VA in the study eye was from 20/40 to 20/640 (Snellen equivalent). Treatment regimens consisted of 5, 7, or 9 intravitreal injections of ranibizumab at 2- or 4-week intervals for 16 weeks, with escalating doses ranging from 0.3 to 2.0 mg. Patients were evaluated through day 140, 4 weeks after their last injection. Safety was assessed based on ocular and non-ocular adverse events, changes in VA, changes in intraocular pressure (IOP), slit-lamp ocular examination, changes in lesion characteristics based on fluorescein angiography and color fundus photography, and the presence of anti-ranibizumab antibodies. A total of 29 patients received an injection at baseline, and 27 patients completed the study through day 140. Results were similar across the 3 treatment groups. All patients experienced ocular adverse events, most of which were mild. The most common ocular adverse events were iridocyclitis (83%), and injection-site reactions (72%). Inflammation did not increase with repeated injections, despite the increasing ranibizumab doses. Transient mild IOP elevations were common after ranibizumab injection. No serum anti-ranibizumab antibodies were detected. In general, median and mean VAs in the study eyes improved by day 140 in all 3 groups. Only 3 of the 27 patients lost significant vision. There was no significant lesion growth, and a decrease in area of leakage from choroidal neovascularization was detected through day 140. The authors concluded that multiple intravitreal injections of ranibizumab at escalating doses ranging from 0.3 to 2.0 mg were well-tolerated and biologically active in eyes with neovascular AMD through 20 weeks. Mild transient ocular inflammation was the most
common post-injection adverse event.

In a multi-center, controlled, open-label, phase I/II clinical study, Heier and associates (2006) evaluated the safety of repeated intravitreal injections of ranibizumab in treating neovascular AMD, and assessed changes in VA and AMD lesion characteristics. A total of 64 patients with sub-foveal predominantly or minimally classic AMD-related choroidal neovascularization were enrolled. In part 1, patients were randomized to monthly intravitreal ranibizumab for 3 months (4 injections of 0.3 mg or 1 injection of 0.3 mg followed by 3 injections of 0.5 mg; n = 53) or usual care (UC; n = 11). In part 2, patients could continue their regimen for 3 additional months or cross over to the alternative treatment. Main outcome measures were adverse events, IOP, VA, and lesion characteristics assessed by fluorescein angiography and fundus photography. Of the 64 randomized subjects, 62 completed the 6-month study. Twenty of 25 subjects (80 %) randomized to 0.3 mg, and 22 of 28 subjects (79 %) randomized to 0.5-mg ranibizumab in part 1 continued on that treatment in part 2; 9 of 11 (82 %) subjects randomized to UC in part 1 crossed over to ranibizumab treatment in part 2. The most common side effects with ranibizumab were reversible inflammation and minor injection-site hemorrhages. Serious side effects were iridocyclitis, endophthalmitis, and central retinal vein occlusion (1 subject each). Post-injection, IOP increased transiently in 22.6 % of ranibizumab-treated eyes in parts 1 and 2. After 4 ranibizumab injections (day 98), mean (+/- standard deviation) VA increased 9.4 +/- 13.3 and 9.1 +/- 17.2 letters in the 0.3- and 0.5-mg groups, respectively, but decreased 5.1 +/- 9.6 letters with UC. In part 2 (day 210), VA increased from baseline 12.8 +/- 14.7 and 15.0 +/- 14.2 letters in subjects continuing on 0.3 and 0.5 mg, respectively. Visual acuity improved from baseline greater than or equal to 15 letters in 26 % (day 98) and 45 % (day 210) of subjects initially randomized to and continuing on ranibizumab, respectively, and areas of leakage and sub-retinal fluid decreased. No UC subject had a greater than or equal to 15-letter improvement at day 98. These investigators concluded that repeated intravitreal injections of ranibizumab had a good safety profile and were associated with improved VA and decreased leakage from choroidal neovascularization in subjects with
neovascular AMD.

In clinical trials, the most common side effects among patients treated with Lucentis (reported in at least 6% more patients than in the control groups in at least one study) included conjunctival hemorrhage, eye pain, vitreous floaters, increased IOP and intraocular inflammation. Although there was a low rate (less than 4%) of arterial thromboembolic events observed in the Lucentis clinical studies that was not statistically different between the Lucentis and control groups, there is a theoretical risk of arterial thromboembolic events following intravitreal use of inhibitors of VEGF. Serious side effects related to the injection procedure occurred in less than 0.1% of intravitreal injections, including endophthalmitis (severe inflammation of the interior of the eye), retinal tear, retinal detachment, and traumatic cataract. Lucentis is contraindicated in patients with hypersensitivity and ocular or periocular infections.

Ranibizumab is available as Lucentis in two dosage forms for intravitreal injection. Lucentis is available as a 0.5mg/0.05 ml intraocular solution, in a single-use 2ml vial designed to deliver 0.05 ml of 10mg/ml ranibizumab. Lucentis is also available as a 0.3mg/0.05 ml intraocular solution, in a single-use 2ml vial designed to deliver 0.05 ml of 6mg/ml ranibizumab.

The FDA-approved labeling of Lucentis for AMD recommends 0.5 mg of Lucentis administered by intravitreal injection once a month. Although less effective, treatment may be reduced to 1 injection every 3 months after the first 4 injections if monthly injections are not feasible. Compared to continued monthly dosing, dosing every 3 months will lead to an approximate 5-letter (1-line) loss of visual acuity benefit, on average, over the following 9 months. Genentech said the average patient will receive only 5 to 7 injections in their 1st year because of the risk of eye pain, inflammation, and increased IOP.

In June 2010, the FDA approved Lucentis (ranibizumab injection) for the treatment of macular edema following retinal vein occlusion (RVO). The FDA approval was based upon 2 randomized controlled clinical studies -- the BRAVO study,
which assessed the safety and efficacy profile of ranibizumab in a total of 397 patients with macular edema following branch-RVO, and the CRUISE study, which assessed the safety and efficacy profile of ranibizumab in a total of 392 patients with macular edema following central-RVO. During the first 6-month period, participants in both trials received monthly injections of either 0.3 mg or 0.5 mg of ranibizumab (n = 527) or monthly sham injections (n = 262). The primary endpoint of both studies was mean change from baseline in best-corrected visual acuity (BCVA) at 6 months compared with patients receiving sham injections. In the BRAVO study, the percentage of patients in the ranibizumab 0.5 mg study arm who gained 15 or more letters in BCVA from baseline at month 6 was 61% (compared with 29% in the sham injection arm). In the CRUISE study, the percentage of patients in the ranibizumab 0.5 mg study arm who gained 15 or more letters in BCVA from baseline at month 6 was 48% (compared with 17% in the sham injection arm). At month 6, patients in BRAVO who received 0.5 mg of ranibizumab had a mean gain of 18.3 letters (compared to 7.3 letters in patients receiving sham injections). In the CRUISE study, at month 6, patients who received 0.5 mg of ranibizumab had a mean gain of 14.9 letters (compared to 0.8 letters for patients receiving sham injections).

In a phase IIIb, multi-center, 12-month, randomized core study and 24-month open-label extension study, Schmidt-Erfurth et al (2014) evaluated long-term efficacy and safety profiles during 3 years of individualized ranibizumab treatment in patients with visual impairment due to DME. Of the 303 patients who completed the randomized RESTORE 12-month core study, 240 entered the extension study. In the extension study, patients were eligible to receive individualized ranibizumab treatment as of month 12 guided by BCVA and disease progression criteria at the investigators' discretion. Concomitant laser treatment was allowed according to the ETDRS guidelines. Based on the treatments received in the core study, the extension study groups were referred to as prior ranibizumab, prior ranibizumab + laser, and laser. Main outcome measures were change in BCVA and incidence of ocular and non-ocular AEs over 3 years. Overall, 208 patients (86.7%) completed the extension study. In patients treated with ranibizumab during the core study, consecutive
individualized ranibizumab treatment during the extension study led to an overall maintenance of BCVA and central retinal subfield thickness (CRST) observed at month 12 over the 2-year extension study (+8.0 letters, -142.1 μm [prior ranibizumab] and +6.7 letters, -145.9 μm [prior ranibizumab + laser] from baseline at month 36) with a median of 6.0 injections (mean, 6.8 injections; prior ranibizumab) and 4.0 (mean, 6.0 injections; prior ranibizumab + laser). In the prior laser group, a progressive BCVA improvement (+6.0 letters) and CRST reduction (-142.7 μm) at month 36 were observed after allowing ranibizumab during the extension study, with a median of 4.0 injections (mean, 6.5 injections) from months 12 to 35. Patients in all 3 treatment groups received a mean of less than 3 injections in the final year. No cases of endophthalmitis, retinal tear, or retinal detachment were reported. The most frequently reported ocular and non-ocular AEs over 3 years were cataract (16.3 %) and nasopharyngitis (23.3 %); 8 deaths were reported during the extension study, but none was suspected to be related to the study drug/procedure. The authors concluded that ranibizumab was effective in improving and maintaining BCVA and CRST outcomes with a progressively declining number of injections over 3 years of individualized dosing. Ranibizumab was generally well-tolerated with no new safety concerns over 3 years.

The main drawbacks of this study included (i) patients with stroke and transient ischemic attack were excluded from this study in contrast to the real-life setting where there is a possibility that a more diverse patient population with multiple co-morbid conditions would receive ranibizumab therapy. Thus, the safety results of this study should be interpreted relative to this exclusion; and (ii) this extension study was not powered to evaluate the occurrence of infrequent but important severe AEs, including systemic events (e.g., stroke). Furthermore, the authors stated that long-term studies such as LUMINOUS conducted in a broad patient population will help to further describe the long-term safety profile, effectiveness, and treatment patterns of ranibizumab in a real-life setting.

The usual dose of Lucentis for treating Macular Edema following RVO is 0.5mg per treatment once monthly (approximately every
The FDA approved ranibizumab injection (Lucentis) for the treatment of diabetic retinopathy (DR) in people with diabetic macular edema (DME) (Genentech, 2015). The FDA granted Lucentis Breakthrough Therapy Designation and Priority Review for this indication based on results from the RISE and RIDE Phase III clinical trials.

RISE and RIDE were two identically-designed, parallel, double-masked, sham treatment-controlled trials in 759 patients with DR and DME at baseline who were randomized into three groups to receive monthly treatment with 0.3 mg Lucentis, 0.5 mg Lucentis or sham injection (Genentech, 2015). The primary outcome in RISE and RIDE was visual acuity gain at 24 months for DME patients.

The safety and efficacy of Lucentis for the treatment of DR with DME was assessed over three years in patients with baseline DR severity scores ranging from 10 to 75 in the study eye (on the ETDRS diabetic retinopathy severity scale) (Genentech, 2015). Secondary and exploratory outcomes were evaluated at 24 months. At Month 24, a higher proportion of patients had observed a three-step or better improvement of their disease compared to sham, as determined by color fundus photography. The safety in the RISE and RIDE Phase III trials was consistent with previous studies.

In the third year of the studies, patients from the control group had the option to cross over to receive monthly treatment with 0.5 mg Lucentis; patients originally randomized to 0.3 mg or 0.5 mg Lucentis continued to receive the same dose and all patients were followed for 12 additional months (Genentech, 2015). The 0.3 mg dose of Lucentis is approved for both DME and for DR in people with DME.

The usual dose of Lucentis for treating Diabetic Retinopathy in patients with Diabetic Macular Edema is 0.3mg per treatment once monthly (approximately every 28 days).
The FDA approved ranibizumab 0.3 mg for the monthly treatment of all forms of diabetic retinopathy, including diabetic retinopathy in people who have been diagnosed either with or without diabetic macular edema (DME) (Genentech, 2017).

The FDA granted Lucentis Priority Review for the treatment of diabetic retinopathy without DME based on an analysis of the Diabetic Retinopathy Clinical Research Network’s (DRCR.net) Protocol S study (Genentech, 2017). The Diabetic Retinopathy Clinical Research Network’s (DRCR.net) Protocol S study was a randomized, active-controlled study comparing ranibizumab to panretinal photocoagulation (PRP) in 305 patients with proliferative diabetic retinopathy, including those with and without diabetic macular edema (DME).

In the Protocol S study, Gross, et al. (2015) evaluated the noninferiority of intravitreous ranibizumab compared with PRP for visual acuity outcomes in patients with proliferative diabetic retinopathy. The randomized clinical trial was conducted at 55 US sites among 305 adults with proliferative diabetic retinopathy enrolled between February and December 2012 (mean age, 52 years; 44% female; 52% white). Both eyes were enrolled for 89 participants (1 eye to each study group), with a total of 394 study eyes. The final 2-year visit was completed in January 2015. Individual eyes were randomly assigned to receive PRP treatment, completed in 1 to 3 visits (n = 203 eyes), or ranibizumab, 0.5 mg, by intravitreous injection at baseline and as frequently as every 4 weeks based on a structured re-treatment protocol (n = 191 eyes). Eyes in both treatment groups could receive ranibizumab for DME. The primary outcome was mean visual acuity change at 2 years (5-letter noninferiority margin; intention-to-treat analysis). Secondary outcomes included visual acuity area under the curve, peripheral visual field loss, vitrectomy, DME development, and retinal neovascularization.

Mean visual acuity letter improvement at 2 years was +2.8 in the ranibizumab group vs +0.2 in the PRP group (difference, +2.2; 95% CI, -0.5 to +5.0; P < .001 for noninferiority). The mean treatment group difference in visual acuity area under the curve over 2 years was +4.2 (95% CI, +3.0 to +5.4; P < .001). Mean
Peripheral visual field sensitivity loss was worse (-23 dB versus -422 dB; difference, 372 dB; 95% CI, 213-531 dB; P < .001), vitrectomy was more frequent (15% vs 4%; difference, 9%; 95% CI, 4%-15%; P < .001), and DME development was more frequent (28% vs 9%; difference, 19%; 95% CI, 10%-28%; P < .001) in the PRP group versus the ranibizumab group, respectively. Eyes without active or regressed neovascularization at 2 years were not significantly different (35% in the ranibizumab group versus 30% in the PRP group; difference, 3%; 95% CI, -7% to 12%; P = .58). One eye in the ranibizumab group developed endophthalmitis. No significant differences between groups in rates of major cardiovascular events were identified. The investigators concluded that, among eyes with proliferative diabetic retinopathy, treatment with ranibizumab resulted in visual acuity that was noninferior to (not worse than) PRP treatment at 2 years. The authors stated that, although longer-term follow-up is needed, ranibizumab may be a reasonable treatment alternative, at least through 2 years, for patients with proliferative diabetic retinopathy.

Beaulieu, et al. (2016) compared patient-centered outcomes in patients with proliferative diabetic retinopathy (PDR) treated with ranibizumab vs panretinal photocoagulation (PRP) from the Protocol S study. The multicenter trial was conducted at 55 U.S. sites and involved 216 adults with 1 study eye out of 305 adults (excluding participants with 2 study eyes, because each eye received a different treatment) with PDR, visual acuity 20/320 or better, no history of PRP. Subjects were assigned to ranibizumab (0.5 mg/0.05 mL) versus PRP. The primary outcome was change from baseline to 2 years in composite and prespecified subscale scores from the National Eye Institute Visual Function Questionnaire-25 (NEI VFQ-25), University of Alabama Low Luminance Questionnaire (UAB-LLQ), and Work Productivity and Activity Impairment Questionnaire (WPAIQ). For the NEI VFQ-25 and UAB-LLQ composite scores, ranibizumab–PRP treatment group differences (95% CI) were +4.0 (-0.2, +8.3, P = .06) and +1.8 (-3.5, +7.1, P = 0.51) at 1 year, and +2.9 (-1.5, +7.2, P = .20) and +2.3 (-2.9, +7.5, P = .37) at 2 years, respectively. Work
productivity loss measured with the WPAIQ was 15.6% less with ranibizumab (-26.3%, -4.8%, P = .005) at 1 year and 2.9% (-12.2%, +6.4%, P = .54) at 2 years. Eighty-three ranibizumab participants (97%) were 20/40 or better in at least 1 eye (visual acuity requirement to qualify for an unrestricted driver's license in many states) at 2 years compared with 82 PRP participants (87%, adjusted risk ratio = 1.1, 95% CI: 1.0, 1.2, P = .005). The authors concluded that, though differences in some work productivity and driving-related outcomes favored ranibizumab over PRP, no differences between treatment regimens for PDR were identified for most of the other patient-centered outcomes considered.

An American Academy of Ophthalmology Preferred Practice Pattern on Diabetic Retinopathy (AAO, 2016) states: "Currently, the role of anti-VEGF therapy in the management of severe NPDR and non-high-risk PDR is under investigation." Regarding the Protocol S study, the AAO states "Very recently, the DRCR.net study protocol S has demonstrated that alternative use of anti-VEGF agents (ranibizumab was used in this protocol), may be an alternative to panretinal laser photoagulation. However, many feel that panretinal photocoagulation remains the first choice for management of PDR. The anti-VEGF alternative could be considered for patients who can follow-up regularly. Further studies are required to determine the long-term implications of using anti-VEGF agents alone."

An editorial accompanying the protocol S study (Olsen, 2015) also raised concerns about the need for compliance with ranibizumab treatments for DRE, and the lack of long-term data. "Several other important and unanswered questions arise as a result of this study. What is the long-term role of the anti-VEGF alternative treatment for high-risk PDR? What happens to the PDR beyond 2 years? Does the PDR involute and eliminate the need for continued injections or PRP? Will high-risk features gradually recur once the anti-VEGF injections stop? If so, in what percentage of patients will high-risk features recur? Will the anti-VEGF treatment alternative lead to a lifetime of frequent visits and intravitreal injections? How often should stable patients be followed up in the absence of PRP? In younger patients with
diabetes and PDR, should earlier PRP be selected to avoid the rare yet known potential complication of endophthalmitis that may result during a lifetime of anti-VEGF injections? Laser treatments are highly cost-effective in the management of PDR. How will the use of anti-VEGF injections affect the cost of care to society, especially given the high and increasing prevalence of diabetes in the United States?"

Bevacizumab

Avastin (bevacizumab), given by intravitreal injection, is considered “medically reasonable and necessary for patients diagnosed with neovascular (wet) AMD.” The American Academy of Ophthalmology (AAO) and the American Society of Retinal Specialists (ASRS) support the use of Avastin (bevacizumab). The NIH-sponsored Ranibizumab and Bevacizumab for Neovascular Age-Related Macular Degeneration CATT study suggests that at one year, Avastin (bevacizumab) and Lucentis (ranibizumab) have equivalent effects on visual acuity when administered according to the same schedule for the treatment of age-related macular degeneration (AMD).

Age-related macular degeneration (AMD), characterized as a progressive degenerative disease of the macula, is the leading cause of blindness in developed countries afflicting approximately 15 million people in the United States. There are various options for the treatment of choroidal neovascularization (CNV) in patients with AMD. Classic CNV responds well to photodynamic therapy (PDT) with "off label" triamcinolone, while occult CNV can be treated by PDT, transpupillary thermotherapy, sub-retinal surgery, macular translocation, and anti-angiostatic therapy. Ladewig and colleagues (2006) stated that the safety and effectiveness of the therapeutic anti-VEGF concept has already been shown for pegaptanib (Macugen) and ranibizumab (Lucentis). Bevacizumab acts as an antibody against all VEGF-A isoforms and has been developed for oncological indications with intravenous application. Initial reports on intra-vitreal administration in patients with neovascular AMD have shown
beneficial morphological and functional effects. In the meantime, bevacizumab has been used off-label in thousands of patients with AMD.

According to the manufacturer, however, there are a number of differences between bevacizumab and ranibizumab (Bandolier, 2007): (i) bevacizumab contains no preservatives, so there could be problems in keeping it sterile when split into small quantities required for retinal treatment; (ii) no preclinical trial toxicity data exists for use of bevacizumab in retinal therapy; (iii) the half-life of bevacizumab is different from ranibizumab, in that it clears from the system 100 times slower; this is important for cancer use, but remaining in the retina for that length of time could be harmful; (iv) ranibizumab binds more strongly to the VGEF protein than bevacizumab; it is this binding that blocks the protein from developing blood vessel growth into the retina (neovascularization); (v) bevacizumab contains full-length antibodies, which can cause inflammation, whereas the antibody fragments in ranibizumab are 1/3 the size of bevacizumab antibodies, so they are capable of better penetration through the retinal layers; and (vi) manufacturing standards differ for cancer and ophthalmic drugs; particulate matter must be very low in drugs used in the eye, and bevacizumab is not manufactured with that in mind. It is also the case that there are some small case series, but little randomized trial evidence exists for benefit from bevacizumab (Avastin), nor much at all for harm, especially rare but serious harm (Bandolier, 2007).

Fung et al (2006) stated that off-label intra-vitreal injections of bevacizumab have been performed for the treatment of neovascular and exudative ocular diseases since May 2005. Since then, the use of intra-vitreal bevacizumab has spread worldwide, but the drug-related adverse events (AE) associated with its use have only been reported in a few retrospective reviews. The International Intra-vitreal Bevacizumab Survey was initiated to gather timely information regarding adverse events from physicians around the world via the internet. An internet based survey was designed to identify AE associated with intra-vitreal bevacizumab therapy. The survey web address was disseminated to the international vitreo-retinal community via email. Rates of
AE were calculated from participant responses. A total of 70 centers from 12 countries reported on 7,113 injections performed on 5,228 patients. Physician-reported AE included corneal abrasion, lens injury, endophthalmitis, retinal detachment, inflammation/uveitis, cataract progression, acute vision loss, central retinal artery occlusion, sub-retinal hemorrhage, retinal pigment epithelium tears, blood pressure elevation, transient ischemic attack, cerebrovascular accident and death. None of the AE rates exceeded 0.21%. The authors concluded that intra-vitreal bevacizumab is being used globally for ocular diseases. Self-reporting of AE following intra-vitreal bevacizumab injections did not reveal an increased rate of potential drug-related ocular or systemic events. These short-term results suggest that intra-vitreal bevacizumab appears safe.

