Intravitreal Angiogenesis Inhibitors for Choroidal Vascular Conditions

Medical Policy

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Description

Angiogenesis inhibitors (e.g., ranibizumab, bevacizumab, pegaptanib, aflibercept) are being evaluated for the treatment of disorders of choroidal circulation. Ophthalmic disorders affecting the choroidal circulation include age-related macular degeneration (AMD), central serous chorioretinopathy (CSC), pathologic myopia, presumed ocular histoplasmosis syndrome, angioid streaks, idiopathic choroidal neovascularization (CNV), uveitis, choroidal rupture or trauma, and chorioretinal scars.

Background

Vascular endothelial growth factor (VEGF) has been implicated in the pathogenesis of a variety of ocular vascular conditions characterized by choroidal neovascularization (CNV) and macular edema. The macula, with the fovea at its center, has the highest photoreceptor concentration and is where visual detail is discerned. The anti-VEGF agents ranibizumab (Lucentis™) and pegaptanib (Macugen®) are approved to treat CNV associated with age-related macular degeneration (AMD) and are being evaluated for the treatment of other disorders of choroidal circulation. Other therapeutic options may include photodynamic therapy (PDT), antioxidants, and thermal laser photocoagulation. The safety and efficacy of each treatment depends on the form and location of the neovascularization. Angiostatic agents block some stage in the pathway leading to new blood vessel formation (angiogenesis). In contrast to palliative treatments for CNV (e.g., thermal photocoagulation and PDT), they are potentially disease modifying by inhibiting the development of newly formed vessels.

The distinct pharmacologic properties of available VEGF inhibitors suggest that safety and efficacy data from one agent cannot be extrapolated to another. These agents may vary by penetration, potency, half-life, localization to the retina, and initiation of the immune system.
Pegaptanib is an oligonucleotide aptamer that binds to the VEGF-165 isomer of VEGF-A. Ranibizumab is an antibody fragment that does not possess the fragment crystallizable domain and is directed at all isoforms of VEGF-A receptors. Bevacizumab (Avastin®) is a full-length anti-VEGF antibody derived from the same murine monoclonal antibody precursor as ranibizumab and inhibits all isoforms of VEGF-A. VEGF Trap-Eye (Eyelea) is a recombinant fusion protein consisting of the VEGF-binding domains of human VEGF receptors 1 and 2 fused to the Fc domain of human immunoglobulin-G1.

Age-Related Macular Degeneration (AMD)

Neovascular AMD is characterized by CNV, which is the growth of abnormal choroidal blood vessels beneath the macula, which causes severe loss of vision and is responsible for most of the loss of vision caused by AMD. In its earliest stages, AMD is characterized by minimal visual impairment and the presence of large drusen and other pigmentary abnormalities on ophthalmoscopic examination. As AMD progresses, 2 distinctively different forms of degeneration may be observed. The first, called the atrophic or areolar or dry form, evolves slowly. Atrophic AMD is the most common form of degeneration and is often a precursor of the second form, the more devastating exudative neovascular form, also referred to as disciform or wet degeneration. The wet form is distinguished from the atrophic form by serous or hemorrhagic detachment of the retinal pigment epithelium and the development of CNV, sometimes called neovascular membranes. Risk of developing severe irreversible loss of vision is greatly increased by the presence of CNV. The pattern of CNV, as revealed by fluorescein or indocyanine angiography, is further categorized as classic or occult. For example, classic CNV appears as an initial lacy pattern of hyperfluorescence followed by more irregular patterns as the dye leaks into the subretinal space. Occult CNV lacks the characteristic angiographic pattern, either due to the opacity of coexisting subretinal hemorrhage or, especially in CNV associated with AMD, by a tendency for epithelial cells to proliferate and partially or completely surround the new vessels. Interestingly, lesions consisting only of classic CNV carry a worse visual prognosis than those made up of only occult CNV, suggesting that the proliferative response that obscures new vessels may also favorably alter the clinical course of AMD.

Intravitreal triamcinolone acetonide is one of the first pharmacologic compounds evaluated for the treatment of CNV secondary to AMD. The most important effects of this treatment consist of the stabilization of the blood-retinal barrier and the down-regulation of inflammation. Triamcinolone acetonide also has anti-angiogenic and anti-fibrotic properties and remains active for months after intravitreal injection. However, cataracts are a common side effect, and steroid-related pressure elevation occurs in approximately one third of patients, with some requiring filtration surgery.

Photodynamic therapy (PD) is a treatment modality designed to selectively occlude ocular choroidal neovascular tissue. The therapy is a 2-step process, consisting initially of an injection of the photosensitizer verteporfin, followed 15 minutes later by laser treatment to the targeted sites of neovascularization in the retina. The laser treatment selectively damages the vascular endothelium. Patients may be re-treated if leakage from CNV persists. Combination therapy with PDT and VEGF antagonists is being investigated (see policy number 9.03.08).

Prior to the availability of angiostatic agents and PDT, CNV was treated with photocoagulation using either argon, green, or infrared lasers. This conventional photocoagulation was limited to extrafoveal lesions due to the risk of retinal burns. Introduction of a scotoma or enlargement of a pre-existing scotoma, with or without visual acuity loss, is an immediate and permanent effect of
photocoagulation surgery. Because of the loss of vision associated with laser photocoagulation, photocoagulation is no longer recommended as the initial treatment of subfoveal neovascularization.

