



Kansas City

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Intraocular Radiation Therapy for Age-Related Macular Degeneration

Policy Number: 9.03.20
Origination: 9/2008

Last Review: 9/2014
Next Review: 9/2015

Policy

Blue Cross and Blue Shield of Kansas City (Blue KC) will not provide coverage for intraocular radiation therapy for age-related macular degeneration. This is considered investigational.

When Policy Topic is covered

Not Applicable

When Policy Topic is not covered

Intraocular placement of a radiation source for the treatment of choroidal neovascularization is considered **investigational**.

Intraocular proton beam therapy for the treatment of choroidal neovascularization is considered **investigational**.

Stereotactic radiation therapy for the treatment of choroidal neovascularization is considered **investigational**.

Description of Procedure or Service

Epiretinal radiation describes the intraocular administration of radiation to the choroidal vascular bed of the retina to treat age-related macular degeneration (AMD).

Background

Age-related macular degeneration (AMD) is characterized in its earliest stages by minimal visual impairment and the presence of large drusen and other pigmentary abnormalities on ophthalmoscopic examination. Two 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 may be a precursor of the more visually impairing exudative neovascular form, also referred to as disciform or wet AMD. The wet form is distinguished from the atrophic form by the development of choroidal neovascularization (CNV) and serous or hemorrhagic detachment of the retinal pigment epithelium. Risk of developing severe irreversible loss of vision is greatly increased by the presence of CNV.

The NeoVista Epi-Rad90™ Ophthalmic System has been developed to treat CNV by focal delivery of radiation to a subfoveal choroidal neovascular lesion. Using a standard vitrectomy procedure, the cannula tip of a handheld (pipette-like) surgical device is inserted into the vitreous cavity and positioned under visual guidance over the target lesion. The radiation source (strontium-90) is advanced down the cannula until it reaches the tip, which is then held in place over the lesion for a “prescribed” time to deliver focused radiation. The system is designed to deliver a one-time peak dose of beta particle energy (24 Gy) for a target area 3 mm in depth and up to 5.4 mm in diameter. This is believed to be below the dose that is toxic to the retina and optic nerve, and radiation exposure outside of the target area is expected to be minimal.

Other Treatments for AMD

Other available therapeutic options for AMD not addressed in this policy include photodynamic therapy and vascular endothelial growth factor (VEGF) antagonists or angiostatics. These may be administered alone or in combination. Angiostatic agents target various points in the pathway leading to new blood vessel formation (angiogenesis): messenger RNA, VEGFs, and endothelial cell proliferation; migration; and proteolysis. Pegaptanib (Macugen®, Eyetech and Pfizer), ranibizumab (Lucentis™, Genentech) and aflibercept (Eylea™, Regeneron Pharmaceuticals) are approved by the U.S. Food and Drug Administration (FDA) for use in AMD. Bevacizumab (Avastin, Genentech) has been used off label to treat AMD.

For those whose visual losses impair their ability to perform daily tasks, low-vision rehabilitative services offer resources to compensate for deficits. Another treatment for AMD that is considered investigational is addressed in a separate policy (transpupillary thermotherapy).

Regulatory Status

An investigational device exemption (IDE) has been granted by the U.S. Food and Drug Administration (FDA) for a Phase III multicenter trial to provide data for application to the FDA; this is a category B procedure

Rationale

This policy was created in 2008 and has since been periodically updated with literature searches using the MEDLINE database. The most recent literature search was performed through January 2, 2014.

A search of the MEDLINE database when this policy was created did not identify any peer-reviewed publications on epiretinal radiation. The original search did identify some older randomized trials using external beam radiotherapy for age-related macular degeneration (AMD)-associated choroidal neovascularization. Little to no benefit in visual acuity was observed following repeated single treatments of 2 Gy to a total of 12 to 20 Gy.(1,2)

Proton Beam

The potential use of proton-beam focal epiretinal radiation for management of choroidal neovascularization was described in 2011 using choroidal endothelial cells for an in vitro dose-response study.(3) The investigators noted that, given the radiation complications reported in clinical trials (including radiation retinopathy), further study is needed to test the differential toxicity of proton beam therapy in choroidal endothelial, retinal ganglion, and pigment epithelial cells.

In 2012, Park et al reported 12- to 36-month follow-up of a pilot study of ranibizumab combined with proton beam irradiation for AMD.(4) Six eyes (6 patients) were treated with 4 monthly combined ranibizumab and 24-Gy proton beam irradiation, followed by ranibizumab treatment if needed. No radiation retinopathy was observed at follow-up. A randomized trial of the combination treatment is in progress.

Stereotactic Radiotherapy

INTREPID is a randomized sham-controlled double-masked trial with 230 patients that assessed the efficacy and safety of stereotactic radiotherapy (SRT) to treat neovascular AMD.(5) Both SRT and sham-control patients received ranibizumab as needed. After 1 year, treatment with either 16-Gy or 24-Gy SRT reduced the number of ranibizumab treatments (median of 2 vs 3.5 for sham-controls) with no significant differences from control in changes in

visual acuity over the 1-year of follow-up. There were no safety concerns identified in the first 12 months; safety follow-up is continuing.