Spaide et al (2006) described the short-term anatomical and visual acuity responses after intra-vitreal injection of bevacizumab in patients with CNV secondary to AMD. These investigators performed a retrospective study of patients with CNV secondary to AMD who were treated with intra-vitreal injection of bevacizumab (1.25 mg) during a 3-month period. Patients underwent best-corrected Snellen visual acuity testing, optical coherence tomography, and ophthalmoscopic examination at baseline and follow-up visits. There were 266 consecutive eyes of 266 patients who received injections, and follow-up information was available for 251 (94.4%). The mean age of the patients was 80.3 years, the mean baseline visual acuity was 20/184, and 175 (69.7%) had inadequate response to alternate methods of treatment. At the 1-month follow-up (data available for 244 patients), the mean visual acuity was 20/137 (p < 0.001 as compared with baseline), and 74 (30.3%) of patients had improvement in visual acuity as defined by a halving of the visual angle. At the 2-month follow-up (data available for 222 patients), the mean visual acuity was 20/122 (p < 0.001), and 78 (31.1%) of patients had visual improvement. At the 3-month follow-up (data available for 141 patients), the mean visual acuity was 20/109 (p < 0.001), and 54 (38.3%) of patients had visual acuity improvement. The mean central macular thickness at baseline was 340 microm and decreased to a mean of 247 microm at month 1 (p < 0.001) and 213 microm at month 3 (p < 0.001). At 1
month, two patients had mild vitritis, as did one patient at 2 months, who had a history of recurrent uveitis. No endophthalmitis, increased intraocular pressure, retinal tear, or retinal detachment occurred. The risk for thromboembolic disorders did not seem to be different than reported previously in studies concerning macular degeneration. There were no apparent short-term safety concerns for intra-vitreal bevacizumab injection for CNV. Treated eyes had a significant decrease in macular thickness and improvement in visual acuity. The results of this study are in agreement with those of Inturralde et al (2006, 16 eyes/15 patients), Bashshur et al (2006, 17 eyes/17 patients), Rich et al (2006, 53 eyes/50 patients), and Avery et al (2006, 81 eyes/79 patients).

A German review on new treatments for neovascular AMD (authors not listed, 2006) stated that therapeutic options include laser photocoagulation, PDT with verteporfin, triamcinolone and its possible combination with PDT, anecortave acetate, pegaptanib and ranibizumab. It noted that extra-foveal classic CNV should be treated with thermal laser coagulation. For sub-foveal lesions with predominantly classic CNV, or occult forms with non-classic CNV, a lesion size less than or equal to 4 macular photocoagulation study (MPS) disc areas (DA) and recent disease progression, PDT with verteporfin is a safe and effective therapy. For the remaining subtypes, VEGF inhibitors (e.g., pegaptanib, ranibizumab, bevacizumab) for intra-vitreal use are now available as therapeutic alternatives. The review stated that the results of the phase III studies for pegaptanib and ranibizumab, however, are not comparable, in particular with reference to the outcomes in the control groups. Since bevacizumab (Avastin) and ranibizumab are comparable in their pharmacological profile, bevacizumab may be an alternative in the off-label treatment of neovascular AMD. The switch to alternative treatment modalities should be considered in particular when the first line treatment is ineffective. The recommendations from this review provided evidence-based guidance for non-surgical therapies in the management of neovascular AMD.

In an editorial on the use of intra-vitreal Avastin as the low cost alternative to Lucentis published in the American Journal of
Ophthalmology, Rosenfeld (2006) stated that "[c]urrently, there appears to be a global consensus that the treatment strategy using intravitreal Avastin is logical, the potential risks to our patients are minimal, and the cost-effectiveness is so obvious that the treatment should not be withheld".

On March 20, 2006, a survey by the American Society of Retinal Specialists of its membership was completed. It found that 92% of 289 respondents felt intra-vitreal bevacizumab was "somewhat better" or "much better" than other FDA-approved or covered therapies. Only 4% of respondents had seen any thromboembolic complications thought to be related to the intra-vitreal bevacizumab, and 96% thought intra-vitreal bevacizumab was the same or better in terms of overall safety compared to other FDA-approved or covered therapies.

On April 20, 2006, the American Academy of Ophthalmology (AAO) wrote to the Centers for Medicare and Medicaid Services (CMS) supporting the reimbursement for treating AMD with intra-vitreal injections of bevacizumab, to meet the medical needs of patients who have not responded to therapy with PDT with verteporfin or intra-vitreal pegaptanib. The AAO's support for reimbursement is limited to "such patients who are deemed by their treating physician to have failed FDA-approved therapies, or in the judgment of their treating physician, based on his/her experience, are likely to have greater benefit from the use of intra-vitreal bevacizumab".

On October 5, 2006, the National Institutes of Health's National Eye Institute said it will fund a multi-center clinical trial to compare Lucentis with Avastin in the treatment of AMD (NIH, 2006).

Available evidence indicates that anti-VEGF therapy with either ranibizumab or bevacizumab plays an important role in the management of diabetic macular edema. An NIH-sponsored, multi-center, randomized clinical trial demonstrated that ranibizumab in combination with macular laser photocoagulation is superior to macular laser photocoagulation alone at 12 months of follow-up (Diabetic Retinopathy Clinical Research Network,
The need for re-treatment was determined by retinal thickness as measured by optical coherence tomography (OCT) and visual acuity. The 1-year mean change in the visual acuity letter score from baseline was significantly greater in the ranibizumab + prompt laser group (+9, p < 0.001) and ranibizumab + deferred laser group (+9, p < 0.001) but not in the triamcinolone + prompt laser group (+4, p = 0.31) compared with the sham + prompt laser group (+3). Intravitreal ranibizumab with prompt or deferred laser is more effective through at least 1 year compared with prompt laser alone for the treatment of DME involving the central macula.

A second single-center, randomized clinical trial also demonstrated that intravitreal injection of bevacizumab every 6 weeks based on clinical response determined by OCT and visual acuity is superior to macular photocoagulation every 4 months (Michaelides et al, 2010). The authors reported the odds of gaining greater than or equal to 10 ETDRS letters over 12 months were 5.1 times greater in the bevacizumab group than in the laser group (adjusted odds ratio, 5.1; 95 % confidence interval [CI]: 1.3 to 19.7; p = 0.019).

Astam and colleagues (2009) evaluated the short-term effectiveness of intra-vitreal bevacizumab injection for the management of macular edema due to diabetic retinopathy and retinal vein occlusion. Standardized ophthalmic evaluation, ETDRS visual acuity measurement, and central macular thickness were performed at baseline and 1 month intervals after injection. There were 23 eyes of 21 patients with macular edema due to diabetic retinopathy (14 eyes of 12 patients), and retinal vein occlusion (9 eyes of 9 patients). The mean baseline logMAR visual acuity and central macular thickness were 0.82 +/- 0.27 and 604.71 +/- 123.62 mum, respectively, in patients with diabetic retinopathy. There was no statistically significant difference between the mean logMAR visual acuity (p = 0.22) and central retinal thickness (p = 0.16) measurements at baseline and 3 months follow-up. The mean baseline logMAR visual acuity and central macular thickness were 0.94 +/- 0.48 and 557 +/- 113.9 mum, respectively, in patients with retinal vein occlusion. There was a statistically significant difference between the mean
logMAR visual acuity and central retinal thickness measurements at baseline and 3 months follow-up (p < 0.01). Almost all of the eyes (88.8 %) regained normal foveal configuration. The authors concluded that although the follow-up period was short and the number of patients were limited to provide specific treatment recommendations, intra-vitreal bevacizumab seems to be more effective for macular edema due to retinal vein occlusion than diabetic macular edema. The favorable short-term findings suggested that further study is needed. This is in agreement with the observations of Badala (2008) as well as Wu et al (2008).

In a review on diabetic retinopathy (DR), Cheung et al (2010) noted that although anti-VEGF therapy has promising clinical applications for the management of DR, its long-term safety in patients with diabetes has not yet been established. Local adverse events of IVB include cataract formation, infection, retinal detachment, vitreous hemorrhage, as well as potential loss of neural retinal cells. Furthermore, a significant portion of anti-VEGF agents injected into the eye could pass into the systemic circulation. Thus, systemic inhibition of angiogenesis is a potential risk. Also, although clinical trials on the use of intra-vitreal anti-VEGF therapy for the treatment of AMD generally show low (0.6 to 1.2 %) rates of stroke, this risk could be increased in patients with DR because of pre-existing diabetes-related vascular disease.

Nicholson and Schachat (2010) stated that many observational and pre-clinical studies have implicated VEGF in the pathogenesis of DR, and recent successes with anti-VEGF therapy for age-related macular degeneration have prompted research into the application of anti-VEGF drugs to DR. These investigators reviewed the numerous early studies that suggest an important potential role for anti-VEGF agents in the management of DR. The authors concluded that for diabetic macular edema, phase II trials of intra-vitreal pegaptanib and intra-vitreal ranibizumab have shown short-term benefit in visual acuity. Intra-vitreal bevacizumab also has been shown to have beneficial short-term effects on both visual acuity and retinal thickness. For proliferative diabetic retinopathy (PDR), early studies suggest that IVB temporarily decreases leakage from diabetic neovascular
lesions, but this treatment may be associated with tractional retinal detachment. Furthermore, several studies indicate that bevacizumab is likely to prove a helpful adjunct to diabetic pars plana vitrectomy for tractional retinal detachment. Finally, 3 small series suggest a potential beneficial effect of a single dose of bevacizumab to prevent worsening of DME after cataract surgery. The authors noted that use of anti-VEGF medications for any of these indications is off-label. Despite promising early reports on the safety of these medications, the results of large, controlled trials to substantiate the safety and efficacy of anti-VEGF drugs for diabetic retinopathy are eagerly awaited.

Badala (2008) noted that intra-vitreal bevacizumab appears to be a safe and effective treatment for macular edema associated with branch retinal vein occlusion, at least in the short-term. However, further randomized, controlled studies are needed to evaluate long-term safety and effectiveness of this approach. Wu et al (2008) stated that longer studies are needed to ascertain what role, if any, intra-vitreal injection of bevacizumab may play in the long-term treatment of macular edema secondary to branch retinal vein occlusion. Furthermore, Fraser-Bell et al (2008) noted that there remains no proven intervention that consistently prevents or reverses visual loss from diabetic macular edema in all patients. A variety of promising new medical and surgical therapies including intra-vitreal bevacizumab are under investigation, but further research is needed to determine their role alone or in combination.

An evidence review by Scanlon and Stratton (2008) for the National Library of Health stated that bevacizumab and other vascular endothelial growth factor inhibitors have not been studied in diabetic eye disease and that there are only early reports of their use. A recent systematic evidence review found insufficient evidence for the use of bevacizumab or other anti-VEGFs in diabetic eye disease (Mohamed et al, 2007). An ongoing randomized controlled clinical trial sponsored by the National Eye Institute is comparing the effects of laser treatment, intravitreal bevacizumab, and combined intravitreal bevacizumab and laser or sham injection on diabetic macular edema (National Eye Institute, 2008).
In an interventional, retrospective, multi-center study, Arevalo et al (2009a) determined the feasibility, safety, and clinical effect of intra-vitreal (IVT) bevacizumab in patients with refractory cystoid macular edema (CME) following cataract surgery. A total of 36 eyes of 31 patients with refractory CME after cataract surgery and with a mean age of 68.2 years (range of 67 to 87 years) were included in this study. Patients were treated with at least 1 IVT injection of 1.25 or 2.5 mg bevacizumab. Patients were followed-up for 12 months. Main outcome measures included best-corrected visual acuity (BCVA) and central macular thickness (CMT) by optical coherence tomography (OCT). Twenty-six eyes (72.2 %) showed improvement of BCVA (greater than or equal to 2 Early Treatment Diabetic Retinopathy Study [ETDRS] lines), and no eye experienced worsening of visual acuity (greater than or equal to 2 ETDRS lines). Mean baseline BCVA was 20/200 (0.96 logarithm of the minimum angle of resolution [logMAR] units), and the mean 12-month BCVA was 20/80 (0.62 logMAR units; p < 0.0001). Optical coherence tomography demonstrated that mean CMT at baseline was 499.9 microm (range of 298 to 784 microm) and decreased to a mean of 286.1 microm (range of 168 to 499 microm) at 12 months (p < 0.0001). Four (11 %) eyes received 2 injections, 10 (27.8 %) eyes received 3 injections, 10 (27.8 %) eyes received 4 injections, 1 (2.8 %) eye received 5 injections, and 1 (2.8 %) eye received 6 injections. The mean number of injections was 2.7 (range of 1 to 6), and the mean interval between injections was 15.1 weeks (range of 4 to 45 weeks). No ocular or systemic adverse events were observed. The authors concluded that short-term results suggest that IVT bevacizumab is well-tolerated in patients with refractory pseudophakic CME. Treated eyes had a significant improvement in BCVA and decrease in macular thickness by OCT at 12 months. They stated that these results are promising and suggested the need for further evaluation with longer follow-up and a larger series of patients.

In a retrospective, multi-center, interventional, comparative case series, Arevalo et al (2009b) reported the 24-month anatomic and ETDRS BCVA response following primary intra-vitreal bevacizumab ([IVB] 1.25 or 2.5 mg) in patients with diffuse diabetic macular edema (DDME). In addition, a comparison of the 2 different doses of IVB used was presented. The clinical
records of 115 consecutive patients (139 eyes) with DDME at 11 centers from 8 countries were reviewed. Patients were treated with at least 1 IVT injection of 1.25 or 2.5 mg of bevacizumab. All patients were followed-up for 24 months. Patients underwent ETDRS BCVA testing, ophthalmoscopic examination, OCT, and fluorescein angiography (FA) at the baseline, 1-, 3-, 6-, 12-, and 24-month visits. Main outcome measures included changes in BCVA and OCT results. The mean age of the patients was 59.4 +/- 11.1 years. The mean number of IVB injections per eye was 5.8 (range of 1 to 15 injections). In the 1.25-mg group at 1 month, BCVA improved from 20/150 (0.88 logarithm of the minimum angle of resolution [logMAR] units) to 20/107, 0.76 logMAR units (p < 0.0001). The mean BCVA at 24 months was 20/75 (0.57 logMAR units; p < 0.0001). Similar BCVA changes were observed in the 2.5-mg group: at 1 month, BCVA improved from 20/168 (0.92 logMAR units) to 20/118 (0.78 logMAR units; p = 0.02). The mean BCVA at 24 months was 20/114 (0.76 logMAR units; p < 0.0001). In the 1.25-mg group, the mean CMT decreased from 466.5 +/- 145.2 microm at baseline to 332.2 +/- 129.6 microm at 1 month and 286.6 +/- 81.5 microm at 24 months (p < 0.0001). Similar results were obtained in the 2.5-mg group. The authors concluded that primary IVB at doses of 1.25 to 2.5 mg seem to provide stability or improvement in BCVA, OCT, and FA in DDME at 24 months. The results show no evident difference between IVB at doses of 1.25 or 2.5 mg. Moreover, they stated that the results are promising and suggested the need for further investigation especially randomized controlled trials comparing IVB and focal or grid photocoagulation.

In a Cochrane review on anti-angiogenic therapy with anti-VEGF modalities for diabetic macular edema, Parravano and colleagues (2009) concluded that there is insufficient high quality evidence from large RCTs supporting the use of either single or multiple anti-VEGF intra-vitreal injections to treat diabetic macular edema. Results from ongoing studies on several compounds should assess not only treatment efficacy but also, if a benefit is found, the number of injections needed for maintenance and long-term safety. Furthermore, the Spanish Retina and Vitreous Society's guidelines on management of diabetic retinopathy and macular oedema (Pareja-Ríos et al, 2009) stated that the role of
anti-angiogenics is not yet sufficiently defined.

In a randomized 3-arm clinical trial, Soheilian et al (2009) compared the results of IVB injection alone or in combination with intra-vitreal triamcinolone acetonide (IVTA) versus macular laser photocoagulation (MPC) as a primary treatment of DME. A total of 150 eyes of 129 patients with clinically significant DME and no previous treatment were included in this study. The eyes were randomly assigned to 1 of the 3 study arms: (i) the IVB group, patients who received 1.25 mg IVB (50 eyes); (ii) the IVB/IVTA group, patients who received 1.25 mg of IVB and 2 mg of IVTA (50 eyes); and (iii) the MPC group, patients who underwent focal or modified grid laser (50 eyes). Re-treatment was performed at 12-week intervals whenever indicated. Subjects were followed at 12 week intervals through 36 weeks. Outcome measures included changes from baseline in BCVA and CMT. Overall, re-treatment was required for 27 eyes up to 36 weeks (14 in the IVB group, 10 in the IVB/IVTA group, and 3 in the MPC group). In regards to reduction of CMT, the authors found that there was no meaningful superiority of the IVB and IVB/IVTA groups over the MPC group. The IVB/IVTA group showed an initial significant improvement in visual acuity over the MPC group; however, no statistically significant difference in visual improvement was seen at weeks 24 and 36. The IVB group showed a significant improvement in visual acuity over the MPC group, but by 36 weeks, this difference was of marginal statistical significance. The authors found no adjunctive effect of IVTA. The authors stated that larger studies with long-term follow-up evaluating the therapeutic effects of bevacizumab focusing on different features of DME are recommended.

In a prospective, randomized, masked cohort study, Takamura et al (2009) determined the feasibility and clinical effectiveness of IVB combined with cataract surgery for management of the post-operative increase of retinal thickness in patients with diabetic maculopathy. A total of 42 eyes with DME of 42 patients with type 2 diabetes mellitus were included in this analysis. Patients were randomly assigned to receive either cataract surgery only (control; 21 eyes) or combined with IVT injection of 1.25 mg bevacizumab (21 eyes). Efficacy measures included BCVA testing,
OCT, and ophthalmoscopic examination. Retinal thickness (RT) on OCT and BCVA were measured at baseline and 1 and 3 months after surgery. There were no significant differences in RT, BCVA, severity of cataract, or systemic condition between the control and bevacizumab groups at the baseline. One and 3 months after surgery, the control group showed a significant increase in RT, whereas the bevacizumab group showed a significant decrease. Although post-operatively the eyes in both groups showed a significant improvement of BCVA, bevacizumab-treated eyes showed significantly better results (mean logarithm of the minimum angle of resolution, 0.38) than the control group (0.51) at month 3. There was a significant relationship between RT and VA post-operatively in the control ($p = 0.0001$) and bevacizumab ($p = 0.0141$) groups. No systemic or ocular adverse events were observed. The authors concluded that short-term results suggested that IVT bevacizumab has the potential not only to prevent the increase in RT, but also reduce the RT of eyes with DME following cataract surgery. Moreover, they stated that these results seem promising and further investigation with a longer follow-up and a larger series of patients may be needed.

In a retrospective, consecutive, interventional case series, Wakabayashi et al (2008) assessed the effectiveness of intravitreal bevacizumab (IVB) for iris neovascularization (INV) or neovascular glaucoma (NVG) in patients with ischemic retinal disorders. A total of 30 patients (41 eyes) with INV or NVG secondary to ischemic retinal disorders were included in this study. Patients received IVB (1 mg) as the initial treatment for INV or NVG and were followed-up for at least 6 months. Ophthalmic evaluations included measurement of visual acuity and intra-ocular pressure (IOP), a complete ophthalmic examination, and fluorescein angiography. Patients were divided into 3 subgroups: (i) INV without elevated IOP (INV group), (ii) NVG with an open angle (O-NVG group), and (iii) NVG with angle closure (C-NVG group) for outcomes analysis. Main outcome measures included the controllability of IOP by IVB, incidence of recurrence, and requirement for surgery to treat NVG. No significant ocular or systemic adverse events developed during follow-up (range of 6 to 22 months; mean of 13.3 months). The mean IOP levels were 14.7, 31.2, and 44.9 mmHg at baseline in the INV, O-NVG, and
C-NVG groups, respectively. In the INV group (9 eyes), the INV regressed or resolved after 1 injection. Iris neovascularization recurred in 4 eyes by 6 months and stabilized after repeated injections without IOP elevation. In the O-NVG group (17 eyes), rapid neovascular regression with successful IOP normalization (less than or equal to 21 mmHg) occurred in 12 eyes (71 %) within 1 week after 1 injection. Five (29 %) of the 17 eyes required surgery by 6 months despite repeated IVB injections, and a total of 7 eyes (41 %) underwent surgery during follow-up. In the C-NVG group (15 eyes), IVB caused INV resolution but failed to lower the IOP. Fourteen (93 %) of 15 eyes required surgery by 2 months after initial IVB and achieved IOP stabilization. The mean interval between IVB and surgery was significantly shorter in the C-NVG group than in the O-NVG group (p < 0.001). The authors concluded that intra-vitreal bevacizumab is well-tolerated, effectively stabilized INV activity, and controlled IOP in patients with INV alone and early-stage NVG without angle closure. In advanced NVG, IVB can not control IOP but may be used adjunctively to improve subsequent surgical results. They stated that further evaluation in controlled randomized studies (with long-term results) is needed to elucidate the appropriate use of bevacizumab in the management of neovascular glaucoma.