Central Serous Chorioretinopathy (CSC)

CSC is the fourth most common retinopathy after AMD, diabetic retinopathy, and branch retinal vein occlusion. CSC refers to an idiopathic disease in which there is a serous detachment of the macula due to leakage of fluid from the choriocapillaris through the retinal pigment epithelium. CSC can be divided into acute, recurrent, and chronic conditions. Usually, serous retinal detachments have spontaneous resolution with recovery of visual function; however, a subset of patients may experience permanent deterioration of visual function attributable to chronic CSC or multiple recurrences of CSC. The pathogenesis of CSC is believed to be ischemia and inflammation, which lead to abnormal permeability of the inner choroid and elevation of the retinal pigment epithelium, causing serous epithelial detachments. The separated retinal pigment epithelium can then undergo tiny rips (blowouts) with a break in continuity. The change in permeability of the retinal pigment epithelium results in focal leakage and retinal detachment. Neovascularization can occur as a secondary complication. In about 90% of cases, CSC resolves spontaneously with detachment resolution within 3 months. The traditional management of acute CSC is observation. Recurring or chronic CSC can be treated with focal laser photocoagulation if the leaks are extrafoveal. Although laser may shorten the duration of symptoms, it does not have any impact on the final vision or the recurrence rate of CSC. In addition, laser photocoagulation causes collateral damage creating symptomatic scotomas and a risk of triggering secondary CNV. Photodynamic therapy is not a standard treatment for CSC due to complications that may include CNV, although low-fluence PDT is being evaluated.

Other Causes of Choroidal Neovascularization (CNV)

Other causes of CNV include pathologic myopia, presumed ocular histoplasmosis syndrome, angiod streaks, idiopathic CNV, uveitis, choroidal rupture or trauma, and chorioretinal scars. Treatments that have been evaluated for CNV not related to AMD include submacular surgery, laser photocoagulation, and PDT. Efficacy of these treatment modalities is limited.

Regulatory Status

Pegaptanib (Macugen®, Eyetech and Pfizer), ranibizumab (Lucentis™, Genentech) and aflibercept (Eylea™, Regeneron Pharmaceuticals), are presently the only angiosstatic drugs approved by the U.S. Food and Drug Administration (FDA) for use in AMD. Pegaptanib was the first VEGF antagonist to be approved by the FDA for use in neovascular (wet) AMD in 2004. Ranibizumab was approved for the treatment of patients with neovascular (wet) AMD in 2006. Pegaptanib and ranibizumab bind extracellular VEGF to inhibit the angiogenesis pathway and are administered by intravitreous injections every 4–6 weeks. Pegaptanib binds to the VEGF-165 isomer of VEGF-A while ranibizumab is an antibody fragment directed at all isoforms of VEGF-A.

Aflibercept (previously called VEGF Trap-Eye) is a recombinant fusion protein consisting of the VEGF binding domains of human VEGF receptors R1 and R2 fused to the Fc domain of human immunoglobulin-G1. Aflibercept was approved by the FDA in 2011 for the treatment of neovascular (wet) age-related macular degeneration. The recommended dose for EYLEA™ is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (monthly) for the first 3 months, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months).
Ranibizumab and aflibercept are also approved by the FDA for retinal vascular conditions such as diabetic macular edema and macular edema following retinal vein occlusion (see policy No. 9.03.27).

Bevacizumab (Avastin®) is derived from the same murine monoclonal antibody precursor as ranibizumab, which binds to all isoforms of VEGF-A. Bevacizumab has been developed and approved for use in oncology but has not been licensed for use in the eye.

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**Policy**

Anti-vascular endothelial growth factor therapies (anti-VEGF), i.e., pegaptanib (Macugen®*), ranibizumab (Lucentis™*), bevacizumab (Avastin™), and aflibercept (Eylea™*), may be considered **medically necessary** as a treatment of neovascular (wet) age-related macular degeneration.

Anti-vascular endothelial growth factor therapies (anti-VEGF) may be considered **medically necessary** for the treatment of choroidal neovascularization due to angiod streaks, central serous chorioretinopathy, choroidal rupture or trauma, idiopathic choroidal neovascularization, multifocal choroiditis, pathologic myopia, presumed ocular histoplasmosis syndrome, and uveitis.

Anti-vascular endothelial growth factor therapies (anti-VEGF) are considered **investigational** for the treatment of chorioretinal scars.

*FDA-approved indication

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**Rationale**

This policy was created in 2011 and updated periodically using the MEDLINE database. The most recent literature update was performed through February 13, 2013.

**Age-related Macular Degeneration**

A 2008 Cochrane review evaluated anti-vascular endothelial growth factor (anti-VEGF) therapies for neovascular age-related macular degeneration (AMD). (1) Five randomized controlled trials (RCTs) on pegaptanib and ranibizumab were included in the review; all were conducted by pharmaceutical companies. The trials compared pegaptanib or ranibizumab versus sham, ranibizumab versus photodynamic therapy (PDT), and ranibizumab plus PDT versus PDT alone. Fewer patients treated with pegaptanib lost 15 or more letters of visual acuity at 1-year follow-up compared to sham (pooled relative risk [RR]: 0.71). In a trial of ranibizumab versus sham, RR for loss of 15 or more letters visual acuity at 1 year was 0.14 in favor of ranibizumab. The pooled RR for gain of 15 or more letters of visual acuity at 1 year was 5.81 for ranibizumab versus sham, 6.79 for ranibizumab versus verteporfin PDT, and 4.44 for ranibizumab plus verteporfin PDT versus verteporfin PDT. The review concluded that pegaptanib and ranibizumab reduce the risk of visual acuity loss in patients with neovascular AMD and that ranibizumab causes gains in visual acuity in many eyes. Details of relevant trials are described below.
Pegaptanib

