Bevacizumab (Avastin) for the Treatment of Ocular Disease
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Abstract. The use of intravitreal bevacizumab (Avastin) has greatly expanded since its introduction into ophthalmic care 3 years ago. A PubMed search on 1 August 2008 revealed 51 ocular disease processes that have been treated with bevacizumab. The majority of publications consist of case reports or retrospective case series and their number is increasing quickly. It is important to collate the experiences gained to date to properly inform our clinical decision making and improve the design of future clinical trials. Current studies cannot easily be combined in a meta-analysis given the lack of standardized data and the wide variety of disorders studied in small numbers. This paper will describe the attempted uses of intravitreal bevacizumab and its efficacy for each ocular disease in addition to discussing safety. Comments regarding appropriate use of this treatment are based on our current level of knowledge. It is clear that the initial encouraging results described in this paper warrant further study of intravitreal bevacizumab in larger, controlled, randomized trials. (Surv Ophthalmol 54:372–400, 2009. © 2009 Elsevier Inc. All rights reserved.)

Key words. Avastin • bevacizumab • intravitreal • macular degeneration • macular edema • neovascularization

The use of intravitreal anti-vascular endothelial growth factor (anti-VEGF) agents has increased dramatically over the course of 3 years. Pegaptanib (Macugen, OSI Eyetech) was the first intravitreal medication to become commercially available in early 2005 for the treatment of choroidal neovascularization associated with exudative age-related macular degeneration (AMD). Its widely expanding use was curtailed later that year as reports began to surface of the successful use of off-label intravitreal bevacizumab (IVB) (Avastin, Genentech) for the treatment of exudative AMD. Bevacizumab is a humanized monoclonal antibody to VEGF that is Federal Drug Administration (FDA)-approved for adjunct antiangiogenic treatment of metastatic colorectal cancer. It was initially studied for the treatment of exudative AMD with intravenous delivery, with promising results. During the same time period, intravitreal ranibizumab (Lucentis, Genentech), a fab fragment of the bevacizumab humanized monoclonal antibody, was undergoing FDA clinical trial testing. Results from these clinical trials suggested that treatment of exudative AMD with intravitreal ranibizumab was superior to those reported in the pegaptanib phase III trials. However, ranibizumab was not commercially available at the time, pending completion of registration trials. This led to the study of intravitreal administration of bevacizumab for the treatment of exudative AMD. The adverse side effects associated with intravenous bevacizumab
treatment appeared to be avoided with intravitreal administration. The visual acuity and anatomical results were sufficiently compelling to lead to a tremendous increase in the use of off-label IVB as a first-line therapy for exudative AMD by early 2006. July, 2006, marked the release of the FDA-approved ranibizumab for treatment of exudative AMD. Since its release there has been continual debate on the preferred treatment medication for exudative AMD, focusing on the effectiveness, safety, and cost differences between bevacizumab and ranibizumab.

Although the primary focus has remained on the treatment of exudative AMD, the spectrum of diseases treated with anti-VEGF agents has quickly expanded. The vast majority of the attempted uses have utilized the much less expensive bevacizumab. This article reviews the reported ocular uses of bevacizumab over the last 3 years and provides comments regarding the utility of such efforts. Fifty-one ocular entities (Table 1) have been treated with bevacizumab. The majority of publications are limited to small case series or case reports; thus, the conclusions made in this article are not based on strong evidence. However, given the extensive use of bevacizumab, it is prudent to review the rationale and findings of such studies. Safety is discussed at the conclusion of the article.

Choroidal Neovascularization

EXUDATIVE AGE-RELATED MACULAR DEGENERATION

The most common cause of choroidal neovascularization (CNV) is exudative AMD. Intravitreal bevacizumab has been widely used off-label for the treatment of exudative AMD since early 2006 (Fig. 1). Following the initial successful administration for exudative AMD in May 2005, numerous case series were published illustrating the effectiveness of this treatment in a high proportion of patients. More recent studies have corroborated initial findings (Table 2).

