Photodynamic Therapy for Choroidal Neovascularization

Policy Number: 9.03.08
Origination: 10/2000
Last Review: 10/2016
Next Review: 10/2017

Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for photodynamic therapy for choroidal neovascularization when it is determined to be medically necessary because the criteria shown below are met.

When Policy Topic is covered
Photodynamic therapy may be considered medically necessary as a treatment of choroidal neovascularization associated with age-related macular degeneration, chronic central serous chorioretinopathy, choroidal hemangioma, pathologic myopia, or presumed ocular histoplasmosis.

When Policy Topic is not covered
Photodynamic therapy is considered investigational, as monotherapy for other ophthalmologic disorders.

Photodynamic therapy is considered investigational when used in combination with one or more of the anti-vascular endothelial growth factor therapies (anti-VEGF), i.e., pegatanib (Macugen®), ranibizumab (Lucentis®), bevacizumab (Avastin®), aflibercept (Eylea™) as a treatment of CNV associated with age-related macular degeneration, chronic central serous chorioretinopathy, choroidal hemangioma, pathologic myopia, presumed ocular histoplasmosis or for other ophthalmologic disorders.

Considerations
The U.S. Food and Drug Administration (FDA) labeling for verteporfin indicates that the physician should re-evaluate the patient every 3 months and, if choroidal neovascular leakage is detected on fluorescein angiography, therapy should be repeated. However, the total number of treatments is not addressed by the FDA. Evidence defining when treatment should stop is not available, but expert opinion (convened by Novartis, Visudyne manufacturer) suggested stopping “when the situation is judged to be ‘futile’” (Verteporfin Roundtable Participants 2005). FDA labeling states “safety and efficacy of Visudyne beyond 2 years have not been demonstrated.”
Acute central serous chorioretinopathy refers to self-limiting disease that resolves spontaneously over a few months without any treatment. Chronic central serous chorioretinopathy has been defined as a serous macular elevation, visible biomicroscopically or detected by optical coherence tomography, that is associated with retinal pigment epithelial atrophic areas and subtle leaks or ill-defined staining by fluorescein angiography, and which does not resolve spontaneously within a few months. (1)

**Description of Procedure or Service**

<table>
<thead>
<tr>
<th>Individuals</th>
<th>Interventions</th>
<th>Comparators</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>With CNV due to AMD, pathologic myopia, presumed ocular histoplasmosis, chronic CSC, or choroidal hemangioma</td>
<td>Interventions of interest are: • Photodynamic therapy</td>
<td>Comparators of interest are: • Antivascular endothelial growth factor medications</td>
<td>Relevant outcomes include: • Symptoms • Change in disease status • Functional outcomes • Quality of life</td>
</tr>
<tr>
<td>With CNV due to polypoidal choroidal vasculopathy, angioid streaks, or inflammatory chorioretinal disease</td>
<td>Interventions of interest are: • Photodynamic therapy</td>
<td>Comparators of interest are: • Antivascular endothelial growth factor medications</td>
<td>Relevant outcomes include: • Symptoms • Change in disease status • Functional outcomes • Quality of life</td>
</tr>
<tr>
<td>With CNV due to any etiology&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Interventions of interest are: • Photodynamic therapy in combination with antivascular endothelial growth factor medications</td>
<td>Comparators of interest are: • Photodynamic therapy alone</td>
<td>Relevant outcomes include: • Symptoms • Change in disease status • Functional outcomes • Quality of life</td>
</tr>
</tbody>
</table>

AMD: age-related macular degeneration; CNV: choroidal neovascularization; CSC: central serous chorioretinopathy.

Photodynamic therapy (PDT) 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, thereby occluding choroidal neovascularization tissue. Patients may be re-treated if leakage from choroidal neovascularization (CNV) persists.

The evidence for PDT in individuals who have CNV due to age-related macular degeneration (AMD), pathologic myopia, presumed ocular histoplasmosis, chronic central serous chorioretinopathy (CSC), or choroidal hemangioma includes randomized controlled trials (RCTs), nonrandomized comparative trials, and
systematic reviews of controlled trials. Relevant outcomes are symptoms, change in disease status, functional outcomes, and quality of life. The RCT evidence supports the efficacy of PDT in reducing visual loss and decreasing retinal thickness. Comparative studies of PDT versus antivascular endothelial growth factor (anti-VEGF) medications have reported that anti-VEGF medications are as good as, and possibly superior to, PDT for reducing visual loss. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

The evidence for PDT in individuals who have CNV due to polypoidal choroidal vasculopathy, angioid streaks, or inflammatory chorioretinal disease includes RCTs, nonrandomized comparative trials, and case series. Relevant outcomes are symptoms, change in disease status, functional outcomes, and quality of life. RCT evidence is limited for these conditions, and most published studies are case series. The case series have reported improved visual acuity following treatment, but this study design lacks sufficient methodologic rigor to allow conclusions. The evidence is insufficient to determine the effects of the technology on health outcomes.

The evidence for PDT in combination with anti-VEGF medications in individuals who have CNV of any etiology (eg, AMD, chronic CSC, choroidal hemangioma, pathologic myopia, presumed ocular histoplasmosis, choroidal vasculopathy, angioid streaks, inflammatory chorioretinal disease) includes RCTs, nonrandomized comparative studies, and systematic reviews of controlled trials. Relevant outcomes are symptoms, change in disease status, functional outcomes, and quality of life. RCTs of combination therapy have reported that PDT can decrease the number of anti-VEGF injections needed, but PDT is not associated with improved visual acuity compared to anti-VEGF alone. Some studies have reported that the change in visual acuity after PDT is noninferior, but others have found that it is inferior to anti-VEGF alone. Further research is needed to better determine the tradeoff between fewer anti-VEGF injections and possible reduction in visual acuity. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Background**
Severe vision loss can occur with ocular neovascularization, the growth of abnormal blood vessels in the retina or choroid. Neovascularization occurs in a number of ocular diseases, including age-related macular degeneration (AMD). Available therapeutic options for choroidal neovascularization include photodynamic therapy (PDT), antioxidants, thermal laser photocoagulation, corticosteroids, and vascular endothelial growth factor (VEGF) antagonists or angiostatics. The safety and efficacy of each treatment depends on the form and location of the neovascularization. For those whose visual losses impair their ability to perform daily tasks, low-vision rehabilitative services offer resources to compensate for deficits.

PDT 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 and occludes the neovascularized tissue. Patients may be retreated if leakage from CNV persists.

Before 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 preexisting 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 photoocoagulation, photocoagulation is no longer recommended as the initial treatment of subfoveal neovascularization. More recently, infrared lasers used at a low-power setting have been investigated as a technique to photocoagulate subfoveal lesions.

Combining PDT with angiostatic agents, either concurrently or sequentially, has a biological basis and is under active investigation. Angiostatic agents block some stage in the pathway leading to new blood vessel formation (angiogenesis). Drugs currently under study target various parts of the angiogenic pathway: messenger RNA; vascular endothelial growth factors (VEGFs); endothelial cell proliferation, migration, and proteolysis. The angiostatic agents being studied in trials include pegaptanib, ranibizumab, bevacizumab, anecortave acetate, squalamine, vatalanib, and triamcinolone acetonide. In contrast to palliative treatments for CNV (e.g., thermal photocoagulation and photodynamic therapy), they are potentially disease modifying by inhibiting the development of newly formed vessels.

Intravitreal triamcinolone acetonide was one of the first pharmacologic compounds evaluated for the treatment of choroidal neovascularization 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.

**Age-Related Macular Degeneration**

AMD is a painless, insidious process. In its earliest stages, it 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.