Pegaptanib was compared with sham in 2 concurrent multicenter double-masked studies by the VEGF Inhibition Study in Ocular Neovascularization (VISION) Clinical Trial Group in 2004. (2) Patients with all angiographic subtypes of lesions were enrolled if they had subfoveal sites of choroidal neovascularization (CNV) secondary to AMD. A total of 1,208 patients were randomized to a dose of 0.3, 1.0, or 3.0 mg pegaptanib or sham injections, administered every 6 weeks over a period of 48 weeks. The use of PDT was permitted only in the treatment of patients with predominantly classic lesions by an ophthalmologist who was masked to the treatment assignment. A total of 1,186 patients received at least 1 study treatment, had visual acuity assessments at baseline, and were included in efficacy analyses. Approximately 90% of the patients in each treatment group completed the study, and an average of 8.5 injections was administered per patient. In the combined analysis, there was a significant improvement in the primary endpoint of the proportion of patients who had lost <15 letters of visual acuity for all 3 doses of pegaptanib. In the sham group, 55% of patients lost <15 letters at 54 weeks. In the 0.3-, 1.0-, and 3.0-mg groups, the percentage of patients who lost <15 letters was 70%, 71%, and 65%, respectively. The risk of severe loss of visual acuity (≥30 letters) was reduced from 22% in the sham injection group to 8% to 14% in the pegaptanib groups. More patients receiving pegaptanib maintained their visual acuity or gained acuity (31-37% vs. 23%, respectively). Use of PDT after baseline was similar in the 4 groups, ranging from 17% to 21% of patients. Adverse events associated with a severe loss of visual acuity occurred in 0.1% of patients. Discontinuation of therapy due to adverse events was 1% in the pegaptanib and sham groups.

No RCTs with pegaptanib were identified after 2004.

Ranibizumab

ANCHOR: Ranibizumab was compared with PDT in a multicenter, manufacturer-funded double-blind study (423 patients) designated Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration (ANCHOR) in 2006. (3) Patients with subfoveal CNV and a predominantly classic lesion (n=423) were randomized in a 1:1:1 ratio to receive 0.3 mg (n=137) or 0.5 mg (n=139) of intravitreal ranibizumab plus sham verteporfin or sham injections plus active verteporfin (n=142) monthly. Patients were to receive monthly injections for 2 years in the study eye. Only 1 eye per patient was chosen as the study eye, and only the study eye received ranibizumab with sham PDT or sham injection with active PDT. The primary, intent-to-treat efficacy analysis was at 12 months, with continued measurements to month 24. Key measures included the following: the percentage losing <15 letters from baseline visual acuity score (month 12 primary efficacy outcome measure); percentage gaining >15 letters from baseline; and mean change over time in visual acuity score and fluorescein angiography-assessed lesion characteristics. Adverse events were monitored. Following 12 monthly treatments, patient groups treated with ranibizumab (0.3 or 0.5 mg) and sham verteporfin had 94% to 96% of subjects lose fewer than 15 letters. The patient group treated with monthly sham injection and active verteporfin therapy (average 2.8 times over the year) had 64% of subjects lose fewer than 15 letters. Visual acuity improved by more than 15 letters in 36% and 40% of the ranibizumab groups (average dose-dependent gain of 8.5 and 11.3 letters), in comparison with 5.6% of subjects in the verteporfin group (average loss of 9.5 letters). Intraocular inflammation occurred in 10.2% and 15% of ranibizumab-treated patients, with presumed endophthalmitis in 1.4% and serious uveitis in 0.7% of patients treated with the highest dose.
Brown et al. reported the 2-year results of the trial by the ANCHOR study group in 2009. (4) Of 423 patients, at least 77% in each group completed the 2-year study. Consistent with results at month 12, at month 24, the visual acuity benefit from ranibizumab was statistically significant and felt to be clinically meaningful; 89.9% to 90.0% of ranibizumab-treated patients had lost <15 letters from baseline versus 65.7% of PDT patients; and 34% to 41.0% had gained 15 or more letters versus 6.3% of the PDT group. Changes in lesion anatomic characteristics on fluorescein angiography also favored ranibizumab. There was a trend for an increased incidence of cataract in the ranibizumab groups compared with the PDT group, which was statistically significant at the 0.5-mg dose. There were no statistically significant differences among the 3 treatment groups in the rates of serious nonocular adverse events. In this 2-year study, ranibizumab provided greater clinical benefit than verteporfin PDT in patients with age-related macular degeneration with new-onset, predominantly classic CNV.

Bressler et al. reported a sub-analysis of the patient-reported outcomes from the ANCHOR trial. (5) The National Eye Institute Visual Functioning Questionnaire-25 (NEI VFQ-25) was administered at baseline and at 1, 2, 3, 6, 9, 12, 18, and 24 months. The primary outcome measure was mean change from baseline in NEI VFQ-25 scores at 12 months. At 12 months, patients treated with ranibizumab had mean improvements in NEI VFQ-25 composite scores of 5.9 (range: 3.6 to 8.3) for 0.3-mg dose group and 8.1 (range: 5.3 to 10.8) points for the 0.5-mg dose group; patients treated with PDT had a mean improvement of 2.2 points (range: -0.3 to 4.7). At each dose through 24 months, patients treated with ranibizumab were more likely to improve in most subscales, including the pre-specified subscales (near activities, distance activities, and vision-specific dependency).