Schaal and associates (2009) evaluated the short-term safety and efficacy of intra-vitreal bevacizumab for the treatment of intra-retinal or sub-retinal fluid accumulation secondary to chronic central serous chorioretinopathy (CSC). A total of 12 patients were treated with intra-vitreous injections of 2.5 mg bevacizumab at 6- to 8-week intervals until intra-retinal or sub-retinal fluid resolved. Observation procedures were Early Treatment Diabetic Retinopathy Study BCVA, ophthalmic examination, and OCT, performed at 6- to 8-week intervals. Fluorescein angiography was performed at baseline visit and thereafter depending on clinical and OCT findings. Multi-variate analysis of variance with repeated measures was used to calculate a statistical significance of change in BCVA and mean central retinal thickness, which were the main outcome measures. Patients received 2 +/- 1 intra-vitreal injections of bevacizumab on average during a follow-up of 24 +/- 14 weeks. Mean BCVA increased by 2 +/- 2 lines; the change in BCVA (logMAR) was significant (p < 0.02). Mean central
retinal thickness decreased significantly over follow-up (p < 0.05), with 6 patients (50 %) showing complete resolution of sub-retinal fluid. The authors concluded that anatomical and functional improvement following intra-vitreal bevacizumab injections suggest that VEGF may be involved in fluid leakage in patients with chronic CSC. The results suggested a possible role for anti-VEGF agents in the treatment of chronic CSC. They stated that further evaluation of intra-vitreal bevacizumab for chronic CSC in controlled randomized studies is warranted.

In a prospective, controlled clinical study, Artunay et al (2010) examined the effect of IVB in treatment of persistent CSC. A total of 30 eyes of 30 patients with persistent, symptomatic CSC of 3 months’ duration or more were included in this study. Fifteen eyes of 15 patients were treated with intra-vitreal injections of 2.5 mg (0.1 ml) bevacizumab (treatment group). Fifteen eyes of 15 patients with the same characteristics who declined treatment were an acceptable control group. The visual and anatomical responses were observed with BCVA and central foveal thickness measured by OCT at baseline, 1, 3, and 6 months after treatment. Twelve (80 %) eyes in the IVB group compared with 8 (53.3 %) eyes in the control group showed morphological restitution at 6 months (p < 0.01). All 15 (100 %) treated eyes had stable or improved vision, compared with 10 (66.6 %) eyes in the control group (p < 0.01). At 6 months, the mean +/- SD central foveal thickness for the treatment group remained significantly lower compared to the control group, with 174 +/- 68 microm and 297 +/- 172 microm, respectively (p < 0.001). Injection-related complications were not encountered. The authors concluded that these findings indicate that intra-vitreal bevacizumab injection may be a new, promising treatment option for select patients with idiopathic persistent CSC. They stated that continued studies with IVB in this population will help to establish its long-term efficacy.

Teng and co-workers (2009) examined the effect of sub-conjunctival bevacizumab on primary pterygium. A patient with an inflamed nasal primary pterygium refractory to artificial tears and naphazoline was enrolled in this study. After pre-treatment with topical proparacaine and moxifloxacin, 0.05 ml bevacizumab
(1.25 mg/0.05 ml) was injected sub-conjunctivally at the limbus. Clinical signs of irritation, redness, and vascularization were monitored over 7 weeks. At 1 week post-injection, irritation and hyperemia showed near-total regression. At week 2, the pterygium maintained this appearance. By week 7, the degree of vascularity and symptoms of irritation had regressed to its pre-injection state. The authors concluded that treatment of primary pterygium with subconjunctival bevacizumab results in a short-term decrease in vascularization and irritation. They stated that further long-term studies should investigate the efficacy of bevacizumab as an adjunct to surgical excision or combined topical treatment targeting other growth factors involved in pterygium pathogenesis.

Razeghinejad and associates (2010) assessed the effectiveness of subconjunctival bevacizumab as an adjunctive therapy for primary pterygium surgery. This randomized prospective clinical study was conducted on 30 eyes of 30 patients. After pterygium excision and accomplishing a rotational conjunctival flap, 15 patients (case group) received 1.25 mg (0.1 ml) bevacizumab, and 15 other patients (control group) received 0.1 ml balanced salt solution subconjunctivally. The main outcome measures were recurrence of pterygia, horizontal length of the corneal epithelial defect, conjunctival erythema, lacrimation and photophobia during the first post-operative week. There were no statistically significant differences regarding age, sex or recurrence risk factors between the 2 groups (p > 0.05). The pterygia resolved in 13 (86.6 %) of 15 eyes in both groups, with a recurrence rate of 13.4 % during a mean follow-up period of 8 +/- 1.4 months in the case group and 7.4 +/- 1.5 months in the control group (p = 0.2). There were no statistically significant differences regarding reduction in refractive astigmatism, improvement in visual acuity, corneal epithelial defects, conjunctival erythema, lacrimation or photophobia between the case and control groups (p > 0.05). The authors concluded that a single intra-operative subconjunctival bevacizumab injection had no effect on recurrence rate or early post-operative conjunctival erythema, lacrimation, photophobia or healing of corneal epithelial defects following pterygium excision.
In a case series study, Ghanem and associates (2009) evaluated the effect of intra-vitreal injection of bevacizumab (2.5 mg) in cases of neovascular glaucoma. A total of 16 eyes of 16 patients with rubeosis iridis (RI) and secondary glaucoma were included in this study. The patients were followed for 2 months. These researchers noted partial or complete regression of iris neovascularization 1 week after injection of bevacizumab. Reproliferation of new vessels was detected in 25% of the cases after 2 months. The mean IOP before injection was 28 +/- 9.3 mm Hg under topical ss-blocker and systemic acetazolamide. One week after injection, the IOP decreased to 21.7 +/- 11.5 mm Hg (5 cases without anti-glaucoma drugs, 6 cases with topical ss-blocker, and 5 cases with both topical ss-blocker and systemic acetazolamide). The authors concluded that intra-vitreal bevacizumab injection leads to regression of iris neovascularization with subsequent drop of IOP in eyes with neovascular glaucoma. This was a small study with short-term follow-up; its finding was also confounded by the concomitant use of anti-glaucoma drugs in some cases. These findings need to be validated by well-designed studies.

Batman and Ozdamar (2010) reported the outcomes of the use of intra-cameral bevacizumab for iris neovascularization occurring after silicone oil (SO) removal in eyes undergoing vitre-oretinal surgery (VRS). This study included 12 eyes that had iris neovascularization after SO removal. There were 8 men and 4 women with an average age of 41.6 +/- 12.7 years. All eyes had VRS for various vitreo-retinal diseases. After the mean follow-up period of 9.7 +/- 5.3 months, SO removal was performed. Then, patients were followed for more than 2 months and detailed retinal examinations and IOP were normal during this period, but RI developed. Rubeosis iridis was treated with 1 dose of 1.25 mg bevacizumab into the anterior chamber. After a mean follow-up period of 4.8 +/- 2.2 months, the regression of iris neovascularization was detected and IOP was below 21 mmHg in all eyes. The authors concluded that anterior segment neovascularization (ASNV) may develop through various mechanisms in patients with VRS after SO removal, and anterior chamber injection of bevacizumab may lead to regression of ASNV. Again, this was a small study with short-term follow-up; its
findings need to be validated by well-designed studies.

In a prospective, randomized, clinical trial, Ahn et al (2011) evaluated the effects of pre-operative and IVB injection on the incidence of post-operative vitreous hemorrhage (VH) after vitrectomy for PDR. A total of 107 eyes of 91 patients undergoing pars plana vitrectomy (PPV) for the management of PDR-related complications were enrolled. A total of 107 cases were assigned randomly to either group 1 (intra-vitreal 1.25 mg/0.05 ml bevacizumab injection 1 to 14 days before PPV), group 2 (intra-vitreal 1.25 mg/0.05 ml bevacizumab injection at the end of PPV), or group 3 (no IVB injection). The primary outcome was the incidence of early (less than or equal to 4 weeks) and late (greater than 4 weeks) recurrent VH. Secondary outcome measures were the initial time of vitreous clearing (ITVC) and BCVA at 6 months after surgery. The incidences of early recurrent VH were 22.2 %, 10.8 %, and 32.4 % in groups 1, 2, and 3, respectively (p = 0.087). A subgroup pair-wise analysis showed significantly decreased early VH incidence in group 2 compared with that of group 3 (p = 0.026). The incidences of late recurrent VH were 11.1 %, 16.2 %, and 14.7 % in groups 1, 2, and 3, respectively (p = 0.813). The ITVC in groups 1, 2, and 3 were 26.4 +/- 42.5 days, 10.3 +/- 8.2 days, and 25.2 +/- 26.1 days, respectively. The ITVC was significantly shorter in group 2 compared with that in groups 1 and 3 (p = 0.045 and p = 0.015, respectively). The BCVA at 6 months after surgery did not differ significantly among the 3 groups (p = 0.418). The authors concluded that this study found no substantial evidence to support the adjunctive use of pre-operative IVB to reduce post-operative recurrence of VH in vitrectomy for PDR. For select cases in which adjunctive IVB use is considered, intra-operative administration seems to be the better option for reducing post-operative VH.

Farahvash et al (2011) evaluated the effect of pre-operative IVB on surgery and on the early post-operative course in diabetic patients undergoing vitrectomy for dense VH. A total of 35 patients with dense diabetic VH were randomly assigned to a group that received 1.25 mg of IVB 1 week before vitrectomy (18 patients) or the control group (17 patients). To compare the complexity of 2 groups, intra-operative complexity score and
proliferative diabetic vitreo-retinopathy stage were recorded. Intra-operative bleeding, break formation, number of endodiathermy applications, BCVA, anatomical outcome at month 3 and at final follow-up, and post-operative complications were evaluated. Mean complexity scores and proliferative diabetic vitreo-retinopathy stages of both groups were similar. The mean score of bleeding was 1.05 in the IVB group versus 1.76 in the control group (p = 0.35); endodiathermy applications and break formations were 0.44 versus 0.52 (p = 0.68) and 0.22 versus 0.29 (p = 0.60) in the IVB and control groups, respectively. Anatomical outcome and visual acuity at month 3 and at the final follow-up were similar. The authors concluded that these findings suggested that IVB before vitrectomy for dense diabetic VH has no significant effect on facilitation of surgery or on the early post-operative course.

In a Cochrane review, Smith and Steel (2011) assessed the effect of peri-operative anti-VEGF in reducing the incidence of post-operative vitreous cavity hemorrhage (POVCH). These investigators searched CENTRAL (which contains the Cochrane Eyes and Vision Group Trials Register) (The Cochrane Library 2011, Issue 2), MEDLINE (January 1950 to March 2011), PubMed (10 March 2011), EMBASE (January 1980 to March 2011), Latin American and Caribbean Health Sciences Literature Database (LILACS) (January 1982 to March 2011), the metaRegister of Controlled Trials (mRCT) (www.controlled-trials.com) and ClinicalTrials.gov (www.clinicaltrial.gov). There were no date or language restrictions in the electronic searches for trials. The electronic databases were last searched on March 10, 2011. These researchers included all RCTs that looked at the use of anti-VEGFs and the incidence of POVCH in people undergoing vitrectomy for PDR. Both review authors independently assessed and extracted the data using a standardized form based on the CONSORT statement. They included 4 studies (202 eyes of 198 participants) in this review. The 4 RCTs met the inclusion criteria, but the authors were unable to conduct a meta-analysis due to methodological issues in 3 of the trials. They have provided a summary of the effects of the interventions; and have also provided a summary of the current literature addressing each primary and secondary outcome. The authors concluded that
results from 1 of the included studies support the use of pre-
operative IVB to reduce the incidence of early POVCH. There are
currently no other high-quality RCTs that support the use of anti-
VEGF agents peri-operatively to reduce the incidence of early or
late POVCH. The remaining studies identified by the search
suggested that the pre-operative use of bevacizumab may reduce
the incidence of early POVCH, but it should be recognized that
there are a number of significant methodological issues in these
studies that lead us to be cautious when interpreting their
findings and make any definitive conclusions unwarranted.

Intravitreal bevacizumab is one form of treatment for rare causes
of choroidal neovascularization such as degenerative myopia,
idiopathic, angioid streaks, trauma, choroiditis and retinal
dystrophies. Because these are rare conditions, it is not possible
to perform definitive clinical trials. These diseases are
characterized by a subretinal neovascular process which is similar
to that seen in neovascular age-related macular degeneration.
Therefore, there is strong biologic plausibility that intravitreal
bevacizumab may be effective in these conditions. For these
conditions, intravitreal bevacizumab would be indicated in
persons with visual loss due to the presence of active choroidal
neovascular as seen on fluorescein angiography or ocular
coherence tomography.

In a pilot study, Lo Giudice et al (2009) evaluated the efficacy of
single-session PDT combined with intra-vitreal bevacizumab (IVB)
in the treatment of retinal angiomatous proliferation (RAP) in age-
related macular degeneration. A total of 8 patients with RAP
underwent indocyanine green angiography (ICGA)-guided single-
session verteporfin PDT followed by IVB (1.25 mg) within a 0-day
+/- 1-day interval. All patients were naïve to treatment. Best-
corrected visual acuity, fluorescein angiography, ICGA, and OCT
were performed at baseline and at each follow-up visit. All
patients received 3 consecutive monthly IVB injections; thereafter, retreatment with bevacizumab was performed in the
case of worsening BCVA or a deterioration of angiographic or OCT
findings. All patients had 9 months of follow-up. Complete
resolution of angiographical leakage was achieved in all eyes at 9
months. A significant improvement in the mean BCVA was
observed at 1 month, 3 months, 6 months, and 9 months after combined treatment (p = 0.004). Visual acuity improved in 62.5 % and was stable in 37.5 % of cases. No patients had a decrease in BCVA of 3 or more lines during follow-up. Mean central macular thickness was significantly reduced in all patients (p < 0.0001) as controlled at 1-month, 3-month, 6-month, and 9-month intervals from initial treatment. The mean number of injections for the 9 months were 3.2 +/- 0.4. No ocular complications or systemic events developed. The authors concluded that sequenced combined treatment with single-session PDT and IVB injections may be useful in treating RAP, reducing or eliminating retinal edema, and improving or stabilizing visual acuity. They stated that further investigations are warranted to outline the appropriate treatment paradigm for combination therapy.

Ishikawa et al (2009) evaluated the safety and effectiveness of IVB as a pretreatment of vitrectomy for severe proliferative diabetic retinopathy (PDR). A total of 8 eyes of 6 patients (33 to 64 years old, all male subjects) with severe PDR were investigated. An intra-vitreal injection of 1.25 mg bevacizumab was carried out 3 to 30 days before planned vitrectomy. All cases showed minimum bleeding during surgical dissection of fibro-vascular membrane. Two cases receiving bevacizumab 7 days before the surgery showed strong fibrosis and adhesion of fibro-vascular membrane, resulted in some surgical complications. The cases having IVB for shorter time did not show extensive fibrosis. The authors concluded that pre-treatment of bevacizumab is likely effective in the vitrectomy for severe PDR. The appropriate timing of vitrectomy after bevacizumab injection should be further evaluated.

In a prospective, comparative case series, El-Sabagh and colleagues (2011) evaluated the effects of intervals between pre-operative IVB and surgery on the components of removed diabetic fibro-vascular proliferative membranes. A total of 52 eyes of 49 patients with active diabetic fibro-vascular proliferation with complications necessitating vitrectomy were included in this study. Participant eyes that had IVB were divided into 8 groups in which vitreo-retinal surgery was performed at
days 1, 3, 5, 7, 10, 15, 20, and 30 post-injection. A group of eyes with the same diagnosis and surgical intervention without IVB injection was used for comparison. In all eyes, proliferative membrane specimens obtained during vitrectomy were sent for histopathologic examination using hematoxylin-eosin stain, immunohistochemistry (CD34 and smooth muscle actin), and Masson's trichrome stain. Main outcome measure was comparative analysis of different components of the fibro-vascular proliferation (CD34, smooth muscle actin, and collagen) among the study groups. Pan-endothelial marker CD34 expression levels starting from day 5 post-injection were significantly less than in the control group (p < 0.001), with minimum expression (1+) in all specimens removed at or after day 30 post-injection. Positive staining for smooth muscle actin was barely detected in the control eyes at day 1, and consistently intense at day 15 and beyond (p < 0.001). The expression level of trichrome staining was significantly high at day 10, compared with control eyes (p < 0.001), and continued to increase at subsequent surgical time points. The author concluded that a pro-fibrotic switch was observed in diabetic fibro-vascular proliferation after IVB, and these findings suggest that at approximately 10 days post-IVB the vascular component of proliferation is markedly reduced, whereas the contractile components (smooth muscle actin and collagen) are not yet abundant. Moreover, the authors noted that their histologic findings are in agreement with many published clinical findings and might be predictive of an optimal time interval for the pre-operative use of adjunctive IVB, which makes surgery more successful with less intra-operative bleeding and complications; thus resulting in better visual outcomes. However, such favorable outcomes need validation from large-scale clinical studies.

In a comparative, retrospective case series, Fong et al (2010) compared VA outcomes after bevacizumab or ranibizumab treatment for AMD. These researchers followed 452 patients in a retrospective study of exudative AMD treated with anti-VEGF drugs; 324 patients were treated with bevacizumab and 128 patients with ranibizumab. All treatment-naive patients who received either bevacizumab or ranibizumab were followed for 1 year. Baseline characteristics and VA were recorded using
standard descriptive statistics. Main outcome measure was VA. At 12 months, the distribution of VA improved in both groups with 22.9% of bevacizumab and 25.0% of ranibizumab attaining greater than or equal to 20/40. Improvement in vision was observed in 27.3% of the bevacizumab group and 20.2% of the ranibizumab group. The mean number of injections at 12 months was 4.4 for bevacizumab and 6.2 for ranibizumab. There were 8 (2%) deaths in the bevacizumab group and 4 (3%) in the ranibizumab group. Two patients developed endophthalmitis in the bevacizumab group and the ranibizumab group. The bevacizumab group had slightly worse acuity at baseline, but both groups showed improvement and stability of vision over time. The authors concluded that both treatments seem to be effective in stabilizing VA loss. There was no difference in VA outcome between the 2 treatment groups. Because the study is a non-randomized comparison, selection bias could mask a true treatment difference. Results from the Comparison of the Age-related Macular Degeneration Treatment Trials (CATT) will provide more definitive information about the comparative effectiveness of these drugs.

In a multi-center, single-blind, non-inferiority trial, Martin and colleagues/the CATT Research Group (2011) randomly assigned 1,208 patients with neovascular AMD to receive intravitreal injections of ranibizumab or bevacizumab on either a monthly schedule or as needed with monthly evaluation. The primary outcome was the mean change in VA at 1 year, with a non-inferiority limit of 5 letters on the eye chart. Bevacizumab administered monthly was equivalent to ranibizumab administered monthly, with 8.0 and 8.5 letters gained, respectively. Bevacizumab administered as needed was equivalent to ranibizumab as needed, with 5.9 and 6.8 letters gained, respectively. Ranibizumab as needed was equivalent to monthly ranibizumab, although the comparison between bevacizumab as needed and monthly bevacizumab was inconclusive. The mean decrease in central retinal thickness was greater in the ranibizumab-monthly group (196 μm) than in the other groups (152 to 168 μm, p = 0.03 by analysis of variance). Rates of death, myocardial infarction, and stroke were similar for patients receiving either bevacizumab or ranibizumab (p > 0.20).
The proportion of patients with serious systemic adverse events (primarily hospitalizations) was higher with bevacizumab than with ranibizumab (24.1 % versus 19.0 %; risk ratio, 1.29; 95 % confidence interval [CI]: 1.01 to 1.66), with excess events broadly distributed in disease categories not identified in previous studies as areas of concern. The authors concluded that at 1 year, bevacizumab and ranibizumab had equivalent effects on VA when administered according to the same schedule. Ranibizumab given as needed with monthly evaluation had effects on vision that were equivalent to those of ranibizumab administered monthly. Differences in rates of serious adverse events require further study.

In an editorial that accompanied the afore-mentioned study, Rosenfeld (2011) stated that "The CATT results, together with the totality of global experience, support the use of either bevacizumab or ranibizumab for the treatment of neovascular AMD ... The CATT data support the continued global use of intravitreal bevacizumab as an effective, low-cost alternative to ranibizumab".

Schmucker and associates (2011) performed a systematic review to compare adverse effects (AE) and the reporting of harm in randomized controlled trials (RCTs) and non-RCTs evaluating intravitreal ranibizumab and bevacizumab in AMD. Medline, Embase and the Cochrane Library were searched with no limitations of language and year of publication. Studies which compared bevacizumab or ranibizumab as monotherapy with any other control group were included. Case series were included if they met pre-defined quality standards. The results of phase III trials evaluating ranibizumab showed that the rates of serious ocular AE were low (less than or equal to 2.1 %) but indicated major safety concerns (RR 3.13, 95 % CI: 1.10 to 8.92). A possible signal with regard to thrombo-embolic events (RR 1.35, 95 % CI: 0.66 to 2.77) and a significant increase in non-ocular hemorrhage (RR 1.62, 95 % CI: 1.03 to 2.55) were also noted. In contrast to ranibizumab trials, the RCTs evaluating bevacizumab were of limited value. The main shortcomings are small sample sizes and an apparent lack of rigorous monitoring for AE. A critical assessment of the large number of published case series
evaluating bevacizumab also showed that no reliable conclusions on safety can be drawn using this study design. Therefore, any perception that intravitreal bevacizumab injections are not associated with major ocular or systemic AE are not supported by reliable data. The authors concluded that bevacizumab studies showed too many methodological limitations to rule out any major safety concerns. Higher evidence from ranibizumab trials suggested signals for an increased ocular and systemic vascular and hemorrhagic risk that warrants further investigation.