Pathologic Myopia
Pathologic myopia refers to an abnormal elongation of the eye associated with severe near-sightedness. It generally occurs among people older than 30 years of age and can result in a progressive, severe loss of vision, frequently related to the development of CNV.

Presumed Ocular Histoplasmosis
Presumed ocular histoplasmosis may be the second most common cause of blindness in patients younger than 50 years of age in certain endemic areas (Ohio and Mississippi River Valleys in the United States). This condition is characterized by a positive skin test for histoplasmosis, miliary opacities of the lungs, tiny choroidal scars, peripapillary disruption of the choriocapillaris, and exudation or hemorrhage from choroidal lesions in or near the macula. The condition is asymptomatic and benign, unless the CNV lesions, which may develop many years after chorioretinal scarring has taken place, affect the macula.

Central Serous Chorioretinopathy
Central serous chorioretinopathy 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. This condition is avascular; however, neovascularization can occur as a secondary complication. Although central serous chorioretinopathy often resolves spontaneously in 3 to 4 months, chronic or recurrent central serous chorioretinopathy can result in progressive decline of visual acuity. Central serous chorioretinopathy has been treated with medication and laser photocoagulation, but these treatments have limited efficacy.

Choroidal Hemangioma
Choroidal hemangioma is an uncommon, benign vascular tumor, manifesting as an orange-red mass in the posterior pole of the eye. Visual loss may be progressive and irreversible because of chronic foveal detachment.

Polypoidal Choroidal Vasculopathy
Polypoidal choroidal vasculopathy arises primarily from abnormal choroidal circulation, resulting in characteristic lesions comprising well-defined vascular networks of vessels ending in polyp-like structures. A less common subtype is polypoidal CNV, and it may be considered a subtype of AMD. Eyes that develop a cluster of grape-like polypoidal dilations are at high risk for severe vision loss.
**Angioid Streaks**
Angioid streaks are dehiscences in Bruch membrane and occur in patients with some systemic diseases such as pseudoxanthoma elasticum, Paget disease of bone, or sickle hemoglobinopathy. Vision loss in eyes with angioid streaks occurs most frequently as a result of CNV.

**Inflammatory Conditions**
CNV can occur as a complication of inflammatory conditions such as uveitis, multifocal choroiditis and panuveitis, and punctate inner choroidopathy. About one-third of patients develop choroidal neovascularization, which can result in severe vision loss if it is subfoveal.

**Regulatory Status**
There is currently one intravenous photodynamic therapy (PDT) agent that has received approval by the U.S. Food and Drug Administration (FDA), verteporfin (Visudyne®, Novartis). The FDA-approved indications include the treatment of predominantly classic subfoveal CNV due to age-related macular degeneration (AMD), pathologic myopia, and presumed ocular histoplasmosis. The label notes that there is insufficient evidence for verteporfin use in predominately occult subfoveal CNV, and it is contraindicated in patients with porphyria.

This policy only addresses combined treatment with PDT and VEGF inhibitors. Treatment of choroidal neovascularization with VEGF monotherapy is addressed in a separate policy.

**Rationale**
This evidence review was created in December 2000 and has been updated periodically with literature searches of the MEDLINE database. The most recent literature review was performed through February 2, 2016.

Randomized controlled trials (RCTs) are crucial in determining the efficacy of photodynamic therapy (PDT) treatment and comprise the bulk of the evidence on which the efficacy of this treatment can be evaluated. Where RCTs are lacking, nonrandomized comparative studies provide some evidence for efficacy but are limited by potential selection bias, because patients may prefer selecting 1 treatment over another by disease severity or other clinical factors.

**Age-Related Macular Degeneration**
This evidence review was originally based on a 2000 TEC Assessment that offered the following observations and conclusions:

- Two multicenter, double-masked, randomized placebo-controlled trials including 402 patients reported that, at 1-year follow-up, fewer patients treated with PDT experienced a clinically significant loss of visual acuity compared with those treated with placebo: 38.8% compared with 53.6%, respectively (p<0.001).
Subgroup analysis suggests that the treatment effect is predominantly experienced by patients with age-related macular degeneration (AMD) characterized by at least 50% classic choroidal neovascularization (CNV).

- There were inadequate data to permit scientific conclusions regarding other etiologies of CNV.

### Systematic Reviews

A 2003 Cochrane review concluded that PDT is effective at preventing visual loss in classic and occult CNV due to AMD.\(^2\) An updated Cochrane review in 2007 evaluated results from 3 RCTs (total N=1022 patients), which included the TAP and VIP trials described next.\(^3\) Meta-analysis showed a 24-month risk ratio of losing 6 or more lines of visual acuity of 0.62 compared with the control group. The authors concluded that PDT is probably effective for treating CNV due to AMD, although there was doubt about the size of the effect. In a 2004 meta-analysis of the safety of PDT, Azab et al analyzed data from the 24-month TAP A and B and VIP trials, totaling 948 patients with AMD.\(^4\) The authors concluded that the safety profile of verteporfin therapy did not differ statistically from placebo.

### TAP Trial

In 2001, 2-year results of the pivotal randomized Treatment of Age-Related Macular Degeneration with Photodynamic Therapy (TAP) trial were published.\(^5\) Beneficial outcomes for visual acuity and contrast sensitivity noted after 12 months were sustained through 24 months. At the end of 2 years, 53% of the treatment group, compared with 38% of the placebo group, lost fewer than 15 letters. The average number of applications of verteporfin treatment in the second year (2.2) was lower than that required during the first year (3.4). Subgroup analysis compared results between those patients with predominantly classic CNV (>50% of lesional area) and minimally classic CNV (<50%). For patients with minimally classic disease, no statistically significant differences in visual acuity were noted. Several additional reports from the TAP trial have been published.\(^6\)-\(^8\) They demonstrated positive outcomes with the use of PDT for subfoveal CNV, and further supported the findings of the earlier TAP trial reports. In 2006, Kaiser reported results of a 3-year open-label extension of the TAP study.\(^9\) Of 402 verteporfin-treated patients who completed the 24-month randomized study, 320 (80%) enrolled in the extension protocol. Of the 320 enrolled, 193 (60%) completed the 60-month examination and 122 (38%) discontinued prematurely, 3 (1%) were noncompliant. Yearly treatment rates declined from 3.5 treatments in the first year to 0.1 in the fifth year; patients who remained in the study lost an additional 2.3 lines of letters over the 3-year extension.

### VIP Trial

The Verteporfin in Photodynamic Therapy (VIP) trial is another randomized study that primarily focused on efficacy of PDT in patients with occult but no classic lesions who were presumed to have progressive disease due to visual or anatomic deterioration within the previous 3 months.\(^10\) Of the 339 patients enrolled in the trial, 76% had occult disease; the remainder had early classic CNV with good visual acuity. Similar to other randomized trials, the primary outcome was the proportion of eyes with fewer than 15 letters of visual acuity loss. While there was
no significant difference between the treatment and placebo groups at 12 months, by 24 months, a significantly lower percentage of those with occult CNV who were treated with PDT (55%) had lost vision compared with those who received placebo (68%; p=0.032). These results contrast with those of the TAP trial, although the patient populations differed. The TAP trial required all patients to have some percentage of classic CNV, while the VIP trial recruited patients with occult disease without evidence of classic CNV. In addition, the VIP trial required patients with occult disease to have experienced recent deterioration in vision. Results for the subgroup of patients with classic CNV but good visual acuity were not reported separately.

