BlueCross BlueShield of Alabama

Name of Policy:

Transpupillary Thermotherapy (TTT) for Treatment of Choroidal Neovascular Conditions

Policy #: 079
Category: Surgery

Latest Review Date: February 2014
Policy Grade: C

Background/Definitions:

As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

1. *The technology must have final approval from the appropriate government regulatory bodies;*
2. *The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;*
3. *The technology must improve the net health outcome;*
4. *The technology must be as beneficial as any established alternatives;*
5. *The improvement must be attainable outside the investigational setting.*

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

1. *In accordance with generally accepted standards of medical practice; and*
2. *Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient's illness, injury or disease; and*
3. *Not primarily for the convenience of the patient, physician or other health care provider; and*
4. *Not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.*

Description of Procedure or Service:

Transpupillary thermotherapy (TTT) is a technique in which low level heat is delivered through the pupil using a modified diode laser. TTT is designed to gently heat subfoveal choroidal lesions while limiting damage to the overlying retinal pigment epithelium.

Age-related Macular Degeneration (AMD)

Choroidal neovascularization (CNV) is a common cause of adult-onset blindness, most commonly associated with age-related macular degeneration (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, two distinctively different forms of degeneration may be observed. The first, called the atrophic, 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 choroidal neovascularization (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 composed of only occult CNV, suggesting that the proliferative response that obscures new vessels may also favorably alter the clinical course of AMD.

There is ongoing research interest in the use of transpupillary thermotherapy to treat subfoveal choroidal neovascularization with an “occult” angiographic pattern. Transpupillary thermotherapy (TTT) is a technique in which heat is delivered to the choroid and retinal pigment epithelium through the pupil using a modified diode laser. This laser technique contrasts with the laser used in standard photocoagulation therapy in that TTT uses a lower power laser for more prolonged periods of time and is designed to gently heat the choroidal lesion, thus limiting damage to the overlying retinal pigmented epithelium. It has been used to treat choroidal melanomas.

Other Treatments for CNV Secondary to AMD

Laser photocoagulation has been used to treat CNV; however, patients with subfoveal lesions are generally not candidates for this treatment due to the risk of an immediate reduction in central vision, outweighing any treatment advantage. Photocoagulation of macular drusen is addressed in BCBSAL policy #197, Photocoagulation of Macular Drusen.

Photodynamic therapy (see BCBSAL policy #047, Photodynamic Therapy) has been used with success in treating subfoveal CNV; the treatment has shown the greatest success in treating

patients with classic CNV (as opposed to occult CNV), as defined angiographically. Photodynamic therapy, as a treatment of CNV, uses a nonthermal laser designed to activate verteporfin, the photosensitizing agent.

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 three 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 Choroidal Neovascular Conditions
Other choroidal neovascular conditions include pathologic myopia, presumed ocular histoplasmosis syndrome, angioid 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.

Policy:

Transpupillary Thermotherapy (TTT) does not meet Blue Cross and Blue Shield of Alabama's medical criteria for coverage for the treatment of choroidal neovascularization secondary to ocular conditions, including but not limited to age-related macular degeneration and is considered **investigational.**

Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administers benefits based on the member's contract and corporate medical policies. Physicians should always exercise their best

medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

Key Points:

At the time this policy was created, there were minimal published data regarding TTT. Published evidence through 2005 consisted primarily of uncontrolled case series and in 2005. A TEC Special Report on the treatment of AMD noted that TTT, when used alone, had not been shown to be efficacious. Subsequently, this policy has been updated periodically with searches of the MEDLINE database. The most recent literature update was performed through January 16, 2014. Following is a summary of key studies to date.

Transpupillary Thermotherapy versus Sham

In a presentation at the American Academy of Ophthalmology meeting in October 2004, in New Orleans, Iridex Corporation announced preliminary results of the TTT4 CNV study. The TTT4 CNV study is a nationwide study involving 22 centers that began in March 2000. A total of 336 patients with symptomatic occult CNV that show signs of exudation were to be recruited. Two thirds of eyes would be treated and one third would receive sham treatment. Patients would be followed up for two years. Iridex-reported preliminary results did not show TTT for CNV resulted in significant benefit over sham treatment. Forty-seven percent of 303 patients who received TTT for CNV had modest or severe visual loss after two years, compared with 43% in those who received sham treatment. To date, results of this trial have not been published.