**Eylea**

Eylea (aflibercept injection) is a vascular endothelial growth factor (VEGF) inhibitor administered as an intravitreal injection.

Aflibercept is a fully human recombinant fusion protein that binds all isoforms of VEGFA, and prevents their binding to VEGFR-1 and VEGFR-2. Aflibercept also binds to Placental Growth Factor (PlGF) inhibiting it’ binding to VEGFR-1. Inhibiting the binding to these receptors decreases inflammation and vascular permeability, prevents the progression of neovascular AMD, and prevents further loss of vision.

Eylea (aflibercept injection) has been approved by the FDA for the treatment of neovascular (wet) age-related macular degeneration (AMD), Macular Edema following Retinal Vein Occlusion (RVO), and Diabetic Macular Edema (DME).

In a multi-center, randomized, double-masked study, Heier et al (2011) evaluated anatomic outcomes and vision, injection frequency, and safety during the as-needed (PRN) treatment phase of a study evaluating a 12-week fixed dosing period followed by PRN dosing to week 52 with VEGF Trap-Eye for neovascular (wet) AMD. A total of 159 patients with subfoveal choroidal neovascularization (CNV) secondary to wet AMD were included in this study. Patients were randomly assigned to 1 of 5 intra-vitreal VEGF Trap-Eye treatment groups: 0.5 mg or 2 mg every 4 weeks or 0.5, 2, or 4 mg every 12 weeks during the fixed-dosing period (weeks 1 to 12). From weeks 16 to 52, patients were evaluated monthly and were retreated PRN with their
assigned dose (0.5, 2, or 4 mg). Main outcome measures included change in central retinal/lesion thickness (CR/LT), change in total lesion and CNV size, mean change in BCVA, proportion of patients with 15-letter loss or gain, time to first PRN injection, re-injection frequency, and safety at week 52. The decrease in CR/LT at week 12 versus baseline remained significant at weeks 12 to 52 (−130 μm from baseline at week 52) and CNV size regressed from baseline by 2.21 mm² at 48 weeks. After achieving a significant improvement in BCVA during the 12-week, fixed-dosing phase for all groups combined, PRN dosing for 40 weeks maintained improvements in BCVA to 52 weeks (5.3-letter gain; p < 0.0001). The most robust improvements and consistent maintenance of VA generally occurred in patients initially dosed with 2 mg every 4 weeks for 12 weeks, demonstrating a gain of 9 letters at 52 weeks. Overall, a mean of 2 injections was administered after the 12-week fixed-dosing phase, and the mean time to first re-injection was 129 days; 19% of patients received no injections and 45% received 1 or 2 injections. Treatment with VEGF Trap-Eye was generally safe and well-tolerated, with few ocular or systemic AEs. The authors concluded that PRN dosing with VEGF Trap-Eye at weeks 16 to 52 maintained the significant anatomic and vision improvements established during the 12-week fixed-dosing phase with a low frequency of re-injections. Repeated dosing with VEGF Trap-Eye was well-tolerated over 52 weeks of treatment.

On November 18, 2011, the FDA approved aflibercept ophthalmic solution (Eylea, Regeneron Pharmaceuticals Inc.) for the treatment of neovascular (wet) AMD. The FDA's approval of Eylea was based on positive results from the 2 phase III VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD (VIEW) trials. Both found the drug non-inferior to ranibizumab, which is currently the most potent FDA-approved treatment option for wet AMD. In VIEW 1 (n = 1,217), conducted in the United States, and VIEW 2 (n = 1,240), conducted in Europe, all regimens of the drug, including 2 mg dosed every 2 months (after 3 loading doses), successfully met the primary endpoint of statistical non-inferiority compared with ranibizumab. The proportions of patients who maintained or improved vision over the course of 52 weeks in VIEW 1 were 96%, 95%, and 95% of patients receiving
afibercept 0.5 mg monthly, 2.0 mg monthly, and 2.0 mg every 2 months, respectively. This compared with 94% of patients receiving the standard 0.5-mg monthly dose of ranibizumab. For the secondary endpoint, visual acuity, the new drug was better. Patients receiving 2 mg monthly had a greater mean improvement in visual acuity at week 52, with a gain of 10.9 letters compared with 8.1 letters with ranibizumab (p < 0.01). All other dose groups were not significantly different from ranibizumab with respect to this secondary endpoint. In VIEW 2, vision was maintained in 96% of all afibercept dose groups and in 94% of the ranibizumab group. All doses were statistically non-inferior to ranibizumab, and no differences were noted between the drugs in visual acuity gain.

The most commonly reported AEs in patients receiving afibercept included eye pain, conjunctival hemorrhage, vitreous floaters, cataract, and an increase in eye pressure. Afibercept should not be used in those who have an active eye infection or active ocular inflammation. It has not been studied in pregnant women, so the treatment should be used only in pregnant women if the potential benefits of the treatment outweigh any potential risks. Age-related macular degeneration does not occur in children and afibercept has not been studied in children.

Afibercept is available as Eylea as a 40mg/ml solution in a single-use 3ml vial, designed to provide 0.05 ml for a 2mg dose. The recommended dose for AMD is 2 mg (0.05 ml) every 4 weeks (monthly) for the first 12 weeks, followed by 2 mg every 8 weeks (2 months). Although maintenance dosing can be as frequent as 2mg every month, additional efficacy was not demonstrated with this dosing compared to every 2 months.

Eylea has not been studied in pediatric or geriatric populations. Eylea is contraindicated in patients with ocular or periocular infections, active intraocular inflammation, and a known hypersensitivity to afibercept or any of the excipients in Eylea.

In September of 2012 the FDA approved afibercept injection (Eylea) for use in macular edema following central retinal vein occlusion (CRVO). Boyer et al (2012) conducted a multi-center,
randomized, prospective, controlled trial to assess the efficacy and safety of intravitreal VEGF Trap-Eye in eyes with macular edema secondary to CRV. A total of 189 eyes with macular edema secondary to CRVO were included in this study. Eyes were randomized 3:2 to receive VEGF Trap-Eye 2 mg or sham injection monthly for 6 months. At week 24, 56.1% of VEGF Trap-Eye treated eyes gained 15 letters or more from baseline versus 12.3% of sham-treated eyes (p < 0.001). The VEGF Trap-Eye treated eyes gained a mean of 17.3 letters versus sham-treated eyes, which lost 4.0 letters (p < 0.001). Central retinal thickness decreased by 457.2 µm in eyes treated with VEGF Trap-Eye versus 144.8 µm in sham-treated eyes (p < 0.001), and progression to any neovascularization occurred in 0 and 5 (6.8%) of eyes treated with VEGF Trap-Eye and sham-treated eyes, respectively (p = 0.006). Serious ocular AEs were reported by 3.5% of VEGF Trap-Eye patients and 13.5% of sham patients while incidences of non-ocular serious AEs generally were well-balanced between both groups. Conjunctival hemorrhage, reduced VA, and eye pain were the most common AEs. The investigators concluded that at 24 weeks, monthly intra-vitreal injection of VEGF Trap-Eye 2 mg in eyes with macular edema resulting from CRVO improved VA and CRT, eliminated progression resulting from neovascularization, and was associated with a low rate of ocular AEs related to treatment.

In October 2014, the FDA approved aflibercept injection for the treatment of macular edema following retinal vein occlusion (RVO), which includes macular edema following branch retinal vein occlusion (BRVO) in addition to the previously-approved indication of macular edema following central retinal vein occlusion (CRVO) (Regeneron, 2014). The recommended dosage of aflibercept in patients with macular edema following RVO is 2 milligrams (mg) (0.05 mL) every month (4 weeks) via intravitreal injection.

The expanded indication was based on the previously-approved indication for macular edema following CRVO and the positive results from the double-masked, randomized, controlled Phase 3 VIBRANT study of 181 patients with macular edema following BRVO (Regeneron, 2014). The VIBRANT study compared
afilbercept 2 mg once every 4 weeks with macular laser photocoagulation (control). The study continued for 52 weeks. At 24 weeks, significantly more patients treated with afilbercept gained at least 15 letters in vision (three lines on an eye chart) from baseline as measured on the Early Treatment Diabetic Retinopathy Study (ETDRS) chart, the primary endpoint of the study, compared with patients who received control (53 percent vs. 27 percent; \( P < 0.01 \)). Patients treated with afilbercept achieved a 17.0 letter mean improvement over baseline in best-corrected visual acuity (BCVA) compared to a 6.9 letter mean improvement in patients who received control (\( P < 0.01 \)), a key secondary endpoint.

The incidence of non-ocular serious adverse events (SAE) was 8.8 percent in the afilbercept group and 9.8 percent in the control group (Regeneron, 2014). One death and one Anti-Platelet Trialists' Collaboration (APTC)-defined arterial thromboembolic event (non-fatal stroke) occurred during the trial, both in patients in the control group. The most common ocular adverse events in patients treated with afilbercept included conjunctival hemorrhage and cataract. There were no cases of intraocular inflammation in either group. There was one ocular SAE in a patient in the afilbercept group, which was traumatic cataract.

In June 2014, the U.S. Food and Drug Administration (FDA) approved aflibercept (Eylea) injection for the treatment of diabetic macular edema (DME) (Regeneron, 2014). The FDA approval of aflibercept in DME was based on the one-year data from the Phase 3 VISTA-DME and VIVID-DME studies of 862 patients, which compared aflibercept 2 mg given monthly, aflibercept 2 mg given every two months (after five initial monthly injections), or macular laser photocoagulation (at baseline and then as needed). In the DME studies, after one year, the mean changes in best corrected visual acuity (BCVA), as measured by the ETDRS chart for the monthly and every two month aflibercept groups, were statistically significantly improved compared to the control group and were similar to each other. Across both trials, patients in both aflibercept dosing groups gained, on average, the ability to read approximately two additional lines on an eye chart compared with almost no change.
in the control group. The VISTA-DME and VIVID-DME studies will continue as planned for a total of three years.

In the Phase 3 VISTA-DME and VIVID-DME trials, aflibercept injection 2 mg dosed monthly and aflibercept 2 mg dosed every two months after 5 initial monthly doses achieved statistically significant improvements in the primary endpoint of mean change in BCVA at one year and the secondary endpoint of proportion of patients who gained at least 15 letters in BCVA versus baseline compared to control (Regeneron, 2014).

In the VISTA-DME trial, patients receiving aflibercept 2 mg monthly had a mean change from baseline in BCVA of 12.5 letters (p less than 0.01 compared to control), patients receiving aflibercept 2 mg every two months (after 5 initial monthly injections) had a mean change from baseline in BCVA of 10.7 letters (p less than 0.01 compared to control), and patients receiving control treatment had a mean change from baseline in BCVA of 0.2 letters (Regeneron, 2014). In the VISTA-DME trial, the percentage of patients who gained at least 15 letters in BCVA from baseline, or three lines of vision, was 41.6 percent in the aflibercept 2 mg every month group (p less than 0.01 compared to control), 31.1 percent in the aflibercept 2 mg every 2 months group (after 5 initial monthly injections) (p less than 0.01 compared to control), and 7.8 percent in the control group.

In the VIVID-DME trial, patients receiving aflibercept 2 mg monthly had a mean change from baseline in BCVA of 10.5 letters (p less than 0.01 compared to control), patients receiving aflibercept 2 mg every two months (after 5 initial monthly injections) had a mean change from baseline in BCVA of 10.7 letters (p less than 0.01 compared to control), and patients receiving control had a mean change from baseline in BCVA of 1.2 letters (Regeneron, 2014). In the VIVID-DME trial, the percentage of patients who gained at least 15 letters in BCVA from baseline, or three lines of vision, was 32.4 percent in the aflibercept 2 mg every month group (p less than 0.01 compared to control), 33.3 percent in the aflibercept 2 mg every 2 months group (after 5 initial monthly injections) (P less than 0.01 compared to control), and 9.1 percent in the control group.
In these trials, afilbercept had a similar overall incidence of adverse events (AEs), ocular serious AEs, and non-ocular serious AEs across treatment groups and the control group (Regeneron, 2014). Arterial thromboembolic events as defined by the Anti-Platelet Trialists’ Collaboration (non-fatal stroke, non-fatal myocardial infarction, and vascular death) also occurred at similar rates across treatment groups and the control group. The most frequent ocular treatment emergent AEs (TEAEs) observed in the VISTA-DME and VIVID-DME trials included conjunctival hemorrhage, eye pain, cataract, and vitreous floaters. The most common non-ocular TEAEs included hypertension and nasopharyngitis, which occurred with similar frequency in the treatment groups and the control group.

The recommended dose for afilbercept for DME is 2 mg administered by injection in the eye every 2 months (8 weeks) following 5 initial monthly (4 weeks) injections. Afilbercept may be dosed once per month, but additional benefit was not seen with this dosing plan (Regeneron, 2014).

The FDA approved aflibercept (Eylea) injection for the treatment of diabetic retinopathy in patients with diabetic macular edema (DME) (FDA, 2015).

The approval of aflibercept for the treatment of diabetic retinopathy in DME was based on two year data from the Phase 3 VISTA-DME and VIVID-DME studies of 862 patients, which compared aflibercept 2 mg monthly, aflibercept 2 mg every two months (after five initial monthly injections), or macular laser photocoagulation (at baseline and then as needed) (Regeneron, 2015). In these studies, on the primary endpoint of mean change in Best Corrected Visual Acuity (BCVA) at one year, patients treated with aflibercept monthly or every two months showed statistically significant improvements compared to the control group. Patients in both aflibercept groups gained, on average, the ability to read approximately two additional lines on an eye chart compared with almost no change in the control group.

A pre-specified secondary endpoint in the studies at year 2 evaluated diabetic retinopathy severity based on an established
grading scale measuring retinal damage (Regeneron, 2015). In the VISTA-DME trial, 38 percent of patients receiving aflibercept monthly or every two months (after 5 initial monthly injections) achieved a 2-step or better improvement on the diabetic retinopathy severity scale (DRSS), compared to 16 percent of patients receiving control. In the VIVID-DME trial, approximately 30 percent of patients receiving aflibercept monthly or every two months (after 5 initial monthly injections) achieved a 2-step or better improvement on the DRSS, compared to 8 percent of patients receiving control.

In these trials at year 2, aflibercept had a similar overall incidence of adverse events (AEs), ocular serious AEs, and non-ocular serious AEs across treatment groups and the control group (Regeneron, 2015). Arterial thromboembolic events as defined by the Anti-Platelet Trialists’ Collaboration (non-fatal stroke, non-fatal myocardial infarction, and vascular death) also occurred at similar rates across treatment groups and the control group. The most frequent ocular treatment emergent AEs (TEAEs) observed in the VISTA-DME and VIVID-DME trials included conjunctival hemorrhage, eye pain, cataract, and vitreous floaters. The most common non-ocular TEAEs included hypertension and nasopharyngitis, which occurred with similar frequency in the treatment groups and the control group.

The recommended dosage of aflibercept in patients with diabetic retinopathy in DME is 2 milligrams (mg) every two months (8 weeks) after five initial monthly injections (Regeneron, 2015). Although aflibercept may be dosed as frequently as 2 mg every 4 weeks, additional efficacy was not demonstrated when aflibercept was dosed every 4 weeks compared to every 8 weeks. Aflibercept is available as a single, 2 mg strength intravitreal injection for all approved indications.

In a multi-center, randomized, double-masked, phase II clinical trial, Do and colleagues (2011) compared different doses and dosing regimens of vascular endothelial growth factor (VEGF) Trap-Eye with laser photocoagulation in eyes with diabetic macular edema (DME). Diabetic patients (n = 221) with center-involved DME were included in this study. Participants were
assigned randomly to 1 of 5 treatment regimens: VEGF Trap-Eye 0.5 mg every 4 weeks (0.5q4); 2 mg every 4 weeks (2q4); 2 mg every 8 weeks after 3 initial monthly doses (2q8); or 2 mg dosing as needed after 3 initial monthly doses (2PRN), or macular laser photocoagulation. Main outcome measures included the change in best-corrected visual acuity (BCVA) at 24 weeks (the primary end point) and at 52 weeks, proportion of eyes that gained 15 letters or more in ETDRS BCVA, and mean changes in central retinal thickness (CRT) from baseline. As previously reported, mean improvements in BCVA in the VEGF Trap-Eye groups at week 24 were 8.6, 11.4, 8.5, and 10.3 letters for 0.5q4, 2q4, 2q8, and 2PRN regimens, respectively, versus 2.5 letters for the laser group (p ≤ 0.0085 versus laser). Mean improvements in BCVA in the VEGF Trap-Eye groups at week 52 were 11.0, 13.1, 9.7, and 12.0 letters for 0.5q4, 2q4, 2q8, and 2PRN regimens, respectively, versus -1.3 letters for the laser group (p ≤ 0.0001 versus laser). Proportions of eyes with gains in BCVA of 15 or more ETDRS letters at week 52 in the VEGF Trap-Eye groups were 40.9 %, 45.5 %, 23.8 %, and 42.2 % versus 11.4 % for laser (p = 0.0031, p = 0.0007, p = 0.1608, and p = 0.0016, respectively, versus laser). Mean reductions in CRT in the VEGF Trap-Eye groups at week 52 were -165.4 μm, -227.4 μm, -187.8 μm, and -180.3 μm versus -58.4 μm for laser (p < 0.0001 versus laser). Vascular endothelial growth factor Trap-Eye generally was well-tolerated. The most frequent ocular adverse events with VEGF Trap-Eye were conjunctival hemorrhage, eye pain, ocular hyperemia, and increased intraocular pressure, whereas common systemic adverse events included hypertension, nausea, and congestive heart failure. The authors concluded that significant gains in BCVA from baseline achieved at week 24 were maintained or improved at week 52 in all VEGF Trap-Eye groups. Moreover, they stated that VEGF Trap-Eye warrants further investigation for the treatment of DME.

Other indications

Ciulla and Rosenfeld (2009) stated that anti-VEGF treatments that arrest choroidal angiogenesis and reduce vascular permeability have revolutionized clinical practices for neovascular eye diseases. These researchers reviewed anti-VEGF therapies that
are being evaluated in ocular diseases, other than neovascular AMD, in which neovascularization plays a critical role in pathogenesis. Early studies of the anti-VEGF agents, pegaptanib sodium, ranibizumab, bevacizumab, VEGF trap, and bevasiranib in the treatment of various neovascular diseases (e.g., diabetic macular edema, retinal vein occlusion, choroidal neovascularization) have shown promising results. The efficacy and safety of these agents, either alone or combined with standard treatments (e.g., laser photocoagulation), anti-inflammatory agents, or other non-VEGF-based anti-angiogenic therapies, was actively investigated. Non-VEGF-driven pathways and growth factors other than VEGF may play important roles in pathogenesis and are included in certain combination therapies with VEGF inhibitors. The authors concluded that the discovery of VEGF-A’s role in the pathogenesis of neovascular ocular disease provided a strong rationale for the development of anti-VEGF-based therapies. There is now ample evidence that anti-VEGF therapies are viable treatment options for these diseases. Nevertheless, large, randomized controlled trials are still needed to confirm early safety and efficacy findings from small, open-label prospective studies.

Rodriguez-Fontal et al (2009) stated that ranibizumab is a Fab-Antibody with high affinity for VEGF, and is being designed to bind to all VEGF isoforms. This quality makes it a powerful drug for VEGF inhibition. Diseases of retinal and choroidal blood vessels are the most prevalent causes of moderate and severe vision loss in developed countries. Vascular endothelial growth factor plays a critical role in the pathogenesis of many of these diseases. Results of the pilot studies showed that intra-ocular injections of ranibizumab decrease the mean retinal thickness and improve the best corrected visual acuity in all the subjects. Proliferative diabetic retinopathy, currently treated with destructive laser photocoagulation, represents another potential target for anti-VEGF therapy. The early experience in animal models with proliferative retinopathy and neovascular glaucoma shows that posterior and anterior neovascularizations are very sensitive to anti-VEGF therapy. The outcome of 2 phase III clinical trials will increase the knowledge of the role of ranibizumab in the treatment of diabetic macular edema.
Neovascular glaucoma is a severe, blinding consequence of ocular ischemia. Rubeosis (neovascularization of the iris) develops followed by the onset of neovascular glaucoma once the angle structures are involved. The natural history of the disease is progressive, and may ultimately result in blindness. All cases of rubeosis and neovascular glaucoma require treatment of the underlying condition which caused the retinal ischemia, most often with panretinal photocoagulation (Sivak-Callcott et al, 2001). The onset of the beneficial effect of panretinal photocoagulation takes approximately 3 weeks after treatment to be evident. In patients with fulminant neovascular glaucoma where sight-threatening elevated intraocular pressure is present, treatment involves providing panretinal photocoagulation, or panretinal cryotherapy when the retina is not visible, followed by glaucoma filtration surgery, preferably waiting several weeks for the neovascularization to regress before the filter surgery (Allen et al, 1982). Florid neovascularization that is visible at presentation will slowly regress after panretinal photocoagulation, eventually positively influencing the outcome and reducing the complication rate of filtration surgery. However, during the several weeks waiting for an effect, the patient is at great risk for losing further vision due to glaucoma. For those eyes that have rubeosis with only minimal involvement of the anterior chamber angle with neovascularization, intravitreal bevacizumab may be able to prevent further progression by hastening the regression of neovascularization. Case series have demonstrated that intravitreal bevacizumab will cause the intraocular pressure to drop rapidly. In order to preserve the effect, panretinal photocoagulation must still be performed, but the rapidity with which intravitreal bevacizumab acts in days may save substantial visual function. There is currently substantial published literature documenting the positive effect of bevacizumab-induced regression of anterior segment neovascularization and positive influences on the outcome of glaucoma surgery when it is necessary. This adjuvant use of intravitreal bevacizumab is not a repeated, long-term therapy to treat neovascular glaucoma; rather, it is used as a bridge to create a more favorable intraocular environment for further treatment of the neovascular glaucoma with other modalities like panretinal photocoagulation and filtration surgery. Concerns
about intraocular pressure spikes and resulting secondary ischemia from intravitreal bevacizumab are outweighed by the need for prompt treatment of progressive ischemia from neovascular glaucoma.