**HORIZON:** In 2012, Singer et al. reported a 2-year open-label extension trial of ranibizumab for CNV secondary to AMD in patients who had completed 1 of 3 randomized 2-year clinical trials (ANCHOR, FOCUS, and MARINA, see policy No. 9.03.08). (6) There were 600 patients treated with ranibizumab in the initial studies, 190 patients who were initially in the control arm and crossed over to ranibizumab for the extension study, and 63 patients who remained ranibizumab-naïve. Ranibizumab was administered at the investigator’s discretion (no pre-specified retreatment criteria). Follow-up was scheduled quarterly for 24–40 months, although investigators could see patients more frequently. On average, patients were seen about every 2 months, and the average number of injections was 2.1 for year 1, 4.4 for year 2, and 4.7 for year 3. The primary outcome, ocular safety, did not identify any serious adverse events with intravitreal ranibizumab. While retinal hemorrhage was increased, cataracts were decreased. There was also a decline in visual acuity in the open-label phase with the less frequent treatment. At 24 months from the baseline of the open label phase, best-corrected visual acuity (BCVA) decreased from +9.0 to +2.0 in the ranibizumab treated group and from -9.6 to -11.8 in the 2 control groups.

In 2012, Bressler et al. conducted an exploratory analysis of the rate of cerebrovascular accidents (CVA) with ranibizumab. (7) With data pooled from 5 trials (FOCUS, MARINA, ANCHOR, PIER, and SAILOR), CVA rates were less than 3%. The odds ratios for CVA risk were 1.2 for 0.3 mg ranibizumab versus control, 2.2 for 0.5 mg versus control, and 1.5 for 0.5 mg vs. 0.3 mg ranibizumab. These results are considered preliminary, but do suggest the need for continued monitoring for CVA with anti-VEGF agents.

**Bevacizumab**
ABC Trial: In 2010, Tufail and colleagues reported a randomized multicenter study (ABC Trial) of bevacizumab for neovascular AMD in 131 patients (eyes), 65 of whom received bevacizumab. (8) Outcomes at 54 weeks were compared to patients who had received standard care from the United Kingdom’s National Health Service (NHS), which was considered on a case-by-case basis. Patients with classic or predominantly classic choroidal neovascularization were randomized to photodynamic therapy (PDT) or bevacizumab with sham PDT. Patients with minimally classic or occult CNV were randomized to bevacizumab or (depending on NHS funding) pegaptanib or placebo. The standard care group included 38 patients treated with pegaptanib, 16 treated with verteporfin, and 12 treated with a sham intravitreal injection. Bevacizumab (1.25 mg in 0.05 mL) was prepared in single-use sterile plastic syringes in sealed plastic pouches (shelf life of 6 weeks) and administered once every 6 weeks for the first 18 weeks; further injections were provided based on standardized criteria. Patients received a mean of 7.1 (range 3-9) injections of bevacizumab or 7.3 (range 3-9) sham injections. Active verteporfin PDT was administered at a mean of 3.2 times (range 2-5). Independent assessment of outcomes found that 21 patients (32%) in the bevacizumab group gained 15 or more letters compared with 2 (3%) in the standard care group. More patients receiving bevacizumab lost fewer than 15 letters (91% vs. 67%, respectively). The mean change in visual acuity at 54 weeks increased by +7.0 letters in the bevacizumab group and decreased by –9.4 letters in the standard care group.

Aflibercept

Data submitted to the U.S. Food and Drug Administration (FDA) and published in 2012 included 52-week results from 2 multi-center double-masked, randomized trials (VIEW1 and VIEW2) that compared 3 doses of aflibercept (VEGF Trap-Eye) to ranibizumab (0.5 mg). (9, 10) A total of 2,457 patients with all 3 subtypes of AMD (occult, minimally classic, and predominantly classic) were enrolled in the 2 studies. VIEW1 was conducted primarily in North America and VIEW2 was conducted primarily in Europe, Asia, Australia, and Latin America. Both trials utilized a non-inferiority design with a 10% margin and tested doses of aflibercept at 0.5 mg every 4 weeks (0.5Q4), 2.0 mg every 4 weeks (2Q4), and 2.0 mg every 8 weeks following 3 initial monthly doses (2Q8). Ranibizumab (0.5 mg) was administered every 4 weeks (RQ4).

The primary efficacy endpoint was the proportion of subjects who maintained vision at 52 weeks, defined as losing less than 15 letters compared to baseline. Secondary outcomes included the change from baseline best corrected visual acuity (BCVA) and the proportion of subjects who gained at least 15 letters. The full analysis set (n=2,412) included all randomized patients who received any study drug and had a baseline and at least 1 post-baseline BCVA assessment. The per protocol set (n=2,170) was used for the primary efficacy analysis and included all subjects who received at least 9 injections of study drug or sham, except for those who were excluded because of major protocol violations (e.g., missing 2 consecutive injections). For the proportions of responders, the last observation carried forward was used to impute missing data.

All doses of aflibercept met non-inferiority compared to 0.5 mg ranibizumab, with about 94% of patients maintaining vision (losing less than 15 letters) at week 52. For ranibizumab, the mean change in BCVA from baseline was a gain of 8.1 letters in VIEW1 and 9.4 letters in VIEW2. Letters gained was similar between ranibizumab and all of the doses of aflibercept (around 7-11 letters). The proportion of patients who gained at least 15 letters was also similar in the aflibercept groups compared to ranibizumab. For example, in VIEW2, 34% of patients treated with ranibizumab gained at least 15 letters, compared with 34.8% of 0.5Q4 patients, 29.4% of
2Q4 patients, and 31.4% of 2Q8 patients. None of the doses were found to be superior to ranibizumab.

In addition to VIEW1 and VIEW2, safety and tolerability of aflibercept was evaluated in a 3-year extension study with 157 patients. Intravitreal injections of aflibercept were given as needed, not more frequently than every 4 weeks. The most common adverse reactions (≥5%) reported in patients receiving aflibercept injection were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and increased intraocular pressure. The data provided from these 3 trials were found to support the safety of aflibercept injection in the treatment of patients with neovascular (wet) AMD. The dose of 2 mg every 8 weeks was recommended for the labeling of aflibercept, since it has fewer injections than the other 2 doses studied and has the theoretical benefit of less injection-related risks (i.e. endophthalmitis).