Two small randomized trials (28 and 25 patients) from 2005 and 2006 reported no benefit of TTT in preventing further visual loss in patients with occult CNV who were not candidates for PDT.

TTT versus PDT

The largest published controlled trial randomly assigned 98 patients with occult CNV to TTT (136 mW/mm) with sham PDT (n=52), or to PDT with sham TTT (n=46). Retreatment was given if leakage was documented by fluorescein angiography (follow-up of 6, 12, 18, 24, 36, and 48 weeks). With a mean of 3.0 treatments in the TTT group and 2.3 treatments in the PDT group, a similar percentage of patients had lost fewer than 15 letters at 12 months (75% for TTT and 74% for PDT). There were nonsignificant trends for a larger percentage of patients to have preserved or improved best corrected visual acuity in the TTT group (37%) than in the PDT group (24%) and to have less of a decrease in foveal thickness (15% vs 24%). Patient-reported visual function from this trial was reported in 2010. Outcomes on the National Eye Institute Visual Function Questionnaire 25 were similar in patients treated with TTT (change of +1.2) or PDT (change of +0.7) at 12 months, but the study was underpowered to detect differences in this outcome measure.

In a controlled trial from Asia, patients chose PDT or TTT after an explanation of the costs, benefits, and risks of each treatment. Sixteen patients (16 eyes) selected PDT, and 14 patients (16 eyes) selected TTT; treatments were repeated if dye leakage was evident at follow-up. The average pretreatment visual acuity was similar in the two groups. At six months' follow-up, loss of visual acuity was 15 letters or less in 14 (87%) eyes treated with TTT and in 13 (81%) eyes

treated with PDT; however, more patients with good initial visual acuity (20/63 or greater) had a loss of two or more lines following TTT (4 of 4), than following PDT (1 of 6). Although the authors concluded that patients with good initial visual acuity should be treated with PDT, the study is limited by selection bias and small subject number. The authors of this study and another report from Asia indicated that the rationale for using TTT was the lower cost of this treatment in comparison with PDT.

In 2012, Nowak et al reported on 222 eyes with AMD treated with TTT, 100 eyes treated with PDT, and 104 eyes treated with intravitreal bevacizumab. Assignment into the three groups was based on the angiographic appearance of CNV, and patients who did not meet criteria for the randomized comparison of bevacizumab and PDT were treated with TTT. Following treatment with TTT, there was a mean decline of visual acuity 0.05 log MAR, compared with a decline of 0.12 log MAR following PDT and improvement of 0.03 logMAR following treatment with intravitreal bevacizumab. Out of the 222 eyes treated with TTT, visual acuity improved in 14.9%, remained unchanged in 64.4%, and was reduced in 20.7%. This study is limited by selection bias and differences in baseline visual acuity in the three groups.

TTT Combined with Intravitreal Ranibizumab

In a 2012 report, Soderberg et al randomized 100 patients with neovascular AMD to low-dose TTT and intravitreal ranibizumab or to sham TTT and intravitreal ranibizumab. At 24-month follow-up (78 patients), quarterly TTT was found to decrease the mean number of ranibizumab injections from 8.0 to 6.3 with no significant difference between the sham and active TTT groups in best corrected visual acuity (+4.0 vs +0.9, respectively). Thus, 7 quarterly treatments with TTT resulted in a mean reduction of 1.7 ranibizumab injections. It was not described whether the investigator who determined if the patient met retreatment criteria was masked to treatment allocation. Masked evaluation found no significant difference between the sham and active TTT groups in central retinal thickness (-49.9% vs -36.4%) or lesion area (-0.3% vs -10.6%, both respectively).

Other

One randomized (not masked) study of 26 patients from 2005 did not find a statistically significant improvement for combination treatment with triamcinolone and TTT in comparison with TTT alone.