Mennel et al (2010) reported a case of retinal juxtapapillary capillary hemangioma causing consecutive leakage with macular involvement. The tumor was treated with a combination of anti-VEGF and PDT and was followed for 1 year. A 44-year-old woman with retinal juxtapapillary capillary hemangioma in the right eye experienced a decrease of visual acuity from 20/20 to 20/60 because of a severe leakage from the tumor involving the macula with lipid depositions. Two sessions of PDT (sparing the part of the hemangioma located within the optic disc) and 5 injections of bevacizumab were applied in a period of 5 months. Visual acuity, visual field testing, retinal thickness measurements, fundus photography and fluorescein angiography were performed to evaluate the treatment effect. One year after the last injection, visual acuity increased to 20/40. All lipid exudates at the posterior pole resolved. Retinal thickness decreased from 490 to 150 microm with the restoration of normal central macular architecture. Leakage in fluorescence angiography reduced significantly, but hyper-fluorescence of the tumor was still evident. Visual field testing and angiography did not show any treatment-related vaso-occlusive side-effects. The authors concluded that in this single case, the combination of anti-VEGF and PDT appeared to be an effective strategy for the treatment of retinal juxtapapillary capillary hemangioma without side-effects. The authors stated that further studies with a greater number of eyes and adequate follow-up are necessary to support these first clinical results.

Nicholson and Schachat (2010) stated that diabetic retinopathy (DR) is a leading cause of vision loss in the working-age population worldwide. Many observational and pre-clinical studies have implicated VEGF in the pathogenesis of DR, and recent successes with anti-VEGF therapy for AMD have prompted research into the application of anti-VEGF drugs to DR. These researchers reviewed the early studies that suggested a potential role for anti-VEGF agents in the management of DR. The authors
concluded that for DME, phase II trials of intra-vitreal pegaptanib and intra-vitreal ranibizumab have shown short-term benefit in visual acuity. Intra-vitreal bevacizumab also has been shown to have beneficial short-term effects on both VA and retinal thickness. For proliferative diabetic retinopathy (PDR), early studies suggest that intra-vitreal bevacizumab temporarily decreases leakage from diabetic neovascular lesions, but this treatment may be associated with tractional retinal detachment (TRD). Furthermore, several studies indicated that bevacizumab is likely to prove a helpful adjunct to diabetic pars plana vitrectomy (PPV) for TRD. Finally, 3 small series suggested a potential beneficial effect of a single dose of bevacizumab to prevent worsening of DME after cataract surgery. Use of anti-VEGF medications for any of these indications is off-label. These investigators stated that despite promising early reports on the safety of these medications, they eagerly await the results of large, controlled trials to substantiate the safety and efficacy of anti-VEGF drugs for DR.

Boscia (2010) noted that DR is a major cause of blindness in Europe and North America, and the incidence is expected to increase in parallel with the rising incidence of diabetes mellitus. Boscia reviewed the current state of knowledge of the epidemiology, clinical presentation and pathophysiology of DR and its principal associated complications, DME and neovascularization, and then proceeded to the primary focus of clinical management. A series of major randomized controlled trials conducted over the past few decades has confirmed that tight glycemic regulation is the most effective measure to reduce the risk of developing DR and to minimize the likelihood of its progression, and that control of blood pressure is also an important feature of preventive management. Laser-based therapies remain the cornerstone of treatment, with pan-retinal photocoagulation indicated for PDR and severe non-PDR and focal photocoagulation indicated for treatment of DME. For patients who do not benefit from these approaches, vitrectomy may provide therapeutic benefits. Medical therapies include 2 broad classes of agents: anti-inflammatory drugs and agents with molecular targets. The utility of oral anti-inflammatory drugs remains to be established, as dose-finding studies have yet to
provide definitive conclusions. Intra-vitreal corticosteroids may be of value in specific circumstances, although adverse effects include cataract progression and elevated IOP. However, these complications appear to have been limited with new extended-release technologies. With respect to molecular targets, evidence has been adduced for the roles of VEGF, tumor necrosis factor (TNF)-alpha and protein kinase C (PKC)-beta2 in the pathogenesis of DR, and agents targeting these factors are under intense investigation. Preliminary efficacy of pegaptanib and ranibizumab in the treatment of DME is being confirmed in additional clinical trials with these agents and with the off-label use of bevacizumab, another monoclonal antibody related to ranibizumab. Moreover, other agents targeting VEGF, as well as drugs directed against TNF-alpha and PKC-beta2, are under study. Evaluation of the ultimate utility of these approaches will await the safety and effectiveness results of properly designed phase III trials.

In a review on diabetic retinopathy, Cheung and colleagues (2010) stated that although anti-VEGF therapy has promising clinical applications for management of DR, its long-term safety in patients with diabetes has not yet been established. Moreover, Elman and associates (2011) stated that further investigation is needed to ascertain the role of anti-VEGF drugs in the prevention or treatment of PDR.

Waisbourd et al (2011) summarized the latest developments in the treatment of DR with anti-VEGF drugs. These researchers reviewed recent studies that evaluated the role of the anti-VEGF agents bevacizumab, ranibizumab and pegaptanib in the treatment of DR. There was only 1 large randomized controlled trial that evaluated the role of ranibizumab in DME. Other prospective and retrospective studies provided important insight into the role of anti-VEGF drugs in DR, but most of them were not conducted in large scales. The growing evidence indicates that anti-VEGF drugs are beneficial in DR, especially in DME. The authors concluded that further studies are needed to fully evaluate the role of these agents, especially in PDR and in DR candidates for vitrectomy surgery.
Mintz-Hittner et al (2011) stated that retinopathy of prematurity (ROP) is a leading cause of childhood blindness worldwide. Peripheral retinal ablation with conventional (confluent) laser therapy is destructive, causes complications, and does not prevent all vision loss, especially in cases of retinopathy of prematurity affecting zone I of the eye. Case series in which patients were treated with VEGF inhibitors suggested that these agents may be useful in treating ROP. These researchers conducted a prospective, controlled, randomized, stratified, multi-center trial to assess IVB monotherapy for zone I or zone II posterior stage 3+ (i.e., stage 3 with plus disease) ROP. Infants were randomly assigned to receive IVB (0.625 mg in 0.025 ml of solution) or conventional laser therapy, bilaterally. The primary ocular outcome was recurrence of ROP in 1 or both eyes requiring re-treatment before 54 weeks' post-menstrual age. These investigators enrolled 150 infants (total sample of 300 eyes); 143 infants survived to 54 weeks' post-menstrual age, and the 7 infants who died were not included in the primary-outcome analyses. Retinopathy of prematurity recurred in 4 infants in the IVB group (6 of 140 eyes [4 %]) and 19 infants in the laser-therapy group (32 of 146 eyes [22 %], p = 0.002). A significant treatment effect was found for zone I ROP (p = 0.003) but not for zone II disease (p = 0.27). The authors concluded that IVB monotherapy, as compared with conventional laser therapy, in infants with stage 3+ ROP showed a significant benefit for zone I but not zone II disease. Development of peripheral retinal vessels continued after treatment with IVB, but conventional laser therapy led to permanent destruction of the peripheral retina.

Dani et al (2012) reported the preliminary findings in 7 premature infants with complicated ROP or aggressive posterior ROP (APROP) who were treated with IVB as first line monotherapy or rescue therapy combined with laser treatment. These researchers studied retrospectively 7 preterm infants, who were affected by APROP (n = 4) or pre-threshold ROP (n = 3). Infants were treated with IVB (0.625 mg; Avastin) monotherapy (n = 2) when they were too sick to undergo lengthy laser treatment. Monotherapy IVB (n = 3 eyes) and IVB combined with laser therapy (n = 3 eyes) of APROP cases were followed by regression of the ROP and complete peripheral vascularization. The
combined therapy with IVB and laser therapy of pre-threshold ROP (5 eyes) produced a regression of neovascularization and good retinal anatomical outcome. The authors concluded that in this series, IVB was successful in treating ROP in a small cohort of extremely preterm infants with APROP or pre-threshold ROP, both as monotherapy or rescue treatment after laser therapy, without the development of ocular and systemic short- and long-term adverse effects.

Choovuthayakorn and Ubonrat (2012) reported the effectiveness of IVB injection for advanced ROP patients. A retrospective chart review was performed for 19 advanced ROP patients (34 eyes), who had IVB injection between January 1, 2007 and July 31, 2009. The baseline characteristics including gestational age, post-menstrual age of first injection, anterior and posterior segment changes, and complications between treatments to 1-year followed-up were analyzed. The patients were divided into 2 groups according to the indications for treatment. Group 1 -- 2 patients (4 eyes), received initial IVB injection followed by laser photocoagulation due to APROP. Group 2 -- 17 patients (30 eyes), received IVB injection due to persistence of the vascular activity after laser treatment. There were statistical significant difference between the 2 groups in terms of a mean gestation age, a mean birth weight, and a mean time for first intra-vitreal injection (p = 0.002, 0.008, and 0.007 respectively). However, there was no statistical significant difference between the 2 groups in terms of timing for resolution of vascular activity and retinal vasculogenesis across the laser scar (p = 0.172). One patient with APROP progressed to stage 4A ROP with successful anatomical attachment by pars plana vitrectomy. At 1-year follow-up, no other ocular or systemic side effects were observed. There was no statistical significant difference of a mean spherical equivalent between the 2 groups (p = 0.280). The authors concluded that IVB injection is an effective procedure either as an adjuvant or initial treatment in advanced ROP cases.

Autrata et al (2012) evaluated the safety and effectiveness of intravitreal injection of pegaptanib or bevacizumab and laser photocoagulation for treatment of threshold stage 3+ ROP affecting zone I and posterior zone II, and compared the results in
terms of regression, development of peripheral retinal vessels with conventional laser photocoagulation or combined with cryotherapy. In this prospective comparative study, a total of 174 eyes of 87 premature babies, from January 2008 to December 2011, were included. All infants were diagnosed with stage 3+ ROP for zone I or posterior II. Patients were randomly assigned to receive intravitreal pegaptanib (0.3 mg) or bevacizumab (0.625 mg/0.025 ml of solution) with conventional diode laser photocoagulation (Group A, 92 eyes of 46 infants) or laser therapy combined with cryotherapy (Group B, 82 eyes of 41 infants), bilaterally. The main evaluated outcomes include time of regression and decrease of plus signs and development of peripheral retinal vessels after treatment, final structural-anatomic outcomes compared in the both groups of patients. Risk factors and other characteristics of infants include birth weight, gestational age, Apgar score, duration of intubation and hospitalizations, post-menstrual age at treatment, sepsis, surgery for necrotizing enterocolitis, intra-ventricular hemorrhage. Primary outcome of treatment success was defined as absence of recurrence of stage 3+ ROP in 1 or both eyes (recurrence rate = 0) by 55 weeks’ post-menstrual age. Treatment failure was defined as the recurrence of neovascularization (recurrence rate = 1 or 2) in 1 or both eyes requiring re-treatment. The mean follow-up after treatment was 23.5 months (range of 4 to 45 months) in the Group A, and 25.2 months in the Group B (range of 3 to 48 months). Final favorable anatomic outcome and stable regression of ROP at last control examination have 90.2 % of eyes after adjuvant intravitreal pagaptanib or bevacizumab in the Group A, and 62 % of eyes after only conventional treatment in the Group B (p = 0.0214). Regression of plus disease and peripheral retinal vessels development appeared significantly more rapidly in Group A patients who received intravitreal VEGF inhibitors and laser. An absence of recurrence of neovascularization (stage 3+ ROP) was identified at 87 % of patients in the Group A, and 53 % of patients in the Group B. This difference between the both groups was statistically significant (p = 0.0183). Retinopathy of prematurity recurred in 7 from 92 eyes (7.6 %) in the Group A, and 23 from 82 eyes (28 %) in the group B (p = 0.0276). Significantly better treatment effect was found for adjuvant intravitreal pagaptanib or bevacizumab with laser compared with conventional therapy of
ROP 3+ in zone I and posterior zone II. Peri-operative retinal hemorrhages after laser photocoagulation occurred in 8% of eyes in the Group A, and 11% of eyes in the group B (p = 0.358), in all eyes with spontaneous resorption. No systemic or significant ocular complications of intravitreal anti-VEGF injections, such as endophthalmitis or retinal detachment were found during follow-up period after operation. The authors concluded that a combination of intravitreal pegaptanib or bevacizumab injection and laser photocoagulation showed to be a safe, well-tolerated and effective therapy in patients with stage 3+ ROP in zone I and posterior zone II. Adjuvant intravitreal anti-VEGF injection, as compared with conventional laser or cryotherapy, showed significant benefit in terms of better final anatomic outcome, induction of prompt regression, rapid development of peripheral retinal vascularization and decrease of recurrence rate of neovascularization. The authors concluded that results of this study supported the administration of pegaptanib and bevacizumab as an alternative useful therapy in the management of stage 3+ ROP.

Jalali et al (2013) reported serious adverse events and long-term outcomes of initial experience with intra-ocular bevacizumab in ROP. Consecutive vascularly active ROP cases treated with bevacizumab, in addition to laser and surgery, were analyzed retrospectively from a prospective computerized ROP database. Primary efficacy outcome was regression of new vessels. Secondary outcomes included the anatomic and visual status. Serious systemic and ocular adverse events were documented. A total of 24 ROP eyes in 13 babies, received single intra-ocular bevacizumab for severe stage 3 plus after failed laser (7 eyes), stage 4A plus (8 eyes), and stage 4B/5 plus (9 eyes). Drug was injected intravitreally in 23 eyes and intracamerally in 1 eye. New vessels regressed in all eyes. Vision salvage in 14 of 24 eyes and no serious neurodevelopmental abnormalities were noted up to 60 months (mean of 30.7 months) follow-up. Complications included macular hole and retinal breaks causing rhegmatogenous retinal detachment (1 eye); bilateral, progressive vascular attenuation, perivascular exudation and optic atrophy in 1 baby, and progression of detachment bilaterally to stage 5 in 1 baby with missed follow-up. One baby who
received intra-cameral injection developed hepatic dysfunction. One eye of this baby also showed a large choroidal rupture. The authors concluded that although intra-ocular bevacizumab, along with laser and surgery salvaged vision in many otherwise progressive cases of ROP, vigilance and reporting of serious adverse events is essential for future rationalized use of the drug. These researchers reported 1 systemic and 4 ocular adverse events that require consideration in future use of the drug.

In a prospective, interventional, non-comparative case-study, Martinez-Castellanos et al (2013) evaluated ocular function and systemic development in premature infants treated with IVB injections for ROP over a period of 5 years. The primary outcome measure was VA. The secondary outcomes were structural assessment, other ocular functional measurements, and developmental state. A total of 18 eyes of 13 consecutive patients were divided into 3 groups: Group 1, stage 4 unresponsive to previous conventional treatment (n = 4); Group 2, in which conventional treatment was difficult or impossible because of inadequate visualization of the retina (n = 5); and Group 3, newly diagnosed high-risk pre-threshold or threshold ROP (n = 9). All patients showed initial regression of neovascularization. One patient was diagnosed with recurrence of neovascularization and was treated with IVB. Visual acuity was preserved, and median vision was 20/25 (excluding 2 operated eyes). Twelve eyes developed mainly low myopia over the years, with an overall mean value of 3.2 diopters. Electroretinography was normal in 4 eyes that had no previous detachment. One patient showed delay in growth and neurodevelopment, whereas all the others were within the normal range. The authors concluded that 5 years of follow-up in a small series suggested that IVB for ROP results in apparently preserved ocular function and systemic development.

In a multi-center, retrospective case series, Wu and colleagues (2013) examined the effectiveness and complications associated with the use of bevacizumab, an anti-vascular endothelial growth factor agent, in the treatment of pre-threshold ROP. Data from patients who had received IVB injections for the treatment of ROP were collected from 4 medical centers in Taiwan. The main
outcome measures were the regression of ROP and the complications that were associated with the IVB injections. A total of 162 eyes from 85 patients were included in the study. After receiving IVB injections, 143 eyes (88 %) exhibited ROP regression. Fourteen eyes (9 %) required additional laser treatment for ROP regression after the absence of a positive response to the IVB injections. Three eyes (2 %) progressed to stage 4 ROP and required vitrectomies to re-attach the retinas. Two eyes (1 %) received 1 additional IVB injection to decrease persistent plus disease. All of the eyes (100 %) had attached retinas after the various treatments that they received. The major ocular complications that were associated with IVB injections included vitreous or pre-retinal hemorrhage in 2 eyes (1 %); cataract in 1 eye (1 %); and exotropia in 1 eye (1 %). No notable systemic complications related to the IVB injections were observed. The authors concluded that IVB injection seems to be an effective and well-tolerated method of treating pre-threshold ROP. Laser therapy may still be required as a backup treatment for patients who do not respond to an IVB injection or for those in whom ROP worsens after an IVB injection.

In a retrospective, non-randomized, interventional comparative study, Harder et al (2013) evaluated refractive error in infants who underwent IVB injection for treatment of threshold ROP. The study group included all infants who consecutively received a single IVB (0.375 mg or 0.625 mg) injection for therapy of threshold ROP in fundus zone I or zone II. The control group included infants who had previously undergone retinal argon laser therapy of ROP. The follow-up examination included refractometry under cycloplegic conditions. The study group included 12 children (23 eyes; mean birth weight of 622 ± 153 g; gestational age of 25.2 ± 1.6 weeks) and the control group included 13 children (26 eyes; birth weight of 717 ± 197 g; gestational age of 25.3 ± 1.8 weeks). Both groups did not differ significantly in birth age and weight and follow-up. At the end of follow-up at 11.4 ± 2.3 months after birth, refractive error was less myopic in the study group than in the control group (-1.04 ± 4.24 diopters [median of 0 diopters] versus -4.41 ± 5.50 diopters [median of -5.50 diopters]; p = 0.02). Prevalence of moderate myopia (17 % ± 8 % versus 54 % ± 10 %; p = 0.02; OR: 0.18 [95 %
CI: 0.05, 0.68]) and high myopia (9 % ± 6 % versus 42 % ± 10 %; p = 0.01; OR: 0.13 [95 % CI: 0.03, 0.67]) was significantly lower in the bevacizumab group. Refractive astigmatism was significantly lower in the study group (-1.0 ± 1.04 diopters versus 1.82 ± 1.41 diopters; p = 0.03). In multi-variate analysis, myopic refractive error and astigmatism were significantly associated with laser therapy versus bevacizumab therapy (p = 0.04 and p = 0.02, respectively). The authors concluded that in a 1-year follow-up, a single IVB injection as compared to conventional retinal laser coagulation was helpful for therapy of ROP and led to less myopization and less astigmatism.

Sahin et al (2013) evaluated the treatment outcomes of IVB injections, used as a monotherapy in type 1 ROP. A retrospective chart review was performed for 17 type 1 ROP patients (34 eyes), who had IVB injection between July 2011 and June 2012. Birth weight, gestational age at birth, the stage and the location of ROP, IVB injection time, the time of complete retinal vascularization, and additional treatments if needed, were noted. Bevacizumab (0.625 mg in 0.025 ml) was injected intravitreally. A total of 30 eyes of 17 patients with type 1 ROP were treated with IVB injection enrolled in the study. Of them 7 had APROP, 6 had stage 2 ROP, and 4 had stage 3 ROP. The mean gestational age was 28.44 weeks (range of 26 to 31 weeks); and the mean birth weight was 1,151.88 g (range of 600 to 1,600 g). The mean age for IVB injection was 35.47 weeks. The mean full retinal vascularization time was 136.6 ± 26.6 days. The mean follow-up time was 285.3 ± 70 days. Retinopathy of prematurity was regressed and retinal vascularization was completed in all cases except 1 eye which had threshold disease. The authors concluded that IVB injection, used as a monotherapy, is an effective treatment approach in patients with type 1 ROP. These investigators suggested that timely treatment of stage 2 and early stage 3 ROP cases in which disease progression was observed prevents vitreo-retinal membrane formation in posterior disease.