**Early Retreatment Study Group Trial**
In 2008, Schmidt-Erfurth and Sacu conducted a multicenter RCT of 203 patients with CNV caused by AMD. Patients were randomized to a standard treatment regimen of every 3 months versus a more intensive regimen of every 2 months. Following a 6-month experimental period, both groups were treated at the standard frequency of every 3 months. The primary outcome was BCVA, measured at 6-month intervals up to a follow-up of 24 months. Secondary outcomes were the proportion of patients who had lost at least 3 lines of visual acuity, change in mean lesion size, and number of treatments over the 24-month trial period. There were no group differences on BCVA at any follow-up time points and no difference in mean lesion size. There was a modestly lower percentage of patients who had lost at least 3 lines of visual acuity in the intensive group compared to the standard treatment group (51.9% vs 56.7%).

**PDT Compared With Anti-VEGF Therapies**

**Systematic Review**
A 2008 Cochrane review evaluated antivascular endothelial growth factor (anti-VEGF) therapies for neovascular AMD. Five RCTs on pegaptanib and ranibizumab were included in the review; all were conducted by pharmaceutical manufacturers. The trials compared pegaptanib or ranibizumab to sham, ranibizumab to PDT, and ranibizumab plus PDT to PDT. Fewer patients treated with pegaptanib lost 15 or more letters of visual acuity at 1-year follow-up than those treated with sham (pooled relative risk [RR], 0.71; 95% confidence interval [CI], 0.61 to 0.84). In a trial of ranibizumab versus sham, the RR for loss of 15 or more letters of visual acuity at 1 year was 0.14 (95% CI, 0.1 to 0.22) in favor of ranibizumab. The pooled RR for gain of 15 or more letters of visual acuity at 1 year was 5.81 (95% CI, 3.29 to 10.26) for ranibizumab versus sham, 6.79 (95% CI, 3.41 to 13.54) for ranibizumab versus verteporfin PDT, and 4.44 (95% CI, 1.40 to 14.08) for ranibizumab plus verteporfin PDT versus verteporfin PDT.

**ANCHOR Trial**
Ranibizumab was compared with PDT in a multicenter, double-blind study (423 patients) by the Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration (ANCHOR) study group in 2006. The ANCHOR trial was industry-funded. Patients with subfoveal CNV and a predominantly classic lesion 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 plus sham PDT or sham injection plus active PDT. Following 12 monthly treatments, groups treated with ranibizumab (0.3 or 0.5 mg) and sham verteporfin had 94% to 96% of patients lose fewer than 15 letters. The patient group treated with monthly sham injection plus active verteporfin therapy (average 2.8 times over the year) had 64% of patients lose fewer than 15 letters. Visual acuity improved by more than 15 letters in 36% and 40% of the ranibizumab 0.3-mg and 0.5-mg groups (average dose-dependent gain, 8.5 and 11.3 letters), respectively, compared with 6% of patients in the verteporfin group (average loss, 9.5 letters). Intraocular inflammation occurred in 10% 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.

In 2009, Brown et al evaluated 2-year follow-up results for the ANCHOR trial. Of 423 patients in the 3 treatment groups, follow-up at 24 months was 77% or higher in each group. Results did not differ substantially from those reported at 12 months. The percentage of patients in the ranibizumab groups who lost fewer than 15 letters of visual acuity (89.9% to 90.0%) was higher than in the PDT group (65.7%, p<0.001), and there were differences in lesion size in favor of the ranibizumab groups. Patients treated with ranibizumab had a trend toward a greater incidence of cataracts, but there were no group differences on serious adverse events, including nonocular complications.

Bressler et al (2009) reported a subanalysis of the patient-reported outcomes from the ANCHOR trial. The National Eye Institute Visual Function 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, 276 patients treated with ranibizumab had mean improvements in NEI VFQ-25 composite scores of 5.9 points (95% CI, 3.6 to 8.3 points) for the 0.3-mg dose group and 8.1 points (95% CI, 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 (95% CI, -0.3 to 4.7 points). At each dose through 24 months, 142 patients treated with ranibizumab were more likely to improve on most subscales, including the prespecified subscales (near activities, distance activities, vision-specific dependency). The authors concluded that the ranibizumab groups were more likely to “report clinically meaningful improvements in visual function through 24 months” than the verteporfin PDT group.

**PDT in Combination Therapies for AMD**
Angiostatic agents are being studied in trials include pegaptanib, ranibizumab, bevacizumab, anecortave acetate, squalamine, vatalanib, and triamcinolone.
PDT in Combination With VEGF Antagonists

Systematic Reviews
A systematic review of anti-VEGF injections for treating wet AMD was published in 2015, including a section comparing anti-VEGF monotherapy with anti-VEGF combination therapy with PDT. The 4 RCTs included compared monotherapy with combination therapy, 3 of which are discussed later in this review (DENALI, MONT BLANC, Williams et al). In combined analysis, there was a significant difference in BCVA of 2.74 letters (95% CI, 0.26 to 5.21, p=0.03) in favor of the monotherapy group (note that the conclusions of the systematic review indicate that the difference favored the combination group, which is incorrect). There were no differences between groups on central retinal thickness or lesion size. The authors did not report combined analysis of the number of anti-VEGF injections performed in each group.

In a 2010 editorial, Kaiser reported an ongoing clinical program (SUMMIT) investigating whether treatment with combination PDT and ranibizumab is safe and effective compared with monotherapy. The SUMMIT program is intended to combine results from a North American trial (DENALI, N=321) and a European trial (MONT BLANC, N=255), however, no results of this program have been published. A 2005 TEC Special Report found a number of trials in progress combining an angiostatic agent with PDT. For example, in the pegaptanib trial, PDT was administered at physician discretion, but analysis examining possible synergistic effects was not provided.

DENALI Trial
DENALI was a multicenter, double-masked, randomized phase 3b trial that tested whether ranibizumab in combination with PDT at either standard fluence (n=104) or reduced fluence (n=105) was noninferior to ranibizumab given monthly (n=112). The 2 combination therapy groups received ranibizumab monthly for the first 3 months, followed by retreatment with PDT or ranibizumab as needed based on specified retreatment criteria at monthly monitoring. The ranibizumab monotherapy group received sham PDT, and patients in the combination groups who did not require ranibizumab at the monthly follow-up visit received sham intravitreal injections. The 2 main outcome measures were the change in BCVA from baseline and the proportion of patients in the combination therapy groups with a treatment-free interval of 3 months or more. A ranibizumab-free interval of 3 months or more was achieved in most patients in the standard (92.6%) and reduced (83.5%) fluence combination groups. Patients in the monotherapy arm received an average of 10.5 injections, while patients in the standard and reduced fluence combination groups received an average of 5.1 and 5.7 injections, respectively. About 20% of patients in the combination groups did not receive any ranibizumab retreatments after the loading phase up until month 11. However, the mean BCVA change at 12 months was +5.3 and +4.4 letters for standard and reduced fluence PDT, respectively, compared with +8.1 letters for the ranibizumab monotherapy group. Noninferiority for visual outcomes was not demonstrated. Mean central retinal thickness, measured at a central reading center, was reduced more in the ranibizumab monotherapy group (172.2 μm) than in the reduced...
fluence group (140.9 μm). Fluorescein leakage was higher in the combination therapy groups (standard fluence, 58.2%, p=0.008; reduced fluence, 54.5%, p=0.075) compared with the ranibizumab monotherapy group (41.8%).

