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Ophthalmic Technology Assessment

Therapies for Macular Edema Associated with Branch Retinal Vein Occlusion

A Report by the American Academy of Ophthalmology

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Purpose: To evaluate the available evidence on the ocular safety and efficacy of current therapeutic alternatives for the management of macular edema (ME) secondary to branch retinal vein occlusion (BRVO).

Methods: Literature searches were last conducted on January 31, 2017, in PubMed with no date restrictions and limited to articles published in English, and in the Cochrane Database without language limitations. The searches yielded 321 citations, of which 109 were reviewed in full text and 27 were deemed appropriate for inclusion in this assessment. The panel methodologist assigned ratings to the selected studies according to the level of evidence.

Results: Level I evidence was identified in 10 articles that addressed anti-vascular endothelial growth factor (VEGF) pharmacotherapies for ME, including intravitreal bevacizumab (5), aflibercept (2), and ranibizumab (4). Level I evidence was identified in 6 studies that examined intravitreal corticosteroids, including triamcinolone (4) and the dexamethasone implant (2). Level I evidence also was available for the role of macular grid laser photocoagulation (7) and scatter peripheral laser surgery (1). The inclusion of level II and level III studies was limited given the preponderance of level I studies. The number of studies on combination therapy is limited.

Conclusions: Current level I evidence suggests that intravitreal pharmacotherapy with anti-VEGF agents is effective and safe for ME secondary to BRVO. Prolonged delay in treatment is associated with less improvement in visual acuity (VA). Level I evidence also indicates that intravitreal corticosteroids are effective and safe for the management of ME associated with BRVO; however, corticosteroids are associated with increased potential ocular side effects (e.g., elevated intraocular pressure, cataracts). Laser photocoagulation remains a safe and effective therapy, but VA results lag behind the results for anti-VEGF therapies. *Ophthalmology 2017;■:1–12 © 2017 by the American Academy of Ophthalmology*

The American Academy of Ophthalmology prepares Ophthalmic Technology Assessments to evaluate new and existing procedures, drugs, and diagnostic and screening tests. The goal of an Ophthalmic Technology Assessment is to review systematically the available research for clinical efficacy and safety. After review by members of the Ophthalmic Technology Assessment Committee, relevant subspecialty societies, and legal counsel, assessments are submitted to the Academy's Board of Trustees for consideration as official Academy statements. The purpose of this study by the Ophthalmic Technology Assessment Committee Retina/Vitreous Panel is to review the evidence on the safety and efficacy of current therapies for macular edema (ME) associated with branch retinal vein occlusion (BRVO).

Background

Branch retinal vein occlusion is a common retinal vascular condition that may result in significant visual loss. Clinical features may include sectoral retinal hemorrhages, dilated and tortuous retinal vessels, and cotton-wool spots in the distribution of the occluded vein. Branch retinal vein occlusion is an occlusion of a major branch retinal vein draining 1 quadrant of the retina, a macular branch vein draining the macula, or a peripheral branch vein draining a portion of the retina. Macular edema and macular ischemia are leading causes of visual loss in BRVO and are seen more frequently when a major branch retinal vein is involved. Additional sequelae of BRVO include neovascularization, vitreous hemorrhage, epiretinal membrane, and traction retinal detachment.

The prevalence of BRVO increases with age and varies with race and ethnicity. A pooled analysis of 68 751 individuals for BRVO demonstrated 4.42 cases per 1000 individuals.[1] The pathogenesis of BRVO is thought to involve both retinal vein compression by the corresponding retinal arteriole and damage to the vessel wall, leading to thrombus formation.[2] Vascular occlusion results in increased intraluminal venous pressure and subsequent retinal hemorrhage and capillary dropout.

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Capillary dropout, hypoxia, and local inflammation result in an upregulation of proinflammatory cytokines.[3] Vascular endothelial growth factor (VEGF) is a key upregulated protein in BRVO. This protein has complex interactions with the immune system; it produces local inflammation, and the vascular endothelial cells then stimulate increased vascular permeability and induce vascular endothelial cell proliferation.[3,4]

Although multiple factors play a role in vision loss resulting from BRVO, the most common cause is ME. Other factors that may contribute to vision loss include macular ischemia, neovascular complications (e.g., neovascularization of the disc or retina causing vitreous hemorrhage or neovascular glaucoma), and traction retinal detachment. Over the last few decades, therapy directed at ME associated with BRVO has evolved significantly. In the early 1980s, the National Eye Institute sponsored one of the early landmark therapeutic trials for BRVO that focused on macular grid laser photocoagulation.[5]