Kim et al (2014) examined the anatomical outcome of combined IVB injection and zone I sparing laser ablation in patients with type 1 ROP in zone I. The medical records of consecutive 18 eyes of 10 infants, who underwent combined IVB (0.25 mg) injection
and zone I sparing laser ablation for the treatment of type 1 ROP in zone I, were retrospectively reviewed. Laser photocoagulation was performed on the avascular retina anterior to the margin of zone I extending to the ora serrata. Anatomical outcomes including progression to stage 4/5, macular changes, and vitreous organization were reviewed. The mean gestational age at birth and the birth weight of included patients were 24.0 weeks and 628 g, respectively. The timing of IVB injection ranged from post-menstrual age 33 to 35 weeks (mean of 34.3 weeks). Post-menstrual age at last follow-up ranged from 74 to 107 weeks (mean of 83.6 weeks). All 18 eyes demonstrated prompt regression of neovascular pathology and plus disease without recurrence. Previously avascular zone I retina was vascularized in all eyes after the treatment. All eyes showed excellent anatomical outcome with intact macula, but 1 eye showed mild vitreous organization above the vascular/avascular junction. The authors concluded that combined IVB injection and zone I sparing laser ablation for type 1 ROP in zone I seem to be effective treatment options. Possible advantages include lower dose of anti-VEGF, less recurrence than monotherapy, and preservation of central visual field.

Also, an UpToDate review on “Retinopathy of prematurity” (Paysse, 2013) states that “Treatment consists of ablation of the peripheral avascular retina, usually by laser photocoagulation. Bevacizumab is effective in treating some forms of severe ROP, but long-term systemic and ocular outcomes are unknown”.

Rabinizumab has been used to treat retinopathy of prematurity, with similar results (see, e.g., Castellanos, et al., 2013).

Orozco-Gomez et al (2011) evaluated the effectiveness of combined laser-ranibizumab therapy for ROP with threshold-prethreshold and "plus disease" and studied development of the newborn. This was a prospective, experimental, longitudinal and open study including newborns of either less than 32 weeks of gestation or with a birth weight less than 1,500 g, with threshold-prethreshold retinopathy or "plus disease". The effect of treatment was analyzed and development of the newborn was determined. These investigators studied 34 eyes of 17 patients.
Age at birth was 29.9 ± 2.6 weeks. Birth weight was 1,120 ± 253 g. The statistics demonstrated an important relationship between severity of retinopathy and early birth age, along with a high probability of threshold-prethreshold disease at 29.4 weeks of age or 1,204 g birth weight. The Bayley scale reported normal development in 23.5 % of cases, global retardation in 23.5 %, psychomotor retardation but normal mental behavior in 29.4 %, and mental retardation but normal psychomotor development in 23.5 %. These researchers demonstrated regression of retinopathy in all cases. Persistence of vascular tortuosity was present in 17.6 % of cases without vascular dilatation, and vitreous membrane development was demonstrated in 11.7 % of patients. The authors concluded that laser-ranibizumab treatment has allowed a better control of retinopathy for threshold-prethreshold and "plus disease" in this group of patients.

Lin et al (2012) reported the effects of intravitreal ranibizumab as salvage therapy in an extremely low-birth-weight (ELBW) infant with rush type ROP. This case was a girl of 23 weeks gestational age weighing 480 g at birth. At a post-conceptual age of 33 weeks, she presented with zone 1, stage 3 ROP with plus disease. Despite intravitreal bevacizumab and laser photocoagulation, extra-retinal fibro-vascular proliferation persisted. Intravitreal 0.25 mg (0.025 ml) ranibizumab was injected OU. After treatment, extra-retinal fibro-vascular proliferation disappeared. Fundus examination showed flat retinas and normal vasculature in both eyes. She has been followed-up for 2 years. Intravitreal ranibizumab injection seems effective and well-tolerated as salvage therapy in an ELBW infant with rush type ROP. No short-term ocular or systemic side effects were identified. The authors concluded that more cases and longer follow-up are mandatory.

Mota et al (2012) reported on 2 cases of APROP treated with intravitreal ranibizumab and laser photocoagulation. Two premature females, born at 25 and 26 weeks' gestation with a birth weight of 530 and 550 g, respectively, with AP ROP received combined treatment with laser photocoagulation and intravitreal ranibizumab (0.3 mg [30 µl]) to each eye. Structural outcomes were evaluated by indirect ophthalmoscopy and documented by
retinography. An intravitreal injection was made at 34 weeks of post-menstrual age in the first case, followed by laser photocoagulation 1 week later. There was a partial regression of ROP with treatment. Five weeks later, neovascularization regrowth with bleeding in both eyes (intraretinal and subhyaloid) occurred and re-treatment with combined therapy was performed. In the second case, single therapy with laser photocoagulation was made at 34 weeks of post-menstrual age. In spite of the confluent photocoagulation in the avascular area, progression to 4A ROP stage occurred 1 week later. Both eyes were re-treated 1 week later with intravitreal ranibizumab and laser photocoagulation. Treatment resulted in ROP regression in both cases. There were no signs of systemic or ocular adverse side effects. The authors concluded that these 2 cases showed that combination therapy of indirect laser photocoagulation and intravitreal ranibizumab can be effective in the management of AP ROP. They stated that further investigation on anti-VEGF safety in premature infants is necessary.

In an interventional case-series study, Castellanos et al (2013) evaluated ocular outcome in premature infants treated with intravitreal ranibizumab injections for ROP over a period of 3 years. Premature infants with high-risk prethreshold or threshold ROP with plus disease received an off-label monotherapy with intravitreal injections of ranibizumab. The primary outcome was treatment success defined as regression of neovascularization (NV) and absence of recurrence. The secondary outcomes were ocular and systemic adverse events and VA. A total of 6 eyes were included in the study and treated with intravitreal injections of ranibizumab. All showed complete resolution of NV after a single injection. The anti-angiogenic intravitreal injections allowed for continued normal vessel growth into the peripheral retina, without any signs of disease recurrence or progression during the follow-up period. No ocular or systemic adverse effects were observed. The authors concluded that 3 years of follow-up in a small series suggested that intravitreal ranibizumab injections for ROP result in apparently preserved ocular outcome. Moreover, they stated that further large scale studies are needed to address the long-term safety and effectiveness.
Aflibercept, also known as VEGF Trap-Eye, is a highly potent blocker of VEGF and placental growth factor. It is a fully human fusion protein consisting of portions of VEGF receptors 1 and 2, which binds all forms of VEGF-A, along with the related placental growth factor, which the drug blocks.

Bandello et al (2012) stated that DME is the most important cause of vision loss in patients with diabetes mellitus. Diabetic retinopathy has a remarkable impact on public health and on the quality of life of diabetic patients and thus requires special consideration. The first line of treatment remains the management of systemic risk factors but is often insufficient in controlling DME and currently, laser retinal photocoagulation is considered the standard of care. However, laser treatment reduces the risk of moderate visual loss by approximately 50 % without guaranteeing remarkable effects on visual improvement. For these reasons, new strategies in the treatment of DME have been studied, in particular the use of anti-VEGF drugs. VEGF is a pluripotent growth factor that acts as a vaso-permeability factor and an endothelial cell mitogen. For this reason, it represents an interesting candidate as a therapeutic target for the treatment of DME.

Lang (2012) noted that diabetic retinopathy is one of the major complications of diabetes mellitus and a leading cause of visual loss. Diabetic macular edema is an ocular manifestation of the disease causing visual deterioration. The prevalence of visual impairment due to DME is estimated to be 5.4 % in Europe. Vascular endothelial growth factor is over-expressed in diabetic eyes and plays a key role in the development of DME. VEGF levels were proven to be elevated in the vitreous and retina in patients with diabetic retinopathy. VEGF causes a breakdown of the blood-retinal barrier by influencing the tight junctions of retinal endothelial cells and leading to accumulation of fluid in the macula. Therefore, intravitreal VEGF inhibitors are ideal candidates to treat DME by counteracting VEGF overexpression. The author summarized the results of the most recent prospective, controlled studies on DME with promising novel VEGF inhibitors. It focuses on the efficacy and safety aspects of anti-VEGF treatment of DME.
Zechmeister-Koss et al (2012) addressed the question of whether anti-VEGF lead to better clinical outcomes than current treatments in patients with clinically manifest DME, which is the leading cause of vision loss in the working age population in developed countries. The authors performed a systematic literature search in common databases and compiled the evidence according to the GRADE methodology. The authors analyzed clinically relevant improvement of visual acuity, vision-related quality of life and local or systemic adverse events. In a proportion of patients (on average 25 %), VEGF inhibitors result in better VA ($\geq 15$ ETDRS letters or equivalent) than in patients treated with laser photocoagulation or sham injection. The number of injections required for long-term improvement as well as the general long-term efficacy is unknown. The evidence is not sufficient to confirm safety of the products in patients with DME and does not suggest superiority of a single product. The authors concluded that for some patients with DME, VEGF inhibitors seem to be more effective as a short-term treatment option than alternative therapies. The evidence is not of sufficient quality to confirm safety.

In a review on “Anti-vascular endothelial growth factor drug treatment of diabetic macular edema”, Stewart (2012) noted that diabetic mellitus is the leading cause of blindness in working aged patients in developing nations. Due to the buildup of abnormal metabolites from several overactive biochemical pathways, chronic hyperglycemia causes oxidative stress in the retina, which up-regulates VEGF. Together with other growth factors and metabolites, VEGF causes endothelial cell proliferation, vasodilation, recruitment of inflammatory cells, and increased vascular permeability, leading to breakdown of the blood-retinal barrier. This allows trans-cellular exudation into the interstitial space resulting in DME. For over 3 decades the standard treatment for DME has been laser photocoagulation. Though laser reduces the incidence of vision loss by 50 %, few eyes with diffuse edema experience improved vision. This has led physicians to use the VEGF-binding drugs pegaptanib, ranibizumab, and aflibercept, each of which has been approved for the treatment of exudative macular degeneration, and bevacizumab that is commonly used off-label for a variety of
chorio-retinal disorders. Intravitreal administration of each drug frequently causes rapid improvement of DME with sustained improvement in vision through 2 years. Though these drugs significantly out-perform laser photocoagulation over treatment periods of 1 year of less, the advantages appear to lessen when trials approach 2 years. The author concluded that further studies to better determine relative efficacies of anti-VEGF drugs and laser photocoagulation are continuing.

In a Cochrane review, Virgili et al (2012) evaluated the safety, effectiveness, and cost-effectiveness of anti-VEGF therapy for preserving or improving vision in people with DME. These investigators searched CENTRAL (which contains the Cochrane Eyes and Vision Group Trials Register) (The Cochrane Library 2012, Issue 6), MEDLINE (January 1946 to June 2012), EMBASE (January 1980 to June 2012), the metaRegister of Controlled Trials (mRCT) (www.controlled-trials.com (http://www.controlled-trials.com/)) and the WHO International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en (http://www.who.int/ictrp/search/en)). They did not use any date or language restrictions in the electronic searches for trials. They last searched the electronic databases on June 13, 2012. These researchers included randomized controlled trials (RCTs) comparing any anti-angiogenic drugs with an anti-VEGF mechanism of action versus another treatment, sham treatment, or no treatment in patients with DME. They also included economic evaluations to assess cost-effectiveness. Two review authors independently extracted the data. The risk ratio (RR) of visual loss and visual gain of 3 or more lines was estimated at least 6 months after treatment. Each economic analysis was described narratively using a structured format. A total of 11 studies provided data on 3 comparisons of interest in this review. These investigators based their conclusions on the RR of gain or loss of 3 or more lines of vision at about 1 year, which was more consistently reported as follow-up. Compared with sham treatment, there was evidence of moderate quality in 3 studies (497 participants, follow-up 8 to 12 months) that anti-angiogenic therapy (pegaptanib: 2 studies, 246 participants; ranibizumab: 1 study, 151 participants) doubled and, respectively,
halved, the chance of gaining or losing 3 or more lines of vision (RR: 2.19, 95 % confidence interval (CI): 1.36 to 3.53; RR: 0.28, 95 % CI: 0.13 to 0.59). In meta-analyses, the benefit was larger for ranibizumab compared to pegaptanib, but no significant subgroup difference could be demonstrated regarding our primary outcome. Compared with grid laser photocoagulation, there was evidence of moderate quality that anti-angiogenic therapy (bevacizumab: 2 studies, 167 participants; ranibizumab: 2 studies, 300 participants; aflibercept: 1 study, 221 participants, 89 used for data extraction) more than doubled and, respectively, reduced by at least 2/3, the chance of gaining or losing 3 or more lines of vision (RR: 3.20, 95 % CI: 2.07 to 4.95 and RR: 0.13, 95 % CI: 0.05 to 0.34, respectively). In meta-analyses, no significant subgroup difference could be demonstrated between bevacizumab, ranibizumab and aflibercept regarding our primary outcome, but, again, there was little power to detect a difference. Compared with grid laser photocoagulation alone, there was high quality evidence that ranibizumab plus photocoagulation (3 studies, 783 participants) doubled and, respectively, at least halved, the chance of gaining or losing 3 or more lines of vision (RR: 2.11, 95 % CI 1.67 to 2.67; RR: 0.29, 95 % CI: 0.15 to 0.55). Systemic and ocular adverse events were rare in the included studies. Meta-analyses conducted for all anti-angiogenic drugs compared with either sham or photocoagulation (9 studies, 104 events in 2,159 participants) did not show a significant difference regarding arterial thromboembolic events (RR: 0.85 (0.56 to 1.28). Similarly, no difference was suggested regarding overall mortality (53 events, RR: 0.95 (0.52 to 1.74), but clinically significant differences could not be ruled out. The authors concluded that there is moderate quality evidence that anti-angiogenic drugs provide a definite, but small, benefit compared to current therapeutic options for DME, i.e., grid laser photocoagulation, or no treatment when laser is not an option. The quality and quantity of the evidence was larger for ranibizumab, but there was little power to investigate drug differences. Most data were obtained at 1 year, and a long-term confirmation is needed, since DME is a chronic condition. Safety of both drug and the intravitreal injection procedure were good in the trials, but further long-term data are needed to exclude small, but clinically important differences regarding
systemic adverse events.

In a meta-analysis, Hu and colleagues (2014) evaluated the safety and effectiveness of bevacizumab in the treatment of pterygium and explored its effects on recurrence rate and complications. These investigators searched MEDLINE, EMBASE, Web of Science, and Cochrane Central Register from the inception to July 2013 for relevant RCTs that examined bevacizumab therapy for pterygium. Data concerning study design, patient characteristics, treatment, and outcomes were extracted. The methodological quality of the studies included was assessed using the Jadad score. Relative risk (RR) was calculated for recurrence rate and complications. A total of 474 patients with 482 eyes in 9 RCTs were analyzed. The pooled estimate showed that bevacizumab had no statistically significant effect on preventing pterygium recurrence [RR 0.90, 95% CI: 0.77 to 1.07, p = 0.23]. None of the subgroup analyses yielded significant results in favor of bevacizumab (surgery group: RR 0.77, 95% CI: 0.50 to 1.18, p = 0.23; non-surgery group: RR 0.98, 95% CI: 0.86 to 1.11, p = 0.76; primary pterygium group: RR 0.82, 95% CI: 0.53 to 1.26, p = 0.36; recurrent pterygium group: RR 0.95, 95% CI: 0.82 to 1.09, p = 0.44). There were no statistically significant differences in the complications between the 2 groups (RR 1.00, 95% CI: 0.73 to 1.37, p = 1.00). However, the bevacizumab group was associated with a higher risk of developing subconjunctival hemorrhage (RR 3.34, 95% CI: 1.07 to 10.43, p = 0.04). The authors concluded that topical or subconjunctival bevacizumab was relatively safe and well-tolerated, but it had no statistically significant effect on preventing pterygium recurrence. They stated that a large-scale trial with a suitable dosage and a longer follow-up would be needed to rule out the possibility of any treatment benefit.

Moradi et al (2013) stated that diabetic retinopathy (DR) is the most common cause of visual loss among working age individuals. Diabetic macular edema (DME) is an important complication of DR that affects around 1/3 of the patients with DR. Several treatments have been approved for DME ranging from blood pressure and glycemic control to photocoagulation and more recently the use of vascular endothelial growth factor (VEGF) antagonists. These investigators discussed aflibercept
(EYLEA®-Regeneron Pharmaceuticals, Inc., Tarrytown, New York, NY, and Bayer Healthcare Pharmaceuticals, Berlin, Germany) in the context of other VEGF antagonists currently available for the treatment of DME. They performed a systematic search of literature on PubMed, Scopus, and Google Scholar with no limitation on language or year of publication. Pre-clinical studies of aflibercept have shown a higher affinity of this molecule for VEGF-A along with a longer duration of action as compared to other VEGF antagonists. Recent clinical trials have shown visual outcome results for aflibercept to be similarly favorable as compared to other available agents with the added benefit of fewer required injections and less frequent monitoring. The authors concluded that aflibercept presents a potential exciting new addition to the armamentarium of current VEGF antagonists available for the treatment of DME and other retinal vascular diseases. However, they stated that further studies are needed to confirm the role, safety, and efficacy of aflibercept for DME.

In a cost-effectiveness analysis of treatment of DME, Pershing et al (2014) reported that VEGF inhibitor monotherapy was sometimes preferred over laser treatment plus a VEGF inhibitor, depending on the reduction in quality of life with loss of visual acuity. When the VEGF inhibitor bevacizumab was as effective as ranibizumab, it was preferable because of its lower cost. This study did not include aflibercept in the analysis.

On behalf of the Diabetic Macular Edema Treatment Guideline Working Group, Mitchell and Wong (2014) provided evidence-based recommendations for DME management based on updated information from publications on DME treatment modalities. A literature search for "diabetic macular edema" or "diabetic maculopathy" was performed using the PubMed, Cochrane Library, and ClinicalTrials.gov databases to identify studies from January 1, 1985 to July 31, 2013. Meta-analyses, systematic reviews, and randomized controlled trials with at least 1 year of follow-up published in the past 5 years were preferred sources. Although laser photocoagulation has been the standard treatment for DME for nearly 3 decades, there is increasing evidence that superior outcomes can be achieved with anti-VEGF therapy. Data providing the most robust evidence from large
phase II and phase III clinical trials for ranibizumab demonstrated visual improvement and favorable safety profile for up to 3 years. Average best-corrected visual acuity (BCVA) change from baseline ranged from 6.1 to 10.6 ETDRS letters for ranibizumab, compared to 1.4-5.9 ETDRS letters with laser. The proportion of patients gaining greater than or equal to 10 or greater than or equal to 15 letters with ranibizumab was at least 2 times higher than that of patients treated with laser. Patients were also more likely to experience visual loss with laser than with ranibizumab treatment. Ranibizumab was generally well-tolerated in all studies. Studies for bevacizumab, aflibercept, and pegaptanib in DME were limited but also in favor of anti-VEGF therapy over laser. The authors concluded that anti-VEGF therapy is superior to laser photocoagulation for treatment of moderate to severe visual impairment caused by DME.

Also, an UpToDate review on “Diabetic retinopathy: Prevention and treatment” (Fraser and D'Amico, 2014) notes that “VEGF inhibitors for ME -- VEGF inhibitors (pegaptanib, bevacizumab, ranibizumab) have been widely studied as a treatment for diabetic ME, and this therapy represents a major treatment advance. In 2012, the US Food and Drug Administration (FDA) approved a 0.3 mg intravitreal dose of ranibizumab for treatment of diabetic ME. Consequently, for many patients and clinicians, intravitreal pharmacotherapy with ranibizumab will be the initial treatment of choice, but the precise interrelation between this treatment and other modalities is not yet conclusively defined”. This review does not include aflibercept as a therapeutic option of DME.

The National Institute for Health and Care Excellence clinical practice guideline on “Aflibercept in combination with irinotecan and fluorouracil-based therapy for treating metastatic colorectal cancer that has progressed following prior oxaliplatin-based chemotherapy” (NICE, 2014) states that “Aflibercept in combination with irinotecan and fluorouracil-based therapy is not recommended within its marketing authorization for treating metastatic colorectal cancer that is resistant to or has progressed after an oxaliplatin-containing regimen. People currently receiving aflibercept in combination with irinotecan and
fluorouracil-based therapy for treating metastatic colorectal
cancer that is resistant to or has progressed after an oxaliplatin-
containing regimen should be able to continue treatment until
they and their clinician consider it appropriate to stop”.

Aravantinos et al (2014) conducted a systematic literature review
to identify available safety and effectiveness data for
bevacizumab in ovarian cancer as well as for newer anti-
angiogenic agents in development. These researchers analyzed
published data from randomized, controlled phase II/III clinical
trials enrolling women with ovarian cancer to receive treatment
with bevacizumab. They also reviewed available data for
emerging anti-angiogenic agents currently in phase II/III
development, including trebananib, afiblercept, nintedanib,
cediranib, imatinib, pazopanib, sorafenib and sunitinib.
Significant efficacy gains were achieved with the addition of
bevacizumab to standard chemotherapy in 4 randomized, double-
blind, phase III trials, both as front-line treatment (GOG-0218 and
ICON7) and in patients with recurrent disease (OCEANS and
AURELIA). The type and frequency of bevacizumab-related
adverse events was as expected in these studies based on
published data. Promising efficacy data have been published for a
number of emerging anti-angiogenic agents in phase III
development for advanced ovarian cancer. The authors
concluded that further research is needed to identify predictive
or prognostic markers of response to bevacizumab in order to
optimize patient selection and treatment benefit; data from
phase III trials of newer anti-angiogenic agents in ovarian cancer
are awaited.