**MONT BLANC Trial**
MONT BLANC was a multicenter, double-masked, randomized noninferiority trial that compared combination PDT/ranibizumab to as-needed ranibizumab monotherapy (with sham PDT) in 255 patients with CNV related to AMD. Both groups received 3 consecutive monthly injections followed by as-needed retreatments (active or sham) based on specified retreatment criteria. As with the DENALI trial, the 2 main outcome measures were change in BCVA from baseline and the proportion of patients in the combination therapy group with a treatment-free interval of 3 months or longer. At 12 months, the proportion of patients with a treatment-free interval of 3 months or more was similar in the 2 groups (96% combination therapy, 92% monotherapy), and the change in BCVA with combination therapy (+2.5 letters) was noninferior to ranibizumab monotherapy (+4.4 letters). On average, patients received 4.8 ranibizumab injections in the combination group compared with 5.1 injections in the monotherapy group over 12 months. Decreases in mean central retinal thickness were similar in the combination (115.3 μm) and monotherapy (107.7 μm) groups. This well-conducted study found that PDT did not reduce the number of ranibizumab injections when ranibizumab was administered as-needed.

**FOCUS Trial**
The FOCUS study group reported first- and second-year results of a masked phase 1/2 multicenter RCT of ranibizumab (0.5 mg) combined with PDT. Patients with subfoveal CNV secondary to AMD were randomized in a 2:1 ratio to ranibizumab (n=106) or sham (n=56) injection (initially 7 days) following verteporfin PDT. PDT was repeated only if fluorescein angiography revealed persistent or recurrent leakage from CNV at evaluation visits (3-month intervals). A higher than expected rate of serious intraocular inflammation occurred in the first patients, and the 2 treatments were subsequently scheduled no closer than 21 days apart. ITT analysis showed an average improvement in acuity of 5 letters at both 12 and 24 months (85% retention) with ranibizumab compared with a decrease of 8 letters in the PDT-alone group. Twenty-nine percent of patients in the ranibizumab group received additional PDT (average, 0.4 treatments) compared with 93% of patients in the PDT-alone group (average, 3 treatments). Visual acuity improved by 15 or more letters in 25% of patients treated with ranibizumab (plus PDT as needed) compared with 7% of patients treated with PDT alone. Endophthalmitis or intraocular inflammation was observed in 16 (15%) patients treated with ranibizumab. Most adverse events (9%) reported for the PDT-alone group related to AMD (ie, CNV, macular degeneration, retinal hemorrhage).

In addition to the above trials, several smaller randomized trials have been published. In 2015, Semeraro et al published an RCT of 75 patients with treatment-naive exudative CNV due to AMD. Patients were randomized into 3 groups: ranibizumab monotherapy, ranibizumab combined with reduced-fluence verteporfin PDT, and ranibizumab combined with ketorolac eye drops. At the 12-
month follow-up, BCVA (SD) was superior in the ranibizumab plus ketorolac group (-0.25 [0.60] logMAR), compared with ranibizumab monotherapy (-0.14 [0.52] logMAR) or ranibizumab combined with PDT (-0.10 [0.30] logMAR). Change in mean (SD) central retinal thickness was also superior in the ranibizumab plus ketorolac group (-141 [21] µm) compared with the ranibizumab monotherapy group (-125 [15] µm) and the ranibizumab plus PDT group (-130 [15] µm).

In a multicenter, unmasked trial, Williams et al (2012) randomized 60 patients to ranibizumab with half-fluence PDT or ranibizumab alone. The difference between groups in the number of injections did not differ significantly. BCVA improved by 9.9 letters in the ranibizumab group and by 2.6 letters in the combined treatment group. This difference did not differ significantly. A similar number of patients gained 15 or more letters (33% monotherapy vs 31% combination therapy). A small RCT by Lim et al (2012) included 31 patients with AMD and 10 patients with polypoidal choroidal vasculopathy who were randomized to bevacizumab monotherapy or bevacizumab in combination with PDT. At 12 months, the monotherapy and combined treatment groups showed similar improvements in BCVA and central foveal thickness, and the total number of bevacizumab injections was not reduced when PDT was given. A randomized, open-label assessor-blinded trial from Croatia with short-term (3-month) follow-up evaluated combined treatment with bevacizumab and PDT (N=165 eyes). At 3-month follow-up, 22 (42%) of 52 patients improved by more than 0.2 logMAR (logarithm of the minimum angle of resolution) following combined treatment, compared with 1 (2%) patient treated with bevacizumab alone and none treated with PDT alone.

**PDT in Combination With Corticosteroids**

The Retinologists Evaluating Triamcinolone In Neovascular AMD (RETINA) Study, a multicenter double-blind RCT of 100 patients with CNV related to AMD, found that combination PDT plus intravitreal triamcinolone therapy did not result in a significant difference in the primary outcome of visual acuity at 1 year compared with PDT with sham injection. Patients who received triamcinolone required fewer retreatments to control lesion leakage/activity (1.28 vs 1.94, respectively). The triamcinolone group also had a larger proportion of patients with elevated, although managed, intraocular pressure (18 vs 4, respectively).

A second prospective, randomized study in Italy evaluated combination corticosteroids plus PDT. Investigators compared the long-term effect of intravitreal triamcinolone acetonide (IVT) combined with PDT to PDT alone for neovascular AMD. Eighty-four patients were enrolled to receive PDT (n=41) or IVT treatment followed by PDT (n=43) within a 7- to 15-day interval. All patients were naive to treatment. At baseline and at follow-up visits at 3, 6, 12, and 24 months, measurement of BCVA, fluorescein angiography, indocyanine green angiography, and optical coherence tomography were performed. Mean changes in visual acuity and retreatment rates were primary outcomes. Mean visual acuity increased at 1-month follow-up but decreased by 24 months in both groups (p=0.74). Retreatment rates were significantly lower in the combined therapy group. Choroidal hypoperfusion/nonperfusion and areas with decreased/absent fundus autofluorescence within the PDT spot area were significantly greater with
combined therapy. The authors concluded that “… combination IVT treatment with PDT seemed to be more effective for managing neovascular age-related macular degeneration, but long-term analysis failed to demonstrate functional benefits.”

**Triple Therapy**
Triple therapy (PDT, intravitreal dexamethasone, intravitreal bevacizumab) for AMD has been reported. Thirty-two eyes of 30 patients received reduced-fluence PDT followed immediately by intravitreal dexamethasone. At 1 and 7 weeks after PDT and dexamethasone, patients received a bevacizumab injection. At 13 weeks after PDT, patients were evaluated with optical coherence tomography and fluorescein angiography, with additional triple-therapy treatment cycles as needed for visible leakage or increased foveal thickness with vision loss. At 12-month follow-up, the mean number of treatment cycles was 1.4 and the mean number of bevacizumab injections was 2.8. Mean visual acuity improved from 0.74 to 0.53 logMAR. Mean foveal thickness decreased from 328 to 216 μm. Ninety-four percent of patients lost fewer than 3 lines, 31% gained more than 3 lines, and 6% lost more than 3 lines.

**Section Summary: Age-Related Macular Degeneration**
PDT monotherapy is an established treatment for CNV secondary to AMD, with evidence from multiple RCTs supporting benefit compared with placebo. Although PDT is established as superior to no treatment, recent comparative trials showed anti-VEGF therapy to be superior to PDT. For combination therapy, the literature to date includes 2 high-quality randomized trials, several smaller RCTs, and a meta-analysis of the existing trials. This evidence does not demonstrate an improvement in BCVA with combination therapy compared with anti-VEGF monotherapy. Combination therapy may lead to a reduction in the number of intravitreal injections needed, but this is not consistently reported across studies. Combination therapy with PDT and corticosteroids shows no improvement in outcomes or reduction in the number of intravitreal injections. Comparative trials are needed to evaluate the efficacy of triple therapy with intravitreal steroids, anti-VEGF agents, and PDT.