Four nonrandomized studies of TTT in eyes with CNV related to AMD were identified from 2003 and 2004. The largest series is from Nagpal et al, who reported on TTT for CNV in 160 eyes (99 classic and 61 occult) of patients of Indian descent. The authors reported that in eyes with classic CNV, 29.3% improved, 39.4% stabilized, and 31.3% deteriorated at 12-month follow-up. In occult CNV, 19.6% improved, 57.4% stabilized, and 22.9% deteriorated. Nagpal et al concluded that there was effectiveness with TTT in Indian eyes, which responded to lower energy levels than did Caucasian eyes in their experience.

In 2011, Peyman et al reported treatment of a small series of patients (n=4) with peripapillary CNV that was recalcitrant to other treatments, including intravitreal angiostatic agents. These investigators used a variation of TTT with indocyanine green dye as a thermal enhancing agent, which permitted use of a lower energy level (oscillatory thermotherapy). The photodynamic

treatment was combined with bevacizumab and intravitreal dexamethasone, and visual acuity was found to remain stable (1 of 4 improved visual acuity) at a mean 12-month follow-up. Small case series from Asia describe the use of TTT for central serous chorioretinopathy and choroidal hemangioma.

Adverse Events
A case series reported macular burn as a complication of TTT in 8.6% of 35 patients available for follow-up.

Questions have been raised about the potential harms of this treatment if given at higher intensity, while Peyman et al note that a major limitation of TTT is the inability to titrate the energy level and subsequently control both the rate and the total amount of temperature rise during the procedure.

Summary
TTT is a technique in which low-level heat is delivered through the pupil using a modified diode laser. TTT is designed to gently heat subfoveal choroidal lesions while limiting damage to the overlying retinal pigment epithelium. Evidence on TTT is limited. The available studies comparing TTT with sham have not shown a benefit of this procedure. Although trials comparing TTT to PDT show similar outcomes for the 2 treatments, there may be an increase in adverse events with TTT. TTT has not been compared with angiogenesis inhibitors. Evidence is insufficient to determine whether TTT is as beneficial as the established alternative; this procedure is considered investigational.

Practice Guidelines and Position Statements
Recent practice guidelines on treatment of age-related macular degeneration from the American academy of Ophthalmology (AAO) do not mention TTT. In the 2006 Preferred Practice Patterns the AAO indicated that there was insufficient evidence to guide treatment recommendations for TTT. Preferred Practice Patterns from 2008 and 2011 and the AAO's 2013 Summary Benchmark do not describe TTT as a treatment option.

Key Words:
Transpupillary thermotherapy (TTT), choroidal neovascularization (CNV), age-related macular degeneration (ARMD)

Approved by Governing Bodies:
IRIS Medical® OcuLight® SLx Infrared Laser Photocoagulator-FDA approved May 2002

Benefit Application:
Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.
ITS: Home Policy provisions apply
BellSouth/AT&T contracts: Considers investigational

FEP contracts: FEP does not consider investigational and will be reviewed for medical necessity

Current Coding:

CPT codes:

67299	Unlisted procedure, posterior segment. **(Effective 01/01/2011)**

Previous Codes:

CPT Codes:

0016T	Destruction of localized lesion of choroid, (e.g., choroidal neovascularization) transpupillary thermotherapy **(Deleted 01/01/2011)**

References:

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Policy History:

Medical Policy Group, November 2002
Medical Policy Administration Committee, November 2002
Available for comment December 18, 2002-February 3, 2003
Medical Policy Group, November 2003
Medical Policy Group, November 2005 **(1)**

Medical Policy Group, November 2007 **(1)**
Medical Policy Group, February 2009 **(1)**
Medical Policy Group, February 2010 **(1):** Key Points added
Medical Policy Group, December 2010; 2011 Code updates
Medical Policy Group, June 2011; Updated Key Points & References
Medical Policy Group, February 2012 **(1):** Update to Description, Key Points and References related to MPP update; no change in policy statement.
Medical Policy Panel, February 2013
Medical Policy Group, February 2013 **(3)**: Update to Title, Description, Policy Statement clarification – secondary conditions, Key Points and References
Medical Policy Panel, February 2014
Medical Policy Group, February 2014 **(1):** Update to Key Points and References; no change to policy statement;