Conclusions. There is RCT evidence supporting the efficacy of all 4 agents (bevacizumab, ranibizumab, pegaptanib, aflibercept) for preserving visual acuity in patients with age-related macular degeneration. These trials report that VEGF inhibitors are superior to placebo and superior to PDT. A preliminary report of increased stroke rates in patients treated with ranibizumab was published in 2012.

Comparative efficacy of different agents

CATT: One-year results of the National Eye Institute-sponsored multicenter (44 sites) Comparison of AMD Treatment Trials (CATT) were published in 2011. (11) CATT was a randomized single-blind head-to-head comparison of the safety and effectiveness of ranibizumab and bevacizumab in treating wet AMD. A total of 1,208 patients with previously untreated active CNV due to AMD (neovascularization, fluid, or hemorrhage under the fovea) and visual acuity between 20/25 and 20/320 on electronic visual acuity testing were enrolled in the study.

Patients were randomly assigned to receive intravitreal injections of ranibizumab (0.5 mg) or bevacizumab (1.25 mg) on either a monthly schedule or as needed with monthly evaluation. Every 28 days, patients in the groups that received study drugs as needed underwent time-domain optical coherence tomography (OCT) and were evaluated for treatment. Signs of active neovascularization were defined as fluid on OCT, new or persistent hemorrhage, decreased visual acuity as compared with the previous examination, or dye leakage or increased lesion size on fluorescein angiography. The mean number of injections on the as needed schedule was 6.9 for ranibizumab and 7.7 for bevacizumab over the first year of the study (significantly different). Treatment decisions by study ophthalmologists were found to be consistent with the retreatment protocol for 71.5% of examinations in the group assigned to ranibizumab as needed, and 74.3% in the group assigned to bevacizumab as needed. Among the 1,161 patients who were alive 1 year after enrollment, visual-acuity scores were available for 1,105 patients (95.2%).

The primary outcome measure was a change in visual acuity at 1 year, with a noninferiority limit of 5 letters on the eye chart. Secondary outcome measures were the proportion of patients with a decrease or gain of visual acuity, anatomical changes in the retina, number of treatments, adverse events, and cost. When administered according to the same schedule, bevacizumab and ranibizumab had equivalent (not inferior) effects on visual acuity. With bevacizumab and ranibizumab administered monthly, patients gained an average of 8.0 and 8.5 letters, respectively. When administered as needed, the number of letters gained with bevacizumab
was similar to that of ranibizumab, with 5.9 and 6.8 letters gained, respectively. Ranibizumab as needed was also found to be equivalent (not inferior) to monthly ranibizumab. The comparisons of bevacizumab as needed versus monthly bevacizumab (5.9 vs. 8.0 letters, respectively) and bevacizumab as needed versus monthly ranibizumab (5.9 vs. 8.5 letters gained, respectively) were inconclusive. At 1-year, there were no significant differences in the proportion of patients who lost or gained ≥15 letters.

There were significant differences in the anatomy of the retina with the different treatments. At 1 year, monthly ranibizumab decreased central retinal thickness to a greater extent (196 microns) than the other 3 groups (152 to 168 microns). The proportion of patients who had complete resolution of fluid ranged from 19.2% among patients who received bevacizumab as needed to 43.7% among those who received ranibizumab monthly. The absolute between-drug difference in the amount of residual fluid was small; at 1 year, total thickness at the fovea was 266 microns for the ranibizumab monthly group and close to 300 microns for the other 3 groups. In comparison, the retinal thickness of healthy eyes measured by OCT at the fovea averages 212 microns. (12) Dye leakage was absent on angiography in 58.8% of patients in the ranibizumab-monthly group, 57.7% in the bevacizumab-monthly group, 46.7% in the ranibizumab-as-needed group, and 41% in the bevacizumab-as-needed group.

Rates of death, myocardial infarction (MI), and stroke were similar for patients receiving either bevacizumab or ranibizumab. However, the proportion of patients with serious systemic adverse events (primarily hospitalizations) was higher with bevacizumab than with ranibizumab (24.1% vs. 19%, respectively; risk ratio [RR]: 1.29; 95% confidence interval [CI]: 1.01 to 1.66). It was noted that these events were broadly distributed in disease categories not considered to be areas of concern for use of bevacizumab and were not dose-dependent.

An accompanying editorial notes that although the OCT retinal thickness measurements favor ranibizumab, this difference is not reflected in any of the visual-acuity or angiographic outcomes; whether this difference is associated with changes in vision should become clear during the second year of follow-up. (13) Results from the second year of the study (described below), will provide more information regarding the relative risk of adverse events, as well as the possible association between anatomical changes in the retina and visual acuity.

In 2012, the CATT Research Group reported 2-year follow-up on 1,107 out of the 1,185 patients enrolled in the trial. (14) Visual acuity gains at 2 years were similar to those obtained at 1 year, ranging from 5.0 to 8.8 letters. When following the same treatment regimen, the mean gain in visual acuity was similar for ranibizumab and bevacizumab. When compared to as-needed treatment, monthly treatment resulted in a modest gain (2.4 letters) in visual acuity. The proportion of eyes without fluid was similar to observations at 1 year, which ranged from 13.9% in the bevacizumab-as-needed group to 45.5% in the ranibizumab monthly group. Rates of death and arteriothrombotic events were similar for the 2 drugs. The proportion of patients with 1 or more systemic serious adverse events was higher with bevacizumab (39.9% vs. 31.7%), although most of the excess events were not previously associated with systemic VEGF inhibitors.