**Pathologic Myopia**
PDT has also been investigated in patients with CNV related to pathologic myopia.

**PDT in Comparison With Placebo**
A second arm of the VIP trial focused on 120 patients with pathologic myopia and CNV, either classic, occult, or mixed (although 90% of patients had classic CNV) who were randomized in a 2:1 ratio to receive PDT or placebo. Patients received an average of 3.4 PDT treatments over the course of 12 months. The primary outcome was the proportion of eyes with fewer than 8 letters of visual acuity lost at 12 months by ITT analysis. Visual acuity, contrast sensitivity, and fluorescein angiographic outcomes were better in the PDT eyes than in the placebo-treated eyes at every follow-up examination through 12 months. At month 12, PDT-treated eyes lost fewer than 8 letters on a standard eye chart in 72% (n=58) of patients versus 44% (n=17) who were receiving placebo. Improvement of at least 5 letters was observed in 32% (n=26) of PDT-treated eyes compared with 15%
(n=6) of placebo-treated eyes. Fluorescein angiography showed progression of classic CNV in 36% of PDT-treated eyes compared with 54% of the placebo group. The authors concluded that verteporfin therapy increased the chance of stabilizing or improving vision compared with placebo treatment for at least 1 year. Results were not reported separately for those with predominantly classic CNV versus occult CNV.

**PDT in Comparison With VEGF Antagonists**

El Matri et al (2011) reported a retrospective comparison of PDT and bevacizumab for myopic CNV. 32 Eighty eyes (80 patients) with myopic CNV were treated with standard PDT (2005-2007, n=40) or bevacizumab (2008-2009, n=40). Retreatment was given every 3 months in the PDT group and every 4 weeks in the bevacizumab group as needed; patients received a mean of 1.8 bevacizumab injections and 1.6 PDT treatments during 12 months. At baseline, BCVA was 0.9 logMAR (20/159 Snellen equivalent) in the bevacizumab group and 0.88 logMAR (20/152 Snellen equivalent) in the PDT group. At 3-, 6-, and 12-month follow-up, mean logMAR BCVA was significantly better in the bevacizumab group (range, 0.5-0.6 logMAR) than in the PDT group (range, 0.85-0.86 logMAR). BCVA improved by 3 lines or more in 70% of eyes in the bevacizumab group and in 23% of the PDT group. Mean central retinal thickness was similar at baseline (421 μm vs 393 μm) and significantly lower in the bevacizumab group compared with the PDT group at 3 (328 μm vs 393 μm), 6 (300 μm vs 370 μm), and 12 (306 μm vs 352 μm) months, respectively. Chorioretinal atrophy developed in 6 (15%) eyes treated with bevacizumab and in 24 (60%) eyes treated with PDT. Although limited by the retrospective nature of the comparison, these results are strongly suggestive of the superiority of anti-VEGF treatment over PDT for myopic CNV.

**PDT in Combination With VEGF Antagonists**

**Bevacizumab Monotherapy**

Chenet al (2011) compared bevacizumab monotherapy (n=17) with combination treatment of bevacizumab with PDT (n=6) in a retrospective analysis of patients with CNV secondary to causes other than AMD; approximately half of patients had myopic CNV. 33 Most observed differences between groups were not statistically significant, likely due to the small sample size. For example, mean change in visual acuity at 12-month follow-up was 1.7 lines in the monotherapy group and 2.8 lines in the combination therapy group, and 36% of the monotherapy group gained 3 lines or more compared with 60% in the combination therapy group. The combination group received fewer reinjections (average injections, 2.6 vs 4.8), but this difference was not statistically significant (p=0.11). Subgroup analysis for cases of myopic CNV showed no significant difference between groups in mean acuity gains (2.0 lines in the monotherapy group vs 2.3 lines in the combination therapy group) with fewer reinjections (2 vs 7.2, p<0.05) needed in the combination group during the 12-month follow-up. No serious ocular complications were observed. Prospective comparison with a larger number of patients is needed.
Section Summary: Pathologic Myopia
PDT has been shown in 1 RCT to be more effective than placebo for myopic CNV, and these findings have been corroborated in nonrandomized studies. RCTs are needed to evaluate the efficacy and safety of combined PDT and anti-VEGF therapy in patients with myopic CNV.

Presumed Ocular Histoplasmosis
There are few published data on the use of PDT in patients with CNV related to ocular histoplasmosis. Food and Drug Administration approval was based on an open-label safety study involving 26 patients with ocular histoplasmosis. Visual acuity improved by an average of more than 1 line (6.7 letters) on a standard eye chart at 12 months, with 28% of patients experiencing an improvement of at least 3 lines (15 letters). Visual acuity decreased by less than 3 lines in 88% of patients during the same time period.

Central Serous Chorioretinopathy
In 2010, Chan et al published a systematic review of PDT for nonstandard indications, which included 12 case series (119 eyes) of PDT for central serous chorioretinopathy. Additionally, several nonrandomized comparative studies and RCTs with reduced-dose (verteporfin) and reduced-fluence (laser) PDT have been identified.

A Cochrane systematic review on the treatment of CSC, both acute and chronic, was published in 2015. For PDT monotherapy, there was 1 low-quality trial of patients with acute CSC comparing PDT to no treatment using a sham control. There was a small improvement in visual acuity for the PDT group (mean difference, -0.10 logMAR; 95% CI, -0.18 to -0.02). There was also a decrease in recurrence of CSC (risk ratio, 0.10; 95% CI, 0.01 to 0.81) and a trend toward a lower risk of persistent CSC (risk ratio, 0.12; 95% CI, 0.01 to 1.02). Two low-quality trials compared anti-VEGF agents with PDT and reported no difference in BCVA at 1 year. There was a trend toward less recurrence and less persistent CSC in the PDT group, but these results were inconsistent across trials.

Acute Central Serous Chorioretinopathy
Chan et al (2008) conducted a randomized, double-masked, placebo-controlled trial of reduced-dose verteporfin PDT versus placebo for acute central serous chorioretinopathy. Reduced-dose verteporfin was tested because full-dose PDT had to adverse effects, including CNV. A total of 63 patients were randomized in a 2:1 ratio to half-dose verteporfin or placebo before laser treatment. Thirty-nine patients in the verteporfin group completed the trial while 19 in the placebo group did. The primary outcome measure—the proportion of eyes with absence of subretinal fluid at the macula at 12 months—was observed in 95% (n=37) of eyes in the verteporfin group and 58% (n=11) of eyes in the placebo group. Mean central foveal thickness in the verteporfin group was lower than in the placebo group at 12 months (161 μm vs 278 μm). At 3 months after treatment, mean logMAR of the PDT group was 0.00 (Snellen equivalent 20/20), whereas the placebo group improved to 0.08 (Snellen equivalent 20/24). At 12 months, mean logMAR remained statistically better in the PDT group than in the placebo group (-
0.05 vs 0.05; \( p=0.008 \)); however, because this is equivalent to visual acuity of 20/18 versus 20/22, this result was not a clinically meaningful difference. Mean increase of BCVA was 1.8 lines in the verteporfin compared with 0.6 lines in the placebo group; a difference of 2 lines is considered clinically meaningful. No ocular or systemic adverse event was encountered.