The pharmacologic era began with the use of corticosteroid therapies. Corticosteroids inhibit numerous local inflammatory modulators, including VEGF, and may decrease edema through stabilization of vascular permeability.[6] Multiple formulations have been examined, including triamcinolone and dexamethasone (OZURDEX, Allergan, Inc., Irvine, CA). Intravitreal triamcinolone (IVTA) has been used off-label in multiple formulations to treat ME secondary to BRVO. The intravitreal dexamethasone sustained-release implant has been approved by the U.S. Food and Drug Administration (FDA) for the management of ME secondary to BRVO.[7]

More recently, anti-VEGF therapies have become some of the most frequently used therapeutics for ME in the setting of BRVO. Four anti-VEGF medications have been evaluated, including ranibizumab (Lucentis, Genentech, Inc., South San Francisco, CA), aflibercept (VTE, EYLEA, Regeneron Pharmaceuticals, Inc., Tarrytown, NY), bevacizumab (AVASTIN, Genentech, Inc., South San Francisco, CA), and pegaptanib sodium (MACUGEN, Valeant Pharmaceuticals International, Inc., Bridgewater, NJ).[8–11] Ranibizumab (48 kDa) is a recombinant humanized immunoglobulin G1 kappa isotype antibody fragment that binds all isoforms of VEGF-A and is FDA approved for the treatment of ME secondary to BRVO.[10] Aflibercept (115 kDa) is a recombinant fusion protein consisting of the VEGF extracellular binding domains of the human VEGF receptors 1 and 2 fused to the Fc domain of human immunoglobulin-G1 and is FDA approved for the treatment of ME secondary to BRVO. In addition to binding VEGF, aflibercept also binds placental growth factors 1 and 2.[12] Bevacizumab (149 kDa) is a full-length humanized monoclonal immunoglobulin-G1 antibody that binds all isoforms of VEGF-A.[11] Unlike the first 3 VEGF inhibitors that bind all isoforms of VEGF-A, pegaptanib is a selective antagonist that binds to the 165 isoform of VEGF.[8,9] Neither bevacizumab nor pegaptanib is FDA approved for the treatment of ME secondary to BRVO, and their use is off label.

In addition to pharmacotherapy, other approaches that have been explored for the treatment of BRVO include laser-induced chorioretinal anastomosis and pars plana vitrectomy, to separate the common adventitia of the crossing artery and vein, to cannulate the vein, and to remove the cortical vitreous and internal limiting membrane (ILM).[13–15] These treatments may address different mechanisms related to the sequelae of BRVO, including potentially improving blood flow and oxygenation.

Resource Requirements

Approximate costs for current anti-VEGF medications are $1950 per dose for ranibizumab, $1850 per dose for aflibercept, and less than $50 per dose for bevacizumab. However, bevacizumab requires compounding for administration. The 2015 Medicare reimbursement for anti-VEGF therapeutics is approximately $1967 for ranibizumab 0.5 mg, $1961 for aflibercept 2 mg, and $17 for bevacizumab. The dexamethasone implant cost is approximately $800. Preservative-free triamcinolone 40 mg/ml suspension (TRIESENCE, Alcon Laboratories, Inc., Fort Worth, TX) costs approximately $134 per dose and is reimbursed by Medicare at $148. The 2015 Medicare Physician Fee Schedule reimbursement for intravitreal injection (Current Procedural Terminology [CPT] code 67028) ranges from $86.74 to $133.48 in the medical office setting and ranges from $85.48 to $131.49 in the hospital outpatient department. The technical fee associated with CPT code 67028 is $297.94 in the hospital outpatient department. The professional fee reimbursement for macular grid laser photocoagulation (CPT code 67210) ranges from $431.84 to $666.30 in the medical office setting and from $419.18 to $646.41 in the hospital outpatient department. The technical fee for CPT code 67210 is $420.39 in the hospital outpatient department.

Question for Assessment

The purpose of this assessment is to address the following question: What is the current safety and efficacy of available therapeutic options for the management of ME associated with BRVO?

Description of Evidence

Literature searches were last conducted on January 31, 2017, in PubMed with no date restrictions and limited to articles published in English, and in the Cochrane Library database without a language limitation. The combined searches yielded 321 citations. The following search terms were used:

(*branch retinal vein occlusion* OR (*occlusion* AND *retinal vein* AND *branch*) OR *brvo*) AND (*macular edema*[MeSH Terms] OR macular edema[tiab])) OR *macular oedema*) AND ((*pegaptanib*[Supplementary Concept] OR *pegaptanib*[All Fields] OR *macugen*[All Fields] OR *bevacizumab*[Supplementary Concept] OR *bevacizumab*[All Fields] OR *avastin*[All Fields] OR *ranibizumab*[Supplementary Concept] OR *ranibizumab* [All Fields] OR *lucentis*[All Fields] OR *aflibercept* [Supplementary Concept] OR *aflibercept*[All Fields] OR