Agarwal and colleagues (2014) stated that the therapeutic
landscape of metastatic castration-resistant prostate cancer
(mCRPC) has been revolutionized by the arrival of multiple novel
agents in the past 2 years. Immunotherapy in the form of
sipuleucel-T, androgen axis inhibitors, including abiraterone
acetate and enzalutamide, a chemotherapeutic agent,
cabazitaxel, and a radiopharmaceutical, radium-223, have all
yielded incremental extensions of survival and have been recently
approved. A number of other agents appear promising in early
studies, suggesting that the armamentarium against castrate-
resistant prostate cancer is likely to continue to expand. Emerging androgen pathway inhibitors include androgen synthesis inhibitors (TAK700), androgen receptor inhibitors (ARN-509, ODM-201), AR DNA binding domain inhibitors (EPI-001), selective AR down-regulators or SARDs (AZD-3514), and agents that inhibit both androgen synthesis and receptor binding (TOK-001/galeterone). Promising immunotherapeutic agents include poxvirus vaccines and CTLA-4 inhibitor (ipilimumab). Biologic agents targeting the molecular drivers of disease are also being investigated as single agents, including cabozantinib (Met and VEGFR2 inhibitor) and tasquinimod (angiogenesis and immune modulatory agent). Despite the disappointing results seen from studies evaluating docetaxel in combination with other agents, including GVAX, anti-angiogenic agents (bevacizumab, aflibercept, lenalinomide), a SRC kinase inhibitor (dasatinib), endothelin receptor antagonists (atrasentan, zibotentan), and high-dose calcitriol (DN-101), the results from the trial evaluating docetaxel in combination with the clusterin antagonist, custirsen, are eagerly awaited. New therapeutic hurdles consist of discovering new targets, understanding resistance mechanisms, the optimal sequencing and combinations of available agents, as well as biomarkers predictive for benefit. Novel agents targeting bone metastases are being developed following the success of zoledronic acid and denosumab. The authors concluded that all of these modalities do not appear curative, suggesting that clinical trial enrollment and a better understanding of biology remain of paramount importance.

Kim and colleagues (2013) compared the short-term effects of bevacizumab and ranibizumab injections on the regression of corneal neovascularization (NV). A total of 16 eyes of 16 patients with corneal NV were randomly assigned for an injection with 2.5 mg of bevacizumab (group 1, n = 8) or 1 mg of ranibizumab (group 2, n = 8) through subconjunctival and intrastromal routes. The patients were prospectively followed-up for 1 month after the injections. Corneal NV areas, as shown on corneal slit-lamp photographs stored in JPEG format, were calculated using Image J software before the injection, 1 week after the injection, and 1 month after the injection. The corneal NV areas were compared before and after the injections. A total of 7 women and 9 men,
with an average age of 51 years, presented with corneal NV secondary to herpetic keratitis (7 cases), graft rejection (6), chemical burn (1), pemphigoid (1), and recurrent ulcer (1). In group I, the pre-operative corneal NV area (8.75 ± 4.33 %) was significantly decreased to 5.62 ± 3.86 % 1 week after the injection and to 6.35 ± 3.02 % 1 month after the injection (p = 0.012, 0.012, respectively). The corneal NV area in group 2 also exhibited a significant change, from 7.37 ± 4.33 % to 6.72 ± 4.16 % 1 week after the injection (p = 0.012). However, no significant change was observed 1 month after the injection. The mean decrease in corneal NV area 1 month after injection in group 1 (28.4 ± 9.01 %) was significantly higher than in group 2 (4.51 ± 11.64 %, p = 0.001). The authors concluded that bevacizumab injection resulted in a more effective and stable regression of corneal NV compared to the ranibizumab injection. Moreover, they stated that the potency and dose of these 2 drugs for the regression of corneal NV require further investigation.

Ahn et al (2014) reported on the case of a 32-year old female diagnosed with herpetic kerato-conjunctivitis with refractory corneal NV despite 2 previous subconjunctival and intrastromal bevacizumab injections, received 2 subconjunctival and intrastromal ranibizumab injections. Six months post-operatively, there was significant regression of the neovascular area and vessel caliber. The authors reported a case of improvement in corneal NV with subconjunctival and intrastromal ranibizumab injections, which was previously refractory to bevacizumab injection. They stated that these findings may suggest a new prospect in treating corneal NV.

Turkcu et al (2014) compared the effectiveness of the topical and subconjunctival (SC) ranibizumab treatment in experimental corneal NV model in rats. A model of NV was generated by cauterizing right corneas of 30 Sprague-Dawley rats with silver nitrate. The animals were separated into 5 groups randomly: first group (control group) received topical artificial tear drops 2 times daily while second and third groups received topical ranibizumab 4 times daily at concentrations of 5 mg/ml and 10 mg/ml, respectively; fourth and fifth groups were given 0.5 mg/0.05 ml and 1 mg/0.1 ml of SC ranibizumab in the 1st, 3rd and 7th days.
The measurements (percentage of NV area and number of vessels) from digital photographs of the corneas were determined and analyzed using analysis software (ImageJ, v1.38). The animals were sacrificed on the 10th day and their corneas were subjected to hemotoxylin-eosin histopathological staining and antisera against CD34 and von-Willebrand factor to evaluate microvascular structures immunohistochemically. The percentage of the corneal NV area and number of vessels in all treatment groups was found to be significantly lower than the control group. There was no significant difference in relation to the percentage of NV area and number of vessels in the treatment groups. Score of the corneal edema was determined to be significantly less in the groups that undertook treatment. Number of vessels and inflammatory cells were significantly lower in the histological and immunohistochemical sections in the treated groups than in the control group. In all treatment groups, fibroblast intensity was significantly lower than the control group (p = 0.005). The authors concluded that topical or SC administration of ranibizumab seems to be a promising and effective medication in the treatment of corneal NV. Moreover, they stated that further research is recommended to assess the potential side effects and effective dose.

In a meta-analysis, Papathanassiou et al (2013) evaluated the therapeutic effect of bevacizumab on corneal NV. A systematic review and meta-analysis of the literature was performed. A total of 7 eligible clinical human studies and 18 eligible experimental animal studies examining the effectiveness of bevacizumab treatment on corneal NV were included in the meta-analysis. Pertinent publications were identified through a systematic search of PubMed. All references of relevant reviews and eligible articles were also screened, and data were extracted from each eligible study. The random-effects model (of DerSimonian and Laird) was used to combine the results from the selected studies. Heterogeneity was explored using available data. Publication bias was also assessed. A significant reduction of corneal neovascularized area was seen in clinical human studies, with a pooled reduction of 36 % [95 % CI: 18 % to 54 %] overall, of 32 % (95 % CI: 10 % to 54 %) for subconjunctival anti-VEGF injections, and 48 % (95 % CI: 32 % to 65 %) for topical treatment. Pooled
mean change in BCVA showed an improvement in BCVA by 0.04. The summary standardized mean difference in animal studies indicated a statistically significant reduction in the area of corneal NV when treated with bevacizumab compared with the control group by -1.71 (95% CI: -2.12 to -1.30). The subtotal pooled standardized mean differences were -1.83 (95% CI: -2.38 to -1.28) for subconjunctival anti-VEGF injections and -1.50 (95% CI: -1.88 to -1.12) for topical treatment. The authors concluded that these findings suggested that both topical and subconjunctival bevacizumab achieve significant reduction in the area of corneal NV. This meta-analysis provided an evidential basis for the new therapeutic concept of treating corneal NV with anti-angiogenic therapy. Moreover, the clinical significance of an improvement in BCVA by 0.04 is unclear.

In a pilot study, Petsoglou et al (2013) evaluated the off-label use of subconjunctival bevacizumab for corneal NV (CoNV). A total of 30 patients with recent-onset CoNV from various causes were randomly assigned into a double-masked, placebo-controlled trial. Each received three 0.1-ml injections containing either 2.5 mg bevacizumab or 0.9 % saline at monthly intervals. Dexamethasone 0.1 % drops were used 4 times a day for the 1st month, when the dose was modified if clinically indicated. The primary outcome was change in area of corneal involvement by CoNV from baseline to 3 months measured using specialized imaging technology. The mean area of CoNV reduced by -36 % (range of -92 % to +40 %) in the 15 eyes that received bevacizumab compared with an increase of 90 % (range of -58 % to +1,394 %) in eyes that received saline placebo (analysis of covariance (ANCOVA); p = 0.007). One outlier in the placebo arm developed corneal graft rejection with aggressive neovascularization (+1,384 %), but even when this patient was excluded the mean reduction in CoNV in the placebo group (-3 %, range of -58 % to +40 %) was still significantly different from the treatment arm (ANCOVA; p = 0.016). Changes in BCVA, central corneal thickness, IOP and endothelial cell counts were similar between groups. The intervention was well-tolerated with no major safety concerns. The authors concluded that 3 subconjunctival injections of 2.5-mg bevacizumab are more effective than placebo at inducing the regression of recent onset
Moreover, they stated that further studies are needed to confirm this effect and these findings suggested that a sample size of 40 patients per treatment group is needed.

Krizova and colleagues (2014) evaluated anti-angiogenic effect of local use of bevacizumab in patients with corneal NV. Patients were divided into 2 groups. All patients suffered from some form of corneal NV. Patients in group A received 0.2 to 0.5 ml of bevacizumab solution subconjunctivally (concentration 25 mg/ml) in a single dose. Group A included 28 eyes from 27 patients. Patients in group B applied bevacizumab eye drops twice-daily (concentration 2.5 mg/ml) for 2 weeks. Group B included 38 eyes from 35 patients. These investigators evaluated the number of corneal segments affected by NV, CDVA, and the incidence of complications and subjective complaints related to the treatment. The minimum follow-up period was 6 months. By the 6-month follow-up, in group A the percentage reduction of the affected peripheral segments was 21.6 % and of the central segments was 9.6 %; in group B the percentage reduction of the central segments was 22.7 % and of the central segments was 38.04 %. In both groups these researchers noticed a statistically significant reduction in the extent of NV. The authors concluded that the use of bevacizumab seems to be an effective and safe method in the treatment of corneal NV, either in the subconjunctival or topical application form. It is unclear whether the statistically significant reduction in the extent of NV is of clinical significance; the findings of this study need to be validated in well-designed studies.

Furthermore, an UpToDate review on “Overview of angiogenesis inhibitors” (Kuo, 2014) does not mention corneal neovascularization as an indication of bevacizumab or ranibizumab.

Coats' disease (Coates' disease, also known as exudative retinitis or retinal telangiectasis) is a very rare congenital, non-hereditary eye disorder, causing full or partial blindness, characterized by abnormal development of blood vessels behind the retina. Coats' disease can also fall under glaucoma.
In a prospective, interventional case series, Goel et al (2011) evaluated the role of IVB in the treatment of Coats' disease diagnosed in adulthood. A total of 3 patients with Coats' disease diagnosed in adulthood were managed with a single intravitreal injection of bevacizumab (1.25 mg) with peripheral laser photocoagulation 3 weeks later. All 3 patients had exudation at the macula (Stage 2B) along with peripheral retinal telangiectasia and aneurysms. They were followed-up for 9 months. An appreciable reduction in the exudation at the macula and macular edema was observed in all cases following IVB therapy. In all patients, the visual acuity improved, and no signs of recurrence were observed at the final follow-up at 9 months. The authors concluded that IVB may be effective as an adjunctive treatment for adult-onset Coats' disease with foveal exudation along with laser photocoagulation to the peripheral retinal vascular abnormalities.

Sisk et al (2010) determined the effectiveness of off-label IVB for the treatment of pediatric retinal and choroidal vascular diseases. Retrospective, non-comparative, open-label, interventional, consecutive case series of all patients younger than 18 years treated with off-label IVB at a single center from January 1, 2005, to January 1, 2008 were selected for analysis. Primary outcome measures with BCVA by age-appropriate testing and central macular thickness by time-domain OCT. A total of 35 eyes of 33 patients were treated with IVB alone or in combination with other treatments for CNV, Coats' disease, familial exudative vitreoretinopathy, and various other indications. Intravitreal bevacizumab was used in 24 eyes to reduce excess retinal fluid and exudation. Mean Snellen VA improved from 20/170 at baseline to 20/100 at 1 month (p = 0.006), 20/80 at 3 months (p = 0.006), and 20/50 at 6 months (p = 0.023). Central macular thickness improved from 356 μm at baseline to 287 μm at 6 months (p = 0.028). Intravitreal bevacizumab was used in 11 eyes to control peripheral retinal neovascularization and iris rubeosis. Although IVB reduced vascular engorgement, it did not prevent the progression of pre-retinal tractional forces. Mean VA was maintained at each time-point. No systemic or ocular adverse
events were directly attributable to IVB in any patient. The authors concluded that IVB reduced vascular leakage and temporarily regressed pathologic neovascularization of the choroid, retina, and iris in this series of pediatric patients. They stated that further prospective studies are needed.

Ramasubramanian and Shields (2012) evaluated the effect of supplemental IVB for management of Coats' disease. This study was a retrospective analysis of 8 patients with Coats' disease manifesting total or partial exudative retinal detachment where the retinal telangiectasia was treated with standard laser photocoagulation and/or cryotherapy plus additional IVB (1.25 mg/0.05 ml). The mean patient age was 88 (range of 7 to 240) months and 63 % were male. Coats' disease was classified as stage 2 (n = 1, 12 %), 3a (n = 3, 38 %) and 3b (n = 4, 50 %). Features included retinal detachment (n = 8, 100 % with mean detachment extent involving 8 clock hours), telangiectasia (n = 8, 100 % with mean extent of 8 clock hours), peripheral retinal ischemia on fluorescein angiography (n = 7, 88 %) and no evidence of neovascularization. Treatment consisted of cryotherapy (n = 8, 100 %), laser photocoagulation (n = 4, 50 %) and IVB (n = 8) with median number of 1 injection per eye (mean of 1.75, and range of 1 to 4 injections). After a mean follow-up of 8.5 months, resolution of retinopathy (n = 8, 100 %), Coats'-related subretinal fluid (n = 8, 100 %) and retinal exudation (n = 6, 75 %) was noted. However, vitreous fibrosis developed (n = 4, 50 %) at a mean of 5 months following a mean of 1.75 IVB injections with 3 (38 %) evolving into traction retinal detachment. The authors concluded that Coats' disease treated with IVB in addition to standard therapy can develop to vitreo-retinal fibrosis and potentially traction retinal detachment. These tractional features are not often found in Coats' disease treated with standard measures without bevacizumab. They stated that caution is advised in the use of IVB for patients with Coats' disease.

Ray and colleagues (2013) compared the effectiveness of IVB plus ablative therapy with ablative therapy alone for Coats' disease. These researchers performed a retrospective review of all pediatric patients who received treatment for Coats' disease from
a single surgeon (GBH) from January 1, 2001 to March 31, 2010. A total of 10 consecutive patients who received IVB as part of their treatment were matched to 10 patients treated with ablative therapy alone by macular appearance, quadrants of subretinal fluid, and quadrants of telangiectasias. Outcomes evaluated were number of treatment sessions, time to full treatment, and resolution of disease. There was no statistical difference between baseline characteristics when comparing the IVB and control groups. Eyes treated with IVB required more treatments over a longer time period compared to the control group. All patients in the IVB group were successfully treated while 2 of the patients in the control group failed ablative techniques. The authors concluded that IVB may play a role as adjuvant therapy in select cases of Coats' disease, but its use does not reduce the time to full treatment. Resolution of disease was seen in the most severe cases treated with IVB plus thermal ablation whereas their matched controls failed therapy with laser and cryotherapy alone.

Raoof and Quhill (2013) noted that traditional methods of managing exudative retinal detachment secondary to Coats' disease have been associated with varying degrees of success. These researchers described a case of a 34-year old male who presented with a sub-total exudative retinal detachment of the right eye that encroached upon the macula, associated with a vaso-proliferative tumor secondary to Coats' disease. The patient underwent successful treatment with 2 IVB injections combined with targeted laser photocoagulation with a 532 nm Pascal laser. The VA improved 5 days after the second IVB injection from 6/18 to 6/5, with no residual macular edema and complete regression of the vaso-proliferative tumor. The improvement in VA was maintained at 12 months post-treatment. These researchers believed this was the first case report describing the successful use of Pascal laser photocoagulation with IVB in the treatment of Coats' disease. Their aim was to defer laser treatment until 'near total' retinal re-attachment and regression of the vaso-proliferative tumor was achieved. The authors concluded that there were, however, reports of vitreous fibrosis in patients with Coats' disease treated with IVB suggesting that further long-term follow-up studies are needed in patients treated with this
approach.

In a single-center, open-label, phase II clinical trial, Toy and associates (2012) evaluated the safety and preliminary efficacy of intravitreal ranibizumab for non-neovascular idiopathic macular telangiectasia Type 2. This study enrolled 5 participants with bilateral non-neovascular idiopathic macular telangiectasia Type 2. Intravitreal ranibizumab (0.5 mg) was administered every 4 weeks in the study eye for 12 months with the contralateral eye observed. Outcome measures included changes in BCVA, area of late-phase leakage on FA, and retinal thickness on OCT. The study treatment was well-tolerated and associated with few adverse events. Change in BCVA at 12 months was not significantly different between treated study eyes (0.0 ± 7.5 letters) and control fellow eyes (+2.2 ± 1.9 letters). However, decreases in the area of late-phase FA leakage (-33 ± 20 % for study eyes, +1 ± 8 % for fellow eyes) and in OCT central subfield retinal thickness (-11.7 ± 7.0 % for study eyes and -2.9 ± 3.5 % for fellow eyes) were greater in study eyes compared with fellow eyes. The authors concluded that despite significant anatomical responses to treatment, functional improvement in visual acuity was not detected. They stated that intravitreal ranibizumab administered monthly over a time course of 12 months is unlikely to provide a general and significant benefit to patients with non-neovascular idiopathic macular telangiectasia Type 2.

Chaudhary et al (2013) stated that VEGF is an important factor in the pathogenesis of multiple retinal neovascular disorders. This report focused on the quality and depth of new evidence for the use of VEGF inhibitors in selected pediatric ocular diseases, including Coats' disease, Best disease, and childhood uveitis. Because much of the literature comprised case reports and retrospective case series, the level of evidence supporting its use as a primary treatment option, or even as adjuvant therapy, is low. The standard of care is treatment of the underlying disorder to prevent neovascularization (retinal or subretinal), vitreous hemorrhage, or subsequent retinal detachment. However, these complications may not present until late in the disease course. It may then be useful to treat with these agents. The authors concluded that prospective studies are needed to further
elucidate the role of anti-VEGF therapy in these diseases.

Do and colleagues (2014) evaluated the effects of 0.3 mg or 0.5 mg of ranibizumab in eyes with macular telangiectasia type 2 without subretinal neovascularization. A total of 10 eyes were randomized to either 0.3 mg or 0.5 mg ranibizumab group in 1 eye only. Study eye received ranibizumab at baseline and at months 1 and 2. Injections at months 3, 4, and 5 were at investigator's discretion. Participants were followed monthly through 6 months with BCVA, fluorescein angiography, and OCT. For study eyes at baseline, median BCVA letter score was 60 (20/64 Snellen equivalent) and central subfield retinal thickness was 181.5 μm. Median number of injections was 6. Median change in BCVA at month 3 was 4 letters (range of -5 to 9 letters) at both doses in the study eye and 3 letters (range of -10 to 5 letters) in the untreated fellow eye. At month 3, retinal leakage decreased 0.87 disk area and 0.76 disk area for 0.3 mg and 0.5 mg ranibizumab, respectively. Median change in central subfield retinal thickness was 1 μm and -11 μm for 0.3 mg and 0.5 mg ranibizumab, respectively. The authors concluded that ranibizumab (0.3 mg or 0.5 mg) decreases leakage secondary to macular telangiectasia type 2, but accompanying improvements in BCVA appeared similar to improvements in the untreated fellow eye where retinal thickness is relatively unchanged.

Zhang et al (2015) noted that CNV secondary to pathologic myopia has a very high incidence in global, especially in Asian, populations. It is a common cause of irreversible central vision loss, and severely affects the quality of life in the patients with pathologic myopia. The traditional therapeutic modalities for CNV secondary to pathologic myopia include thermal laser photocoagulation, surgical management, transpupillary thermotherapy, and PDT with verteporfin. However, the long-term outcomes of these modalities are disappointing. Recently, intra-vitreal administration of anti-VEGF biological agents, including bevacizumab, ranibizumab, pegaptanib, aflibercept, and conbercept, has demonstrated promising outcomes for this ocular disease. The anti-VEGF regimens are more effective on improving VA, reducing central fundus thickness and central retina thickness than the traditional modalities. The authors
stated that these anti-VEGF agents thus hold the potential to become the first-line medicine for treatment of CNV secondary to pathologic myopia.

Gadducci and Guerrieri (2015) stated that pharmacological treatment plays a major role in the management of advanced, persistent or recurrent uterine leiomyosarcoma (LMS), whereas its usefulness in the adjuvant setting is still debated. These investigators performed a thorough literature search using the PubMed databases. Systematic reviews and controlled trials on medical treatment of uterine LMS were collected and critically analyzed. Other study types were secondarily considered when pertinent. Doxorubicin (DOX), ifosfamide and dacarbazine have been long used in the treatment of this malignancy. Novel active agents are represented by gemcitabine, docetaxel, trabectedin, pazopanib and aromatase inhibitors, whereas the role of eribulin, bevacizumab, aflibercept and mammalian target of rapamycin inhibitors is still investigational.