In 2015, Zhao et al reported a double-masked, randomized, noninferiority trial with 131 patients that compared a 50% versus a 30% dose of verteporfin PDT for acute (<6 months) central serous chorioretinopathy. The 2 primary outcome measures were the proportion of eyes with complete absorption of subretinal fluid and the proportion of eyes with complete disappearance of fluorescein leakage at 6 and 12 months. The 30% dose did not achieve noninferiority. At 12 months, the proportion of eyes with complete absorption of retinal fluid was 75.4% in the 30% dose and 94.6% in the half-dose group \( (p=0.004) \). Complete disappearance of fluorescein leakage at 12 months was observed in 68.9% of the 30%-dose group versus 92.9% of the half-dose group \( (p=0.001) \). Visual acuity, a secondary outcome measure, improved from 20/32 to 20/20 in both groups, with a mean difference between the groups of 1.7 letters. In the 30%-dose group, 4 (6.6%) eyes lost 5 or more letters compared with 0 eyes in the half-dose group. This study, although of high methodologic quality, does not provide sufficient evidence of a functional benefit that would outweigh the potential risk of treatment with PDT for acute central serous chorioretinopathy.

**Chronic Central Serous Chorioretinopathy**

Ma et al (2014) conducted a systematic review of PDT for central serous chorioretinopathy. Included were 9 studies with a total of 319 patients (range, 16-67 patients). Six studies were prospective comparisons and 3 were randomized. Only 2 studies masked treatments. Meta-analysis found that PDT was more effective than laser photocoagulation and anti-VEGF medications in resolving subretinal fluid \( (p<0.01) \) and more rapid than anti-VEGF medications in decreasing central macular thickness \( (p<0.01) \). There was no significant difference between treatments for improving BCVA. Both half-dose and half-fluence PDT were effective for improving BCVA, decreasing central macular thickness, and resolving subretinal thickness compared with placebo.

Comparative treatment studies in the systematic review included a small, unblinded, randomized trial of low-fluence PDT versus intravitreal bevacizumab in 22 patients with chronic central serous chorioretinopathy, and a small randomized trial of 16 eyes with chronic or recurrent central serous chorioretinopathy comparing low-fluence PDT versus 3 monthly injections of ranibizumab. Also included were a prospective, multicenter, investigator-masked study that compared half-fluence PDT with conventional PDT in 42 eyes (42 patients) with chronic central serous chorioretinopathy, and a retrospective multicenter study of 60 patients with chronic central serous chorioretinopathy.

Use of reduced-dose verteporfin PDT for chronic central serous chorioretinopathy also has been reported. Uetani et al (2012) compared half-dose versus one-third dose PDT in a small \( (N=16 \text{ eyes}) \) prospective open-label trial. At 3 months, all 10
(100%) eyes in the half-dose PDT group and 2 (33%) eyes in the one-third-dose PDT group had complete resolution of subretinal fluid. Patients in the half-dose PDT group gained an average of 5.4 letters while patients in the one-third-dose group gained 1.7 letters (not significantly different). Chan et al (2008) also reported on reduced-dose verteporfin for the treatment of chronic central serous chorioretinopathy in a prospective series of 48 patients. Mean duration of central serous chorioretinopathy was 8.2 months (range, 3-40 months). At 12 months after PDT, mean BCVA improved from 0.31 to 0.15 logMAR, an improvement of 1.6 lines.

Section Summary: Central Serous Chorioretinopathy
Quality evidence on use of PDT for central serous chorioretinopathy is limited. The available evidence indicates substantial numbers of adverse events with standard PDT. Reduced-dose PDT may result in improved anatomic outcomes for acute central serous chorioretinopathy, but clinically significant improvements in visual acuity have not been shown for this self-limiting disease. For chronic central serous chorioretinopathy, recent comparative studies of reduced fluence and reduced dose PDT have suggested a beneficial effect of this treatment.

Polypoidal Choroidal Vasculopathy
Tang et al published a systematic review in 2015 evaluating treatment for polypoidal choroidal vasculopathy. PDT alone was compared to ranibizumab alone and to combination ranibizumab plus PDT. This review included 3 RCTs and 6 retrospective comparative studies. For PDT alone versus ranibizumab alone, 2 RCTs reported the weighted mean difference in visual acuity was 0.06 logMAR (95% CI, -0.01 to 0.12) in favor of ranibizumab alone, but this difference was not statistically significant. For combination therapy versus PDT alone, a single RCT reported that there was a nonsignificant weighted mean difference of -0.08 (95% CI, -0.20 to 0.04) in favor of combination therapy.

The 2010 systematic review by Chan et al included 30 studies on PDT in patients with polypoidal choroidal vasculopathy. Chan et al found numerous case series reporting favorable anatomic and visual acuity outcomes for patients treated with PDT. Also reported was an ongoing manufacturer-sponsored RCT of PDT as monotherapy or combined with ranibizumab for treatment of polypoidal choroidal vasculopathy.

This ongoing study randomized 31 patients with AMD and 10 patients with polypoidal choroidal vasculopathy to bevacizumab monotherapy or bevacizumab in combination with PDT. Bevacizumab was administered at 6-week intervals for the first 18 weeks, and then at 3-month intervals as needed. At 12 months, the monotherapy and combined treatment groups showed similar improvements in BCVA and central foveal thickness. Patients with polypoidal choroidal vasculopathy did not show significant improvement in BCVA (p=0.050) or central foveal thickness (p=0.088) when analyzed alone; however, the study was likely underpowered for this subset analysis.
EVEREST was a small, exploratory, multicenter, double-masked, randomized trial of verteporfin PDT, ranibizumab, or combination treatment in 61 treatment-naive Asian patients with polypoidal choroidal vasculopathy. Patients in the PDT monotherapy group (angio-occlusive) received sham ranibizumab, and patients in the ranibizumab monotherapy group (antiangiogenic and antipermeability) received sham PDT. The primary end point—proportion of patients with complete regression of polyps at 6 months—showed PDT alone (71.4%) or in combination with ranibizumab (77.8%) to be superior to ranibizumab monotherapy (28.6%) in achieving complete polyp regression. Mean improvement in BCVA was generally similar for the 3 groups (7.5 letters for PDT, 10.9 letters for combined treatment, 9.2 letters for ranibizumab alone). The proportion of patients gaining at least 15 letters was 19% in the PDT group, 21% in the combination group, and 33% in the ranibizumab monotherapy group. Interpretation of the visual acuity results is limited, because the study was not powered to assess differences in BCVA. There were no new safety findings.

Several nonrandomized studies from Asia have been reported. The largest is a prospective consecutive series of 220 eyes of 210 Japanese patients with polypoidal choroidal vasculopathy who were followed for 1 year after the primary PDT treatment. A single physician diagnosed, treated, and followed all patients (not masked). Retreatment was considered every 3 months based on the findings of examinations, and there was an average of 1.37 treatments. Fluid, exudates, and hemorrhages had resolved in 205 (93%) eyes at 1-year follow-up. Average visual acuity improved by more than 0.3 logMAR in 55 (25%) of eyes, remained stable in 143 (65%) of eyes, and decreased more than 0.3 logMAR in 21 (10%) of eyes. Stepwise logistic regression analysis showed that younger age, smaller greatest linear dimension, better baseline visual acuity, less baseline hemorrhage, and the presence of a serous macular detachment at baseline were independent predictors of improvement in visual acuity.