**IVAN:** The “alternative treatments to Inhibit VEGF in Age-related choroidal Neovascularization” (IVAN) study was a multicenter double-masked non-inferiority trial from the United Kingdom (U.K.) that randomized 610 patients to 1 of 4 groups: ranibizumab or bevacizumab given monthly, or ranibizumab or bevacizumab given as needed (PRN). (15) In a prespecified interim analysis at 12 months, the comparison between the 2 drugs was found to be inconclusive.
(bevacizumab was neither inferior nor equivalent with a 3.5 letter limit, bevacizumab - ranibizumab -1.99 letters (95% confidence interval [CI]: -4.04 to 0.06). Foveal thickness was similar for the 2 drugs. There was no significant difference between PRN dosing and monthly dosing for visual acuity. Serum VEGF concentrations were significantly lower for bevacizumab than ranibizumab. Fewer patients receiving bevacizumab were reported to have had an arteriothrombotic event or heart failure; there was no significant difference between the groups for serious systemic events.

**MANTA:** In 2012, the multicenter MANTA research group published a multicenter double-masked randomized non-inferiority trial comparing ranibizumab and bevacizumab in 317 patients with neovascular AMD. (16) Both groups received 3 monthly injections followed by treatment as-needed. The greatest gains were in the first month of treatment with maintenance of the effect through 1 year. At 12 months, (78% follow-up) there was a similar increase in visual acuity for the 2 groups (4.9 letters in the bevacizumab group and 4.1 letters in the ranibizumab group). There were no significant differences between the groups for the decrease of retinal thickness, change of lesion size, or number of adverse events.

In 2010, Curtis and colleagues reported a retrospective cohort study of 146,942 Medicare beneficiaries 65 years or older with a claim for AMD. (17) On the basis of claims, beneficiaries were assigned to 1 of 4 treatment groups (PDT, pegaptanib, bevacizumab, or ranibizumab). Patients were censored if they received a therapy different from the initial therapy. Among patients in the PDT group, 32.6% switched to a different therapy within the year compared with 55.3% patients in the pegaptanib group, 28.1% in the bevacizumab group, and 24.0% in the ranibizumab group. After adjustment for baseline characteristics and comorbid conditions, there were no significant differences in the hazard of mortality or myocardial infarction (MI) between bevacizumab use and the other therapies. There was no statistically significant relationship between treatment group and bleeding events or stroke. A sub-analysis intended to mitigate potential selection bias found no significant differences in study outcomes between the ranibizumab and bevacizumab groups. In contrast, a recent preliminary report of 77,886 Medicare beneficiaries found an 11% higher risk in overall mortality and a 57% higher risk of hemorrhagic cerebrovascular accident following treatment with bevacizumab in comparison with ranibizumab. (18) The authors note that the study is limited by incomplete information on some important confounding factors, e.g., smoking, lipid and blood pressure levels, which would further clarify the relative safety of these treatments in wet AMD.

The potential for an increased risk of adverse events with bevacizumab remains controversial. A randomized study from 2013 found that a single intravitreal injection of bevacizumab led to significantly reduced levels of VEGF in plasma (from 89.7 pg/mL to 22.8 pg/mL) for up to one month after intravitreal injection. (19) However, this large reduction appears to be driven largely by one outlier with plasma VEGF levels of close to 400 pg/mL. VEGF levels in plasma were not affected by ranibizumab or pegaptanib. In 2012, Schmucker et al. reported a meta-analysis of the safety of bevacizumab compared with ranibizumab. (20) Direct comparison (3 trials, 1,333 patients) found a significantly higher rate of ocular and systemic adverse effects with bevacizumab compared to ranibizumab. Arterial thromboembolic events were similar between the 2 conditions. The investigators were unable to evaluate the safety profile of bevacizumab in indirect comparisons (5 trials, 4,054 patients) due to the poor quality of adverse event monitoring and reporting.

**Conclusions.** Evidence on comparative effectiveness indicates there are no substantial differences in efficacy between bevacizumab and ranibizumab for the treatment of AMD. The
evidence on adverse events is not conclusive on whether bevacizumab is associated with a higher rate of adverse effects compared to ranibizumab.

Other Causes of Choroidal Neovascularization (CNV)

The literature on angiogenesis inhibitors for the treatment of other causes of choroidal neovascularization consists of cases series and small controlled trials. Following is a summary of the key literature to date, focusing on controlled trials.

A 2011 U.S. multicenter Phase I trial examined the efficacy of ranibizumab for CNV secondary to causes other than AMD. (21) Thirty patients with pathologic myopia (n=14), ocular histoplasmosis (n=9), angiod streaks (n=3), idiopathic telangiectasia (n=1), idiopathic chorioretinal scar (n=1), choroidal ruptures (n=1), or central serous retinopathy (n=1) were randomly assigned to monthly intravitreal injections of 0.5 mg ranibizumab or 3 monthly injections followed by doing as needed (PRN) at monthly follow-up visits. In the PRN group, retreatment was performed at follow-up visits if the study eye met pre-specified criteria. A mean of 5.93 injections (range, 3-11) were administered to evaluable patients (n=14) in the PRN treatment arm compared to 11.17 injections among evaluable patients (n=12) in the monthly treatment arm. The mean best corrected visual acuity (BCVA) at baseline was 53.5 and 48 letters in the monthly and PRN treatment arms, respectively. At 12 months (87% follow-up), mean visual acuity had improved by 26.9 and 19.2 letters in the 2 groups, respectively. Eight of 12 (66.7%) patients who received monthly injections gained ≥15 letters, compared to 8 of 14 (57.1%) on the PRN schedule. No patient in the study lost ≥15 letters. The mean baseline central retinal thickness was 345 microns and 383 microns in patients in the monthly and PRN treatment arms, respectively. Central retinal thickness decreased by 109.3 microns in the monthly group and 166.6 microns in the PRN treatment group. No statistically significant differences were observed between treatment groups. The most common ocular adverse events included 5 cases of subconjunctival hemorrhage, 4 cases of ocular pain or soreness, 2 cases of vitreous floaters, 1 case of retinal hemorrhage, and 2 cases of transiently elevated intraocular pressure. The authors concluded that intravitreal ranibizumab has a promising safety and efficacy profile in the treatment of CNV unrelated to AMD and that larger, randomized studies are warranted to confirm these findings and to determine the optimal dosing regimen for ranibizumab.