SooHoo and colleagues (2015) stated that neovascular glaucoma (NVG) is a potentially blinding disease associated with ocular ischemia. Use of an anti-VEGF agent has been reported as a treatment option for NVG. In a prospective, interventional case-series study, these researchers investigated initial results regarding the treatment of NVG with intravitreal aflibercept. Patients with newly diagnosed stage 1 or 2 NVG were eligible to participate in this study. A total of 4 patients with newly diagnosed stage 1 or 2 NVG were treated with intravitreal aflibercept at the time of diagnosis, with planned repeat injection at 4 weeks, 8 weeks and then every 8 weeks thereafter up until 52 weeks after study initiation. Primary outcomes were regression of neovascularization of the iris and angle (NVI, NVA). Secondary outcome measurements included VA and IOP. Intravitreal aflibercept resulted in rapid regression of NVI and NVA; IOP was stable or reduced in all patients at the 52-week study visit. The authors concluded that these results suggested that intravitreal aflibercept may be an effective treatment for stage 1 and 2 NVG, resulting in rapid and sustained regression of NVI and NVA as well as control of IOP. Moreover, they stated that further research is needed to determine the full duration of effect
and the optimal dose and timing of administration.

Anti-Vascular Endothelial Growth Factor for Control of Wound Healing in Glaucoma Surgery:

Cheng and colleagues (2016) stated that trabeculectomy is performed as a treatment for glaucoma to lower IOP. The surgical procedure involves creating a channel through the wall of the eye. However, scarring during wound healing can block this channel that will lead to the operation failing. Anti-vascular endothelial growth factor (VEGF) agents have been proposed to slow down healing response and scar formation. In a Cochrane review, these investigators evaluated the effectiveness of anti-VEGF therapies administered by sub-conjunctival injection for the outcome of trabeculectomy at 12 months follow-up and examined the balance of benefit and harms when compared to any other anti-scarring agents or no additional anti-scarring agents. These investigators searched CENTRAL (which contains the Cochrane Eyes and Vision Trials Register) (2015, Issue 10), Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE Daily, Ovid OLDMEDLINE (January 1946 to November 2015), EMBASE (January 1980 to November 2015), the ISRCTN registry (www.isrctn.com/editAdvancedSearch), ClinicalTrials.gov (www.clinicaltrials.gov) and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en). They did not use any date or language restrictions in the electronic searches for trials. They last searched the electronic databases on November 12, 2015. These researchers included RCTs of anti-VEGF therapies administered by sub-conjunctival injection compared to any other anti-scarring agents or no additional anti-scarring agents (no treatment or placebo) in trabeculectomy surgery. They used standard methodological procedures expected by Cochrane. The primary outcome was successful trabeculectomy at 12 months after surgery that was defined as achieving a target IOP (usually no more than 21 mm Hg) without any additional intervention. Other outcomes included: qualified success (achieving target IOP with or without additional intervention), mean IOP and adverse events. These researchers included 5 RCTs (175 participants, 177
that met the inclusion criteria in this review; 1 trial conducted in Iran (37 participants, 37 eyes) compared anti-VEGF (bevacizumab 0.2 mg) versus control (sham injection) in people with refractory glaucoma. They judged this study to be at low risk of bias. The primary outcome of this review was not reported; mean IOP at 3 months was 15.1 mm Hg (standard deviation 1.0) in both anti-VEGF and control groups. Four trials compared anti-VEGF to mitomycin C (MMC) (138 participants, 140 eyes). These studies were conducted in India, Iran, Turkey and the USA. The anti-VEGF agent used in these 4 trials was bevacizumab 2.5 mg (2 trials), bevacizumab 1.25 mg 3 times and ranibizumab 0.5 mg.

Two trials were at high risk of bias in 2 domains and 1 trial was at high risk of bias in 4 domains. Only 1 of these trials reported the primary outcome of this review (42 participants, 42 eyes). Low quality evidence from this trial showed that people receiving bevacizumab 2.5 mg during primary trabeculectomy were less likely to achieve complete success at 12 months compared to people receiving MMC; but the CI was wide and compatible with increased chance of complete success for anti-VEGF (RR 0.71, 95 % CI: 0.46 to 1.08). Assuming that about 81 % of people receiving MMC achieved complete success, the anticipated success using anti-VEGF agents would be between 37.2 % and 87.4 %. The same trial suggested no evidence for any difference in qualified success between bevacizumab and MMC (RR 1.00, 95 % CI: 0.87 to 1.14, moderate quality evidence). Two trials of primary trabeculectomy provided data on mean IOP at 12 months; 1 trial of bevacizumab 2.5 mg and 1 trial of ranibizumab 0.5 mg. Mean IOP was 1.86 mm Hg higher (95 % CI: 0.15 to 3.57) in the anti-VEGF groups compared to the MMC groups (66 people, low quality evidence). Data were reported on wound leak, hypotony, shallow anterior chamber and endophthalmitis, but these events occurred rarely and currently there are not enough data available to detect any differences, if any, between the 2 treatments. The authors concluded that the evidence is currently of low quality that is insufficient to refute or support anti-VEGF sub-conjunctival injection for control of wound healing in glaucoma surgery. They stated that the effect on IOP control of anti-VEGF agents in glaucoma patients undergoing trabeculectomy is still uncertain, compared to MMC; further RCTs of anti-VEGF sub-conjunctival injection in glaucoma surgery are needed, particularly compared
Appendix

Table: Comparison of VEGF Inhibitors for Ophthalmologic Use:

<table>
<thead>
<tr>
<th>Indications</th>
<th>Lucentis (ranibizumab)</th>
<th>Eylea (afilbercept)</th>
<th>Macugen (pegatanib)</th>
<th>Avastin (bevacizumab)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age-related macular degeneration (wet/exudative)</td>
<td>FDA</td>
<td>FDA</td>
<td>FDA</td>
<td>Compendia</td>
</tr>
<tr>
<td>Macular retinal edema post retinal vein occlusion</td>
<td>FDA</td>
<td>FDA</td>
<td></td>
<td>Compendia</td>
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<tr>
<td>Diabetic macular edema</td>
<td>FDA</td>
<td>FDA</td>
<td>Compendia</td>
<td>Compendia</td>
</tr>
<tr>
<td>Retinopathy of prematurity</td>
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<td></td>
<td></td>
<td>Compendia</td>
</tr>
<tr>
<td>Posterior uveitis, noninfectious</td>
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<td></td>
<td></td>
<td>Compendia</td>
</tr>
<tr>
<td>Histoplasmosis</td>
<td></td>
<td></td>
<td></td>
<td>Compendia</td>
</tr>
<tr>
<td>Pathologic myopia</td>
<td></td>
<td></td>
<td></td>
<td>Compendia</td>
</tr>
<tr>
<td>Diabetic retinopathy</td>
<td>Compendia</td>
<td>Compendia</td>
<td>Compendia</td>
<td>Compendia</td>
</tr>
<tr>
<td>Ocular inflammation</td>
<td></td>
<td></td>
<td></td>
<td>Compendia</td>
</tr>
<tr>
<td>Vitrectomy (visualization during surgery)</td>
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<td></td>
<td></td>
<td>Compendia</td>
</tr>
<tr>
<td>Choroidal retinal neovascularization</td>
<td>Compendia</td>
<td></td>
<td>Compendia</td>
<td>Compendia</td>
</tr>
<tr>
<td>Neovascular glaucoma</td>
<td></td>
<td></td>
<td></td>
<td>Compendia</td>
</tr>
</tbody>
</table>
## CPT Codes / HCPCS Codes / ICD-10 Codes

*Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+":*

### CPT codes covered if selection criteria are met:

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<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>67028</td>
<td>Intravitreal injection of a pharmacologic agent (separate procedure)</td>
</tr>
</tbody>
</table>

**Pegaptanib sodium injection (Macugen):**

### HCPCS codes covered if selection criteria are met:

<table>
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<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>J2503</td>
<td>Injection, pegaptanib sodium, 0.3 mg</td>
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</tbody>
</table>

### ICD-10 codes covered if selection criteria are met:

<table>
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<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>H35.3210 - H35.3293</td>
<td>Exudative age-related macular degeneration</td>
</tr>
</tbody>
</table>

### ICD-10 codes not covered for indications listed in the CPB (not all-inclusive):

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A18.50 - A18.59</td>
<td>Tuberculosis of eye</td>
</tr>
<tr>
<td>A51.43</td>
<td>Secondary syphilitic oculopathy [chorioretinitis]</td>
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<tr>
<td>A71.0 - A71.9</td>
<td>Trachoma</td>
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<tr>
<td>B02.30 - B02.39</td>
<td>Zoster ocular disease</td>
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<td>B25.9</td>
<td>Cytomegalovirus disease (retinitis)</td>
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<td>B30.0</td>
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<td>B30.1</td>
<td>Conjunctivitis due to adenovirus</td>
</tr>
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<td>--------------------------------------------------</td>
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<tr>
<td>B30.3</td>
<td>Acute epidemic hemorrhagic conjunctivitis (enteroviral)</td>
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<td>Other viral conjunctivitis</td>
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<td>B39.9</td>
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<td>E10.311 -</td>
<td>Type I diabetes mellitus with ophthalmic complications</td>
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<td>E10.37x9</td>
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<td>Other specified diabetes mellitus with unspecified diabetic retinopathy</td>
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<td>E13.319</td>
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<td>E88.49</td>
<td>Other mitochondrial metabolism disorders [NARP syndrome]</td>
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<td>Hordeolum externum</td>
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<td>H04.301 -</td>
<td>Acute and chronic inflammation of lacrimal passages</td>
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<td>H05.001 -</td>
<td>Cellulitis of orbit</td>
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<td>H10.011 -</td>
<td>Conjunctivitis</td>
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<td>H15.001 -</td>
<td>Scleritis and episcleritis</td>
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<td>H15.9</td>
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<td>H16.001 -</td>
<td>Keratitis</td>
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<td>H16.9</td>
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<td>H30.001 -</td>
<td>Chorioretinal inflammation</td>
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<tr>
<td>H30.93</td>
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<tr>
<td>H31.001 -</td>
<td>Chorioretinal scars</td>
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<td>H31.099</td>
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<td>Code</td>
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<tr>
<td>H31.101 - H31.9</td>
<td>Choroidal degeneration, dystrophy, hemorrhage and rupture, detachment and other disorders</td>
</tr>
<tr>
<td>H32</td>
<td>Chorioretinal disorders in diseases classified elsewhere</td>
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<tr>
<td>H33.001 - H33.8</td>
<td>Retinal detachments and breaks</td>
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<td>H34.00 - H34.9</td>
<td>Retinal vascular occlusions</td>
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<tr>
<td>H35.30</td>
<td>Degeneration of macula and posterior pole [other than exudative age-related macular degeneration]</td>
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<tr>
<td>H35.3110 - H35.3194</td>
<td>Nonexudative age-related macular degeneration</td>
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<tr>
<td>H35.40 - H35.54</td>
<td>Peripheral retinal degeneration</td>
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<tr>
<td>H35.70 - H35.739</td>
<td>Separation of retinal layers</td>
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<tr>
<td>H35.81 - H35.9</td>
<td>Other retinal disorders</td>
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<tr>
<td>H44.00 - H44.39</td>
<td>Disorders of globe</td>
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<tr>
<td>H44.601 - H44.699</td>
<td>Retained (old) intracocular foreign body, magnetic</td>
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<tr>
<td>Q85.6</td>
<td>Other phakomatoses, NEC [von Hippel-Lindau]</td>
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**Ranibizumab (Lucentis) or Bevacizumab (Avastin):**

**CPT codes not covered for indications listed in the CPB:**

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<tr>
<th>Code</th>
<th>Description</th>
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<tbody>
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<td>66030</td>
<td>Injection, anterior chamber of eye (separate procedure); medication</td>
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<td>68200</td>
<td>Subconjunctival injection</td>
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**HCPCS codes covered if selection criteria are met:**

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<tr>
<td>C9257</td>
<td>Injection, bevacizumab, 0.25mg [Avastin] [intraocular dose]</td>
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<tr>
<td>J2778</td>
<td>Injection, ranibizumab, 0.1 mg</td>
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<tr>
<td>J9035</td>
<td>Injection, bevacizumab, 10 mg [Avastin] [chemotherapy dose]</td>
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**ICD-10 codes covered if selection criteria are met:**
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<td>B39.4</td>
<td>Histoplasmosis capsulati, unspecified [retinitis]</td>
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<tr>
<td>B39.5</td>
<td>Histoplasmosis duboisii [retinitis - see H32]</td>
</tr>
<tr>
<td>B39.9</td>
<td>Histoplasmosis, unspecified [retinitis - see H32]</td>
</tr>
<tr>
<td>Code</td>
<td>Description</td>
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<tr>
<td>E08.311,</td>
<td>Diabetes mellitus with retinopathy with macular</td>
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<tr>
<td>E08.3211</td>
<td>edema</td>
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<td>H21.1X1 - H21.1X9</td>
<td>Other vascular disorders of iris and ciliary body [rubeosis iridis]</td>
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<td>H30.001 - H30.049</td>
<td>Focal chorioretinitis and focal retinochoroiditis</td>
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<td>H30.101 - H30.149</td>
<td>Disseminated chorioretinitis and disseminated retinochoroiditis</td>
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<td>H30.90 - H30.93</td>
<td>Unspecified chorioretinal inflammation</td>
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<td>H31.20 - H31.29</td>
<td>Hereditary choroidal dystrophies</td>
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<tr>
<td>H34.8110 - H34.8192</td>
<td>Central retinal vein occlusion</td>
</tr>
<tr>
<td>H34.8310 - H34.8392</td>
<td>Tributary (branch) retinal vein occlusion</td>
</tr>
<tr>
<td>H35.011 - H35.019</td>
<td>Retinal vascular changes; changes in vascular appearance</td>
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<tr>
<td>H35.041 - H35.049</td>
<td>Retinal microaneurysms NOS</td>
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<td>H35.051 - H35.059</td>
<td>Retinal neovascularization NOS</td>
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<td>Other intraretinal microvascular abnormalities</td>
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<td>H35.101 - H35.179</td>
<td>Retinopathy of prematurity</td>
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<td>H35.3210 - H35.3293</td>
<td>Exudative age-related macular degeneration</td>
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<td>H35.33</td>
<td>Angioid streaks of macula</td>
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<td>H35.50 - H35.54</td>
<td>Hereditary retinal dystrophies</td>
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<td>H40.89</td>
<td>Other specified glaucoma [associated with vascular disorders]</td>
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<td>H44.20</td>
<td>Progressive high (degenerative) myopia</td>
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<td>H44.23</td>
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<tr>
<td>Q82.8</td>
<td>Other specified congenital malformations of skin [pseudoxanthoma elasticum]</td>
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**ICD-10 codes not covered for indications listed in the CPB (not all-inclusive):**

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<th>Description</th>
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<td>Tuberculosis of eye</td>
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<td>Secondary syphilitic oculopathy [chorioretinitis]</td>
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<td>Zoster ocular disease</td>
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<tr>
<td>B25.9</td>
<td>Cytomegalovirus disease (retinitis)</td>
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<td>B30.0</td>
<td>Keratoconjunctivitis due to adenovirus</td>
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<tr>
<td>B30.1</td>
<td>Conjunctivitis due to adenovirus</td>
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<tr>
<td>B30.3</td>
<td>Acute epidemic hemorrhagic conjunctivitis (enteroviral)</td>
</tr>
<tr>
<td>B30.8</td>
<td>Other viral conjunctivitis</td>
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<tr>
<td>B58.01</td>
<td>Toxoplasma chorioretinitis</td>
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<td>Malignant neoplasm of retina and choroid</td>
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<td>D18.09</td>
<td>Hemangioma of other sites [retina]</td>
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<td>Other mitochondrial metabolism disorders [NARP syndrome]</td>
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<td>Hordeolum externum</td>
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<tr>
<td>H04.301 - H04.429</td>
<td>Acute and chronic inflammation of lacrimal passages</td>
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<tr>
<td>H05.001 - H05.019</td>
<td>Cellulitis of orbit</td>
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<tr>
<td>H10.011 - H10.9</td>
<td>Conjunctivitis</td>
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<td>Pterygium</td>
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<td>H15.001 - H15.9</td>
<td>Scleritis and episcleritis</td>
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<tr>
<td>H16.001 - H16.9</td>
<td>Keratitis</td>
</tr>
<tr>
<td>H30.20 - H30.819, H31.00 - H31.12</td>
<td>Pars planitis, Harada's disease, chorioretinal scars and degenerations except angioid streaks</td>
</tr>
<tr>
<td>H31.01 - H31.9</td>
<td>Choroidal degeneration, dystropy, hemorrhage and rupture, detachment and other disorders</td>
</tr>
<tr>
<td>H33.001 - H33.8</td>
<td>Retinal detachments and breaks</td>
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<tr>
<td>H34.00 - H34.239</td>
<td>Retinal vascular occlusion, central retinal artery occlusion, arterial branch occlusion, partial arterial occlusion, and transient arterial occlusion</td>
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<td>H34.821 - H34.829</td>
<td>Venous engorgement</td>
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<tr>
<td>H35.021 - H35.029 [Coates' disease]</td>
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<td>H35.031 - H35.039</td>
<td>Hypertensive retinopathy</td>
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<td>H35.071 - H35.079</td>
<td>Retinal telangiectasia</td>
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<tr>
<td>H35.30</td>
<td>Degeneration of macula and posterior pole [other than exudative age-related macular degeneration]</td>
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<td>ICD-10 Code Range</td>
<td>Description</td>
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<tr>
<td>H35.3110 - H35.3194</td>
<td>Nonexudative age-related macular degeneration</td>
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<tr>
<td>H35.40 - H35.54</td>
<td>Peripheral retinal degeneration</td>
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<td>H35.70 - H35.739</td>
<td>Separation of retinal layers</td>
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<tr>
<td>H35.81 - H35.9</td>
<td>Other retinal disorders</td>
</tr>
<tr>
<td>H40.001 - H40.9</td>
<td>Glaucoma [except when associated with vascular disorders]</td>
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<tr>
<td>H44.00 - H44.39</td>
<td>Disorders of globe</td>
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<tr>
<td>H53.001 - H53.039</td>
<td>Amblyopia ex anopsia</td>
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<tr>
<td>Q85.6</td>
<td>Other phakomatoses, NEC [von Hippel-Lindau]</td>
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**Intravitreal aflibercept (Eylea):**

**HCPCS codes covered if selection criteria are met:**

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**ICD-10 codes covered if selection criteria are met:**
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<th>Description</th>
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<td>ICD-10 Code</td>
<td>Description</td>
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<tr>
<td>H34.8110 - H34.8192</td>
<td>Tributary (branch) retinal vein occlusion</td>
</tr>
<tr>
<td>H34.8310 - H34.8392</td>
<td>Exudative age-related macular degeneration</td>
</tr>
<tr>
<td>H35.3210 - E35.32.93</td>
<td>Retinal edema</td>
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<tr>
<td>H35.81</td>
<td>Retinal edema</td>
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**ICD-10 codes not covered for indications listed in the CPB (not all-inclusive):**

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<td>B02.30 - B02.39</td>
<td>Zoster ocular disease</td>
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<tr>
<td>B30.0</td>
<td>Keratoconjunctivitis due to adenovirus</td>
</tr>
<tr>
<td>B30.1</td>
<td>Conjunctivitis due to adenovirus</td>
</tr>
<tr>
<td>B30.3</td>
<td>Acute epidemic hemorrhagic conjunctivitis (enteroviral)</td>
</tr>
<tr>
<td>B30.8</td>
<td>Other viral conjunctivitis</td>
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<tr>
<td>C19</td>
<td>Malignant neoplasm of rectosigmoid junction</td>
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<tr>
<td>C53.0 - C55</td>
<td>Malignant neoplasm of cervix uteri [uterine leiomyosarcoma]</td>
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<td>C56.1 - C56.9</td>
<td>Malignant neoplasm of ovary</td>
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<tr>
<td>C61</td>
<td>Malignant neoplasm of prostate</td>
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<td>Hordeolum externum</td>
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<td>H01.001 - H01.029</td>
<td>Blepharitis</td>
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<tr>
<td>H04.001 - H04.039</td>
<td>Dacryoadenitis</td>
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</table>
The above policy is based on the following references:

Macugen (pegaptanib):


Lucentis (ranibizumab):


33. Elman MJ, Bressler NM, Qin H, et al; Diabetic Retinopathy


53. Genentech, Inc. Lucentis (ranibizumab injection) intravitreal


Eylea (aflibercept):


26. SooHoo JR, Seibold LK, Pantcheva MB, Kahook MY.

**Bevacizumab (Avastin):**


37. Batman C, Ozdamar Y. The effect of bevacizumab for anterior segment neovascularization after silicone oil


48. Ramasubramanian A, Shields CL. Bevacizumab for Coats' disease with exudative retinal detachment and risk of


58. Paysse EA. Retinopathy of prematurity. UpToDate [serial


65. Kuo CJ. Overview of angiogenesis inhibitors. UpToDate [serial online]. Waltham, MA: UpToDate; reviewed July 2014.


There are no amendments for Medicaid.