Many of the published series of IVB use are limited by duration of follow-up, nonrandomization, and lack of a control group. One of the earlier large series in the literature included 81 consecutive eyes with subfoveal choroidal neovascularization treated with IVB 1.25 mg (0.05 cc) at baseline and 1 month later if morphologic changes attributable to the CNV (subretinal fluid, pigment epithelial detachment, retinal thickening) persisted. Seventy-eight percent had prior treatment with pegaptanib, photodynamic therapy (PDT), or both. After one IVB injection, 30 of 81 eyes had resolution of their subretinal fluid. At 2 months, 50% demonstrated resolution of leakage. The mean best corrected visual acuity (BCVA) improved from 20/200 to 20/125 (Snellen equivalent) ($p < 0.0001$). A subsequent study evaluated 266 eyes, 70% of which

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<td>Punctate inner choriodopathy</td>
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<td>Choroidal osteoma</td>
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<td>Toxoplasmosis</td>
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<td>Sickle cell retinopathy</td>
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<td>Retinopathy of prematurity</td>
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<td>Eales disease</td>
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<td>Macular edema</td>
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<td>Diabetic retinopathy</td>
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<td>Branch retinal vein occlusion</td>
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<td>Occlusive vasculitis</td>
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<td>Retinitis pigmentosa</td>
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<td>Breast cancer with choroidal metastasis</td>
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<td>Melanoma associated neovascularization</td>
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<td>Vasoproliferative tumor</td>
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<td>Coats disease</td>
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<td>Juxtapapillary capillary hemangioma</td>
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<td>Idiopathic macular telangiectasis</td>
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<td>Polyoidal choroidal vasculocclusion</td>
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<td>Nonarteritic anterior ischemic optic neuropathy</td>
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<td>Cicatrical pemphigoid corneal neovascularization</td>
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<td>Adjunct to glaucoma filtering surgery</td>
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had prior treatment with PDT or pegaptanib. Central retinal thickness measured by optical coherence tomography (OCT) improved over 3 months from a mean of 340 microns to a mean of 213 microns (p < 0.001). Mean BCVA improved from 20/184 to 20/109 at 3 months (p < 0.001), and 38.3% improved by 2 or more Snellen lines. These results were found despite the inclusion of eyes with longstanding exudative AMD. A study of 50 eyes treated with IVB for exudative AMD found that naïve eyes responded more favorably than previously treated eyes. Forty-three percent of naïve eyes gained 3 lines or more of vision versus 17% of eyes that had undergone prior treatment. The naïve group’s mean visual acuity improved from 20/160 at baseline to 20/63 (p < 0.001) at week 24. Such visual acuity gains were not reported with PDT or pegaptanib treatment and were comparable to the results of the phase III studies of ranibizumab for exudative AMD. For instance, the 1-year results for the MARINA (Minimally classic/occult trial of Ranibizumab In the treatment of Neovascular AMD) trial reported visual acuity improvement of 2 or more lines in 38.8% of eyes. Ninety-five percent lost less than 3 lines at 1 year with the 0.5-mg dose. The initial results of IVB treatment for exudative AMD led to acceptance of this therapy by clinicians around the world. IVB accounts for more than 50% of all anti-VEGF therapy delivered for exudative AMD in the United States.

The most effective treatment regimen of IVB is still being explored. A greater visual acuity effect has been reported in naïve eyes compared to those that have received previous treatment. However, those with longstanding exudative AMD have also been shown to improve with treatment. One retrospective study showed that 25% of those with exudative AMD for 5 months or longer (mean 17.9 months) improved at least 3 lines with treatment.

The frequency of treatment and duration required are also being evaluated. Current treatment regimens vary with some clinicians treating as needed based on OCT findings and clinical examination, whereas others administer treatment on a monthly basis for a preset time period. The PRONTO (Prospective Optical Coherence Tomography Imaging of Patients With Neovascular AMD Treated With Intraocular Ranibizumab) study found that after an initial series of three consecutive monthly intravitreal ranibizumab injections, eyes could be followed monthly with treatment given if there was evidence of CNV activity. Further treatment was needed within 3 months of the most recent injection in 56% of eyes and the average number of injections was 5.6 over a 1-year follow-up. Visual acuity results neared those achieved with consistent monthly administration of treatment. Similar results have been found with IVB as the treatment medication instead of ranibizumab, with a mean BCVA improvement from 45.7 ETDRS (Early Treatment Diabetic Retinopathy Study) letters (20/125) at baseline to 53.1 letters (20/80) at 12 months (p = 0.004), and 47 eyes (92.2%) losing less than 15 letters over a 1-year period, with an average of 3.4 injections required. Another series found that a strict regimen of three injections followed by long-term observation without further treatment is insufficient, as some eyes require a protracted course of therapy and others may develop recurrence of leakage.

As prolonged courses of treatment are often necessary, combination therapy has been studied in an effort to maintain good visual acuity results with less overall intervention. A randomized controlled clinical trial with 156 eyes compared IVB monotherapy with PDT and with combination treatment. Improvement of >0