Chen et al. assessed visual outcomes and retreatment rates in a retrospective comparison of bevacizumab alone or bevacizumab combined with PDT. (22) Included were 23 patients with subfoveal CNV due to causes other than AMD (myopia, presumed ocular histoplasmosis, angiod streaks, choroiditis, idiopathic, and central serous chorioretinopathy). At 12-month follow-up, the mean change in visual acuity was a gain of 1.7 lines in the monotherapy group (n=17) compared with 2.8 lines in the combination therapy group (n=6; p=0.45). At 12 months, 36% in the bevacizumab monotherapy group gained >3 lines of vision compared with 60% in the combination group (p=0.60). The monotherapy group received a mean of 4.8 reinjections, while the combination group received 2.6 injections over 12 months (p=0.11).

Central Serous Chorioretinopathy

Literature searches have identified 2 small controlled studies from Asia that assessed the efficacy of bevacizumab for central serous chorioretinopathy (CSC). In a 2010 report, 32 eyes with acute CSC (<3 months’ duration) were randomized to a single 1.25 mg intravitreal injection of bevacizumab or to observation. (23) Twelve eyes in each group completed 6 months of
follow-up and were included in the analysis; 8 eyes were excluded due to irregular follow-up or lack of post-treatment data. During the 6-months of follow-up, there were no significant differences in visual acuity, central retinal thickness, or remission duration between the bevacizumab and control group. All patients had complete resolution of their macular subretinal fluid during the 6 months of follow-up.

In another prospective study reported in 2010, 15 eyes of 15 patients with persistent CSC treated with a single 2.5-mg intravitreal injection of bevacizumab were compared with 15 eyes with the same characteristics from patients who declined treatment. (24) Inclusion criteria were subfoveal or juxtafoveal persistent CSC >3 months, BCVA of 20/200 or better, clinical findings suggesting idiopathic CSC, and presence of subretinal fluid involving the fovea on OCT. Visual and anatomic responses were measured at baseline and at 1, 3, and 6 months after treatment. Baseline characteristics were similar for the 2 groups. At 6-month follow-up, the mean logMAR BCVA was significantly better in the treatment group (0.03) compared with the control group (0.14), and all 15 (100%) treated eyes had stable or improved vision, compared with 10 (66%) eyes in the control group. The presence of subretinal fluid was seen in 3 (20%) patients treated with bevacizumab and 46.6% of control patients. The baseline mean central foveal thickness was 485 microns for the treatment group and 480 microns for the control group. At 6 months, the mean central foveal thickness for the bevacizumab-treated group remained significantly lower compared to the control group, 174 microns and 297 microns, respectively. Eleven (73.3%) of 15 eyes in the treatment group showed a complete absence of fluorescein leakage compared with 5 (33.3%) of 15 eyes in the control group. Ocular or systemic complications were not encountered in the study.

### Multifocal Choroiditis

In 2010, Parodi et al. reported a pilot randomized clinical trial that compared intravitreal bevacizumab and PDT in 27 patients with CNV associated with multifocal choroiditis. (25) Retreatments (2.8 for bevacizumab and 0.7 for PDT) were performed if any leakage from CNV was noted on fluorescein angiography. At the 12-month follow-up, 5 of 14 eyes (36%) in the bevacizumab group and 0 of 13 eyes (0%) in the PDT group had a gain of >3 lines of vision. Twelve eyes (86%) in the bevacizumab group and 6 eyes (46%) in the PDT group gained more than 1 line. There was a significant difference in BCVA favoring the bevacizumab group at the end of follow-up. The 2 groups showed a similar improvement in central macular thickness.

### Pathologic Myopia

Parodi and colleagues compared intravitreal bevacizumab with laser photocoagulation and PDT in a randomized trial of 54 patients with juxtafoveal CNV secondary to pathologic myopia in 2010. (26) Additional intravitreal bevacizumab injections were administered when OCT revealed persistent or recurrent fluid, or when the fluorescein angiography examination revealed CNV activity or progression. Eyes in the laser therapy or PDT groups that developed recurrent CNV with subfoveal location during follow-up could be retreated using PDT. At 24 months, the bevacizumab group had gained 1.8 lines from baseline with a mean of 3.8 intravitreal bevacizumab injections; 4 of 19 eyes (21%) required intravitreal bevacizumab injections during the second year. The laser photocoagulation group lost 1.1 lines with a mean of 1.17 PDT treatments, and the PDT group lost 2 lines with 2.55 retreatments.