EPI-RAD90™

CABERNET (NCT00454389) is a phase III multicenter, randomized controlled study that enrolled 494 subjects with AMD-related wet choroidal neovascularization (CNV) from 42 sites.(6,7) The safety and efficacy of epiretinal radiation therapy combined with 2 loading injections of ranibizumab (Lucentis®) was compared with ranibizumab monotherapy (2 loading doses and then quarterly). Patients in both arms of the study could receive monthly treatment with ranibizumab as needed. At 24 months, 77% of the patients in the EPI-RAD90™ group lost fewer than 15 letters compared with 90% of the control group. This did not meet the prespecified noninferiority margin. EPI-RAD90™ treatment also did not meet the superiority end point, which was the proportion of participants gaining more than 15 letters (16% vs 26% for the ranibizumab group). The most common serious adverse event was cataract surgery (known to be associated with vitrectomy), which occurred in 40% of the EPI-RAD90™ group compared with 11% of the ranibizumab group. Mild radiation retinopathy occurred in 3% of the EPI-RAD90™ patients. This study does not support the use of epiretinal radiation therapy.

Twelve- and 24-month results from the multicenter MERITAGE study (NCT00809419) were reported in 2012 and 2013.(8-10) MERITAGE was a phase I/II study of the EPI-RAD90™ for the treatment of subfoveal CNV associated with wet AMD in patients requiring continued anti-vascular endothelial growth factor (VEGF) therapy to maintain an adequate response. Following a single 24-Gy dose, the 53 patients in the study received retreatment with ranibizumab administered monthly (as needed). At 12-month follow-up, 81% of patients maintained stable vision (loss of fewer than 15 letters) with a mean of 3.49 anti-VEGF injections (0.29 per month). This was compared with 0.45 injections per participant per month in the 12 months before the study. Over 24 months, 68% of patients maintained stable vision with a mean of 8.7 anti-VEGF injections (0.72 per month), which was not less than the number of injections required in the 12 months before treatment.

Three publications from 2 studies have been reported by Avila et al on epiretinal radiation using the EPI-RAD90™ system.(11-13) One report described 12-month safety and visual acuity results of a feasibility study in 34 treatment-naïve patients from Turkey, Mexico, and Brazil recruited between February 2005 and February 2006.(11) The second report described 12-month safety and visual acuity results from 24-Gy epiretinal radiation combined with bevacizumab in 34 treatment-naïve patients enrolled between June 2006 and April 2007.(12) Adverse events related to the device or procedure included subretinal hemorrhage (n=1), retinal tear (n=1), subretinal fibrosis (n=2), epiretinal membrane (n=1), and cataract (6 of 24; 24 patients were phakic at baseline). All occurrences of cataracts were deemed to be related to the vitrectomy procedure. Two- and 3-year results from this trial were published in 2012.(13) All 34 subjects were followed up for 24 months; 1 site that enrolled 19 patients agreed to re-consent and follow-up the patients for 3 years. On average, the cohort of subjects followed for 36 months received 3.0 bevacizumab injections.

Twelve of the 24 phakic patients (50%) developed cataracts, and 4 had phacoemulsification with intraocular lens implantation. The mean change in visual acuity at 36 months was +3.9 letters. Seven of 13 phakic patients (54%) developed cataracts, and 4 had phacoemulsification with intraocular lens implantation. One case of nonproliferative radiation retinopathy was observed at 36 months of follow-up.

A search of online site www.ClinicalTrials.gov in January 2014 identified the following studies:

NCT00679445 – This is a phase II feasibility study to evaluate the safety and tolerability of the EPI-RAD90™ system, combined with an injection of ranibizumab (Lucentis®), in patients with AMD who have failed primary anti-VEGF therapy. This study has closed recruiting (from 2 sites in the United States) with a projected enrollment of 20 subjects with AMD-related wet CNV and is listed as completed as of July 2011. No results have been posted.

NCT01006538 – This is a multicenter Phase IV randomized controlled trial of macular epiretinal brachytherapy (VIDION® system by NeoVista) versus Lucentis [ranibizumab]-only treatment (MERLOT). The trial is sponsored by King's College Hospital National Health Service Trust in the United Kingdom and targets patients who require frequent injections of ranibizumab to try to reduce or eliminate the need for ongoing, regular eye injections. The active control group will continue to receive intravitreal injections of ranibizumab on a monthly basis as required. Twenty-nine sites in the United Kingdom will participate. The study has an estimated enrollment of 363 patients with study completion expected in November 2014.

Summary

Intraocular radiation describes the administration of radiation to the choroidal vascular bed of the retina to treat age-related macular degeneration (AMD). No intraocular radiation devices have been approved by the Food and Drug Administration for the treatment of AMD. A randomized controlled trial has been published that evaluated epiretinal radiation therapy with the EPI-RAD90™. This treatment did not attain noninferiority for visual outcomes and was associated with a high proportion of adverse events.

A randomized sham-controlled trial of stereotactic radiotherapy (SRT) in patients with neovascular AMD found a reduction in the number of ranibizumab treatments over the first 12 months, but no significant differences compared with control in changes in visual acuity. Longer term follow-up is needed to evaluate safety and to determine whether the modest benefit of SRT extends beyond the first 12 months. Due to the limited evidence base and lack of regulatory approval, intraocular radiation for the treatment of AMD is considered investigational.

Practice Guidelines and Position Statements

The 2011 guidance from the United Kingdom's National Institute for Health and Clinical Excellence states that current evidence on the efficacy of epiretinal brachytherapy for wet AMD is inadequate and limited to small numbers of patients. With regard to safety, vitrectomy has well-recognized complications, and there is a possibility of subsequent radiation retinopathy. Therefore this procedure should only be used in the context of research.(14)

References

1. A prospective, randomized, double-masked trial on radiation therapy for neovascular age-related macular degeneration (RAD Study). Radiation therapy for age-related macular degeneration. *Ophthalmology* 1999; 106(12):2239-47.
2. Stevenson MR, Hart PM, Chakravarthy U et al. Visual functioning and quality of life in the SubFoveal Radiotherapy Study (SFRADS): SFRADS report 2. *Br J Ophthalmol* 2005; 89(8):1045-51.

3. Chalam KV, Balaiya S, Malyappa RS et al. Evaluation of choroidal endothelial cell proliferation after exposure to varying doses of proton beam radiation. *Retina* 2011; 31(1):169-76.
4. Park SS, Daftari I, Phillips T et al. Three-year follow-up of a pilot study of ranibizumab combined with proton beam irradiation as treatment for exudative age-related macular degeneration. *Retina* 2012; 32(5):956-66.
5. Jackson TL, Chakravarthy U, Kaiser PK et al. Stereotactic radiotherapy for neovascular age-related macular degeneration: 52-week safety and efficacy results of the INTREPID study. *Ophthalmology* 2013; 120(9):1893-900.
6. Dugel PU, Bebchuk JD, Nau J et al. Epimacular brachytherapy for neovascular age-related macular degeneration: a randomized, controlled trial (CABERNET). *Ophthalmology* 2013; 120(2):317-27.
7. Jackson TL, Dugel PU, Bebchuk JD et al. Epimacular brachytherapy for neovascular age-related macular degeneration (CABERNET): fluorescein angiography and optical coherence tomography. *Ophthalmology* 2013; 120(8):1597-603.
8. Dugel PU, Petrarca R, Bennett M et al. Macular epiretinal brachytherapy in treated age-related macular degeneration: MERITAGE study: twelve-month safety and efficacy results. *Ophthalmology* 2012; 119(7):1425-31.
9. Petrarca R, Dugel PU, Nau J et al. Macular epiretinal brachytherapy in treated age-related macular degeneration (MERITAGE): month 12 optical coherence tomography and fluorescein angiography. *Ophthalmology* 2013; 120(2):328-33.
10. Petrarca R, Dugel PU, Bennett M et al. Macular epiretinal brachytherapy in treated age-related macular degeneration (MERITAGE): Month 24 safety and efficacy results. *Retina* 2013.
11. Avila MP, Farah ME, Santos A et al. Twelve-month safety and visual acuity results from a feasibility study of intraocular, epiretinal radiation therapy for the treatment of subfoveal CNV secondary to AMD. *Retina* 2009; 29(2):157-69.
12. Avila MP, Farah ME, Santos A et al. Twelve-month short-term safety and visual-acuity results from a multicentre prospective study of epiretinal strontium-90 brachytherapy with bevacizumab for the treatment of subfoveal choroidal neovascularisation secondary to age-related macular degeneration. *Br J Ophthalmol* 2009; 93(3):305-9.
13. Avila MP, Farah ME, Santos A et al. Three-year safety and visual acuity results of epimacular 90strontium/90yttrium brachytherapy with bevacizumab for the treatment of subfoveal choroidal neovascularization secondary to age-related macular degeneration. *Retina* 2012; 32(1):10-8.
14. National Institute for Health and Clinical Excellence. IPG415 Epiretinal brachytherapy for wet age related macular degeneration: guidance. 2011. Available online at: <http://guidance.nice.org.uk/IPG415/Guidance/pdf/English>

Billing Coding/Physician Documentation Information

0190T Placement of intraocular radiation source applicator (List separately in addition to primary procedure)

67036 Vitrectomy, mechanical, pars plana approach;

CPT code 0190T is to be used in conjunction with 67036 (Vitrectomy, mechanical, pars plana approach).

CPT code 0190T differs from code 67218 (destruction of localized lesion of the retina (e.g., macular edema, tumors), one or more sessions; radiation by implantation of source) because the radiation source is not implanted.

Additional Policy Key Words

N/A

Policy Implementation/Update Information

9/1/08	New policy; considered investigational.
9/1/09	No policy statement changes.
9/1/10	No policy statement changes.
9/1/11	No policy statement changes.
9/1/12	No policy statement changes.
9/1/13	Investigational statement added on proton beam therapy and title changed from "Epiretinal Radiation Therapy..." to "Intraocular Radiation Therapy..."
9/1/14	Investigational statement added regarding stereotactic radiation therapy.

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