Akaza et al (2011) reported 3-year follow-up of 43 eyes (43 patients) treated with PDT for polypoidal choroidal vasculopathy. Before the initial PDT, 40 (93%) eyes exhibited polypoidal choroidal vasculopathy in the narrow sense, and 3 (7%) exhibited polypoidal CNV. Number of treatment sessions during follow-up ranged from 1 to 8. At 3-year follow-up, mean visual acuity decreased to below baseline. Polypoidal lesions recurred in 33 (77%) of the 43 eyes at 3 years, although the 3 eyes with polypoidal CNV showed little change except for enlargement and recurrence. Long-term visual outcomes following PDT showed a high frequency of recurrent polypoidal lesions, as well as enlargement and neovascular changes of abnormal vascular networks.

Kang et al (2013) reported 5-year follow-up of 42 eyes (36 patients) treated with PDT for polypoidal choroidal vasculopathy. Patients received a mean of 2.21 PDT treatments during the study, with additional intravitreal injections of anti-VEGF agents if exudative changes were observed. During follow-up, recurrence was observed in 33 (78.6%) eyes, and the mean number of anti-VEGF injections was 6.42 in eyes with recurrence. In the entire group, BCVA improved from 0.78 logMAR at baseline (20/120 Snellen equivalent) to 0.67 logMAR (20/93 Snellen
equivalent) at 5 years. Using a change of at least 0.3 logMAR as a threshold, BCVA improved in 14 (33.3%) eyes, remained stable in 23 (54.8%) eyes, and decreased in 5 (11.9%) eyes. Interpretation of the efficacy of PDT in this study is difficult, because all patients received combination treatment with intravitreal VEGF antagonists without comparison groups.

Kim and Yu (2011) conducted a retrospective review of 39 consecutive patients with polypoidal choroidal vasculopathy who received PDT monotherapy (before April 2007) or a combination of PDT and intravitreal bevacizumab (after April 2007). During 12 months of follow-up, patients in the monotherapy group (n=19) received a mean of 1.89 PDT applications, and patients in the combined therapy group (n=20) received a mean of 1.30 PDT applications and 2.90 bevacizumab injections. BCVA improved by 3.0 lines in the combined therapy group compared with 1.6 lines in the PDT monotherapy group. This level of improvement in BCVA was achieved in 55.0% in the combined therapy group and 36.8% in the monotherapy group.

Section Summary: Polypoidal Choroidal Vasculopathy
Available evidence on the efficacy of PDT for polypoidal choroidal vasculopathy consists of 2 small RCTs, a large number of case series and a retrospective comparative study. Controlled trials with a larger number of patients and longer follow-up are needed to permit conclusions regarding the efficacy of PDT (monotherapy or combined) compared with anti-VEGF therapy.

Choroidal Hemangioma
The 2010 systematic review by Chan et al included 11 case series on PDT in patients with choroidal hemangioma. PDT has been reported to induce complete and irreversible occlusion of the microvasculature, although this may require more than 1 treatment. Several case series demonstrated encouraging visual and anatomic outcomes in 150 patients with circumscribed choroidal hemangioma who were treated with various PDT regimens.

In 2010, Blasi et al reported 5-year outcomes from a prospective series of 25 consecutive patients with symptomatic choroidal hemangioma. Twenty-two (88%) patients received a single PDT session, and 3 eyes received a second PDT session. Follow-up examinations were performed 2 weeks, 1 month, 3 months, and every 6 months after treatment. All tumors with a reduction in size, and there were no recurrences through 5 years of follow-up. At 1 year, BCVA improved by an average of 18.2 letters. Visual acuity improved by 2 or more lines in 20 (80%) eyes and by 3 or more lines in 12 (48%) eyes. No treated eyes lost visual acuity between the 1- and 5-year follow-ups. Foveal center thickness decreased from a mean of 386.20 μm to 179.2 μm at 5 years, and there was resolution of macular exudation in all cases. No treatment-related adverse events were identified.

Angioid Streaks
The 2010 systematic review by Chan et al included 8 case series on PDT in 148 patients with angioid streaks. The authors concluded the PDT might limit or slow vision loss compared with the expected natural course of CNV due to angioid
streaks, but 1 study showed a decrease in visual acuity following PDT, and others showed that substantial proportions of patients continued to lose visual acuity. Thus, further studies are warranted to assess long-term safety and efficacy of PDT in these patients.

**Inflammatory Conditions**
The 2010 systematic review by Chan et al included 15 case reports of PDT in 115 patients with inflammatory eye conditions. Encouraging visual and anatomic outcomes have been reported with PDT for punctuate inner choroidopathy, choroiditis and toxoplasmic retinochoroiditis, and subfoveal CNV secondary to posterior uveitis. While promising, larger and comparative studies are needed to evaluate the effect of PDT on health outcomes for this indication. Therefore, PDT for inflammatory eye conditions is considered investigational.

**Ongoing and Unpublished Clinical Trials**
Some currently unpublished trials that might influence this review are listed in Table 1.

**Table 1. Summary of Key Trials**

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing</td>
<td>NCT02287298 Triple Combination Therapy of Choroidal Neovascularization in Exudative Age-related Macular Degeneration - a Cost Effect and Efficient Therapeutic Treatment</td>
<td>400</td>
<td>Dec 2015</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unpublished</td>
<td>NCT00433017 24-month Randomized, Double-masked, Controlled, Multicenter, Phase II Study Assessing Safety and Efficacy of Verteporfin Photodynamic Therapy Administered in Conjunction With Ranibizumab Versus Ranibizumab Monotherapy in Patients With Subfoveal Choroidal Neovascularization Secondary to AMD</td>
<td>255</td>
<td>Terminated (planned analyses)</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.
*a* Denotes industry-sponsored or cosponsored trial.

**Summary of Evidence**
The evidence for photodynamic therapy (PDT) in individuals who have CNV due to age-related macular degeneration (AMD), pathologic myopia, presumed ocular histoplasmosis, chronic central serous chorioretinopathy (CSC), or choroidal hemangioma includes randomized controlled trials (RCTs), nonrandomized comparative trials, and systematic reviews of controlled trials. Relevant outcomes are symptoms, change in disease status, functional outcomes, and quality of life. The RCT evidence supports the efficacy of PDT in reducing visual loss and decreasing retinal thickness. Comparative studies of PDT versus antivascular endothelial growth factor (anti-VEGF) medications have reported that anti-VEGF medications are as good as, and possibly superior to, PDT for reducing visual loss. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.
The evidence for PDT in individuals who have CNV due to polypoidal choroidal vasculopathy, angioid streaks, or inflammatory chorioretinal disease includes RCTs, nonrandomized comparative trials, and case series. Relevant outcomes are symptoms, change in disease status, functional outcomes, and quality of life. RCT evidence is limited for these conditions, and most published studies are case series. The case series have reported improved visual acuity following treatment, but this study design lacks sufficient methodologic rigor to allow conclusions. The evidence is insufficient to determine the effects of the technology on health outcomes.

The evidence for PDT in combination with anti-VEGF medications in individuals who have CNV of any etiology (eg, AMD, chronic CSC, choroidal hemangioma, pathologic myopia, presumed ocular histoplasmosis, choroidal vasculopathy, angioid streaks, inflammatory chorioretinal disease) includes RCTs, nonrandomized comparative studies, and systematic reviews of controlled trials. Relevant outcomes are symptoms, change in disease status, functional outcomes, and quality of life. RCTs of combination therapy have reported that PDT can decrease the number of anti-VEGF injections needed, but PDT is not associated with improved visual acuity compared to anti-VEGF alone. Some studies have reported that the change in visual acuity after PDT is noninferior, but others have found that it is inferior to anti-VEGF alone. Further research is needed to better determine the tradeoff between fewer anti-VEGF injections and possible reduction in visual acuity. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Supplemental Information**

**Clinical Input Received From 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 2 physician specialty societies and 2 academic medical centers while this policy was under review in 2012. The input agreed that PDT monotherapy is medically necessary for AMD, pathological myopia, presumed ocular histoplasmosis, central serous chorioretinopathy, and choroidal hemangioma. Input was mixed on the use of PDT for other ophthalmologic disorders. Clinical input agreed that PDT in combination with VEGF antagonists is investigational for all ophthalmologic disorders.
Practice Guidelines and Position Statements

American Academy of Ophthalmology
A 2015 Preferred Practice Patterns guideline on AMD from the American Academy of Ophthalmology describes PDT as a treatment option approved by the U.S. Food and Drug Administration for subfoveal lesions and predominantly classic CNV related to AMD.52

The 2015 update states that anti-VEGF therapies have become first-line therapy for treatment and stabilizing most cases of AMD. PDT is a less commonly used treatment for neovascular AMD; recommendations state that the following diagnoses are eligible for PDT treatment with verteporfin:

Macular CNV, new or recurrent where the classic component is >50% of the lesion, and ≤5400 µm in greatest linear diameter
• Occult CNV may be considered for PDT with vision <20/50 or if the CNV is <4 MPS [macular photocoagulation study] disc areas in size when the vision is >20/50
• Juxtafoveal CNV is an off-label indication for PDT but may be considered in select cases

National Institute for Health and Care Excellence
In September 2003, the U.K.’s National Institute for Health and Care Excellence (then the National Institute for Clinical Excellence) issued Technology Appraisal Guidance 68 on the use of PDT for AMD.53 Guidance 1.1 states that:

“Photodynamic therapy (PDT) is recommended for the treatment of wet age-related macular degeneration for individuals who have a confirmed diagnosis of classic with no occult subfoveal choroidal neovascularization (CNV) (that is, whose lesions are composed of classic CNV with no evidence of an occult component) and best-corrected visual acuity 6/60 or better. PDT should be carried out only by retinal specialists with expertise in the use of this technology.”

Canadian Agency for Drugs and Technologies in Health
In 2008, the Canadian Agency for Drugs and Technologies in Health (CADTH) released a health technology assessment on management of neovascular AMD.54 CADTH concluded that “…overall, the efficacy of anti-vascular endothelial growth factor (anti-VEGF) therapies over verteporfin (V-PDT) is well supported by (randomized controlled trials [RCTs]). What remains unclear is whether combination therapy (and which combinations) are superior or equal to monotherapy....”

U.S. Preventive Services Task Force Recommendations
Not applicable.
**Medicare National Coverage**

Since July 2001, use of ocular PDT has been covered by Medicare for the treatment predominantly classical subfoveal CNV (ie, occupies ≥50% of the area of the entire lesion) associated with AMD only when used in conjunction with verteporfin. However, there was no national Medicare coverage policy for other indications. In January 2004, Medicare found evidence to conclude that ocular PDT may be reasonable and necessary for patients with AMD with occult or minimally classic CNV 4 disk areas or less in size with evidence of progression within the 3 months prior to initial treatment. Medicare also reiterated that use of ocular PDT with verteporfin for indications such as pathologic myopia or presumed histoplasmosis syndrome may be eligible for coverage through individual contractor discretion.

**References**


31. Verteporfin in Photodynamic Therapy (VIP) Study Group. Photodynamic therapy of subfoveal choroidal neovascularization in pathologic myopia with verteporfin. 1-year results of a


**Billing Coding/Physician Documentation Information**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>67221</td>
<td>Destruction of localized lesion of choroid (eg, choroidal neovascularization); photodynamic therapy (includes intravenous infusion)</td>
</tr>
<tr>
<td>67225</td>
<td>Destruction of localized lesion of choroid (eg, choroidal neovascularization); photodynamic therapy, second eye, at single session (List separately in addition to code for primary eye treatment)</td>
</tr>
<tr>
<td>C9257</td>
<td>Injection, bevacizumab, 0.25 mg</td>
</tr>
<tr>
<td>J0178</td>
<td>Injection, aflibercept, 1 mg</td>
</tr>
<tr>
<td>J2503</td>
<td>Injection, pegaptanib sodium, 0.3 mg</td>
</tr>
<tr>
<td>J2778</td>
<td>Injection, ranibizumab, 0.1 mg</td>
</tr>
<tr>
<td>J3396</td>
<td>Injection, verteporfin, 0.1 mg</td>
</tr>
</tbody>
</table>

**ICD-10 Codes**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>C9257</td>
<td>Injection, bevacizumab, 0.25 mg</td>
</tr>
<tr>
<td>J0178</td>
<td>Injection, aflibercept, 1 mg</td>
</tr>
<tr>
<td>J2503</td>
<td>Injection, pegaptanib sodium, 0.3 mg</td>
</tr>
<tr>
<td>J2778</td>
<td>Injection, ranibizumab, 0.1 mg</td>
</tr>
<tr>
<td>J3396</td>
<td>Injection, verteporfin, 0.1 mg</td>
</tr>
</tbody>
</table>

**Additional Policy Key Words**

N/A

**Policy Implementation/Update Information**

10/1/00  New policy. Considered medically necessary.
10/1/01  Policy statement revised to include, “Photodynamic therapy is considered investigational for other ophthalmologic disorders, including, but not limited to, other types of choroidal neovascularization or choroidal neovascularization **not** associated with age-related macular
degeneration.”

10/1/02 Policy statement revised to clarify covered indications for Visudyne photodynamic therapy:
- Treatment of age related macular degeneration in patients with predominantly classic subfoveal CNV
- Treatment of predominantly classic subfoveal CNV due to pathologic myopia
- Treatment of predominantly classic subfoveal CNV ocular histoplasmosis

Policy statement revised to clarify investigational indications:
Visudyne photodynamic therapy is considered investigational for other ophthalmologic disorders, including, but not limited to, other types of choroidal neovascularization or choroidal neovascularization not associated with the above three conditions.

10/1/03 No policy statement changes.
10/1/04 No policy statement changes.

10/1/05 Policy statement revised for medical necessity indications:
- Photodynamic therapy may be considered medically necessary as a treatment of choroidal neovascularization associated with age-related macular degeneration, pathologic myopia, or presumed ocular histoplasmosis.

Policy statement revised for investigational indications:
- Photodynamic therapy is considered investigational for other ophthalmologic disorders, including choroidal neovascularization secondary to central serous chorioretinopathy.

10/1/06 No policy statement changes. Title changed from Photodynamic Therapy – Visudyne Therapy to Photodynamic Therapy for Subfoveal Choroidal Neovascularization.

10/1/07 No policy statement changes.
10/1/08 No policy statement changes.
10/1/09 The policy statement has been clarified with the addition of PDT as monotherapy and an additional statement that PDT in combination with anti-VEGF therapies is investigational for all ophthalmic disorders.

10/1/10 Policy statement revised to include medically necessary indications for choroidal neovascularization associated with age-related macular degeneration, pathologic myopia, or presumed ocular histoplasmosis.

10/1/11 No policy statement changes. “Subfoveal” deleted from policy title.
10/1/12 No policy statement changes.

6/1/13 PDT monotherapy considered medically necessary for central serous chorioretinopathy and choroidal hemangioma

10/1/13 No policy statement changes.
10/1/14 No policy statement changes.
10/1/15 No policy statement changes.
10/1/16 No policy statement changes.

State and Federal mandates and health plan contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in
determining eligibility for coverage. The medical policies contained herein are for informational purposes. The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents Blue KC and are solely responsible for diagnosis, treatment and medical advice. No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, photocopying, or otherwise, without permission from Blue KC.