A 2012 study from the same group of investigators compared ranibizumab PRN versus bevacizumab PRN in 48 eyes with neovascularization secondary to pathologic myopia. (27)
Although this randomized study does not appear to be double-masked, the authors reported that visual acuity was assessed by an examiner who was unaware of the purpose of the study. At 18-month follow-up, there was no significant difference in mean BCVA between the 2 groups (0.42 logMAR for ranibizumab vs. 0.53 logMAR for bevacizumab). A 3-line or higher gain was reported for 30% of eyes in the ranibizumab group and 44% of eyes in the bevacizumab group. Stabilization of CNV was observed in 100% of ranibizumab-treated eyes and 84% of bevacizumab-treated eyes. Fewer injections were administered in the ranibizumab group (2.5) compared with the bevacizumab group (4.7).

Another small randomized trial from 2010 compared ranibizumab and bevacizumab in 32 eyes (32 patients) with pathologic myopia. Follow-up was performed at 1, 3, and 6 months. BCVA at baseline was 26.44 letters in the ranibizumab group and 29.50 letters in the bevacizumab group. At 6 months, ranibizumab-treated eyes had gained 17.31 letters and bevacizumab-treated eyes had gained 15.87 letters. Twelve eyes in the ranibizumab group (75%) and 13 in the bevacizumab group (81.2%) gained>10 letters. Foveal center thickness improved from 251 to 206 microns with ranibizumab and from 237 to 185 microns with bevacizumab. No significant differences in BCVA improvement or foveal center thickness reduction were found between the groups. Complete resolution of fluorescein leakage was observed in all 16 bevacizumab-treated eyes and in 15 of 16 (93.7%) of ranibizumab-treated eyes.

There are at least two large-scale, multicentered, double-masked, randomized trials to study the efficacy of VEGF inhibitors for myopic CNV. (29)

- NCT01217944 randomized 331 patients with myopic CNV to intravitreal ranibizumab or to PDT. The study is listed as completed with 12-month follow-up as of February 18, 2013.
- NCT01249664 will randomize 122 patients with myopic CNV to aflibercept or sham injection. The study is listed as ongoing but is no longer recruiting participants. The estimated completion date with 48 week follow-up is September 2013.

**Clinical Input Received through Physician Specialty Societies and Academic Medical Centers**

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

In response to requests, input was received from 1 physician specialty society and 2 academic medical centers while this policy was under review in 2011. The input supported the use of anti-VEGF therapies (ranibizumab, bevacizumab, pegaptanib) for CNV due to AMD, angiod streaks, central serous chorioretinopathy, choroidal rupture or trauma, idiopathic choroidal neovascularization, pathologic myopia, presumed ocular histoplasmosis syndrome, and uveitis; clinical input did not uniformly support the use of anti-VEGF therapies for chorioretinal scars. The evidence provided in support of the medical necessity of anti-VEGF therapy for these conditions consisted of some small controlled trials and numerous case series.

**Summary**
The available literature from randomized controlled trials supports the use of anti-VEGF (vascular endothelial growth factor) therapies (ranibizumab, bevacizumab, pegaptanib, aflibercept) as monotherapy for the treatment of choroidal neovascularization (CNV) associated with age-related macular degeneration (AMD). The use of anti-VEGF therapies for CNV secondary to other relatively rare disorders of choroidal circulation (angioid streaks, central serous chorioretinopathy, choroidal rupture or trauma, idiopathic choroidal neovascularization, multifocal choroiditis, pathologic myopia, presumed ocular histoplasmosis syndrome, and uveitis) is supported by a few small randomized trials, numerous case series, and clinical input. Therefore, anti-VEGF therapies (ranibizumab, bevacizumab, pegaptanib aflibercept) may be considered medically necessary for CNV associated with these conditions. Anti-VEGF therapies are considered investigational for the treatment of chorioretinal scars.

**Practice Guidelines and Position Statements**

In 2008, Preferred Practice Patterns (practice guidelines) on PDT from the American Academy of Ophthalmology (AAO) reviewed the evidence on VEGF inhibitors and thermal laser photocoagulation surgery for CNV. (30) The guidelines state that because of the loss of vision associated with laser photoagulation (82% of treated patients end up with visual acuity worse than 20/200), photocoagulation is no longer the initial treatment for subfoveal neovascularization. The guidelines also indicate that VEGF inhibitors have demonstrated improved visual outcomes compared with other therapies and have become the first-line therapy for treating neovascular AMD.

In April 2008, the Canadian Agency for Drugs and Technologies in Health (CADTH), released a Health Technology Assessment (HTA) titled *Management of Neovascular Age-related Macular Degeneration: Systematic Drug Class Review and Economic Evaluation*. (31) The review of clinical evidence found that, with the exception of trials comparing ranibizumab with PDT, there was a significant lack of trials comparing the other anti-VEGF agents in general. The authors concluded that “…overall, the efficacy of anti-vascular endothelial growth factor (anti-VEGF) therapies over verteporfin (V-PDT) is well supported by RCTs [randomized controlled trials]. What remains unclear is whether combination therapy (and which combinations) are superior or equal to monotherapy. Furthermore the efficacy of one anti-VEGF agent compared with another is also unclear and this has very important practical and economic implications.”

**Medicare National Coverage**

There is no national coverage decision.

**References:**


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ICD-10-PCS codes are only used for inpatient services. There is no specific ICD-10-PCS code for this procedure.

**Type of service**: Vision

**Place of service**: Physician’s office

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**Index**

Age-Related Macular Degeneration; Treatment
Angioid Streaks; Treatment
Central Serous Chorioretinopathy; Treatment
Choroidal Neovascularization; Treatment
Chorioretinal Scars; Treatment
Idiopathic Choroidal Neovascularization; Treatment
Multifocal Choroiditis; Treatment
Pathologic Myopia; Treatment
Presumed Ocular Histoplasmosis; Treatment
Uveitis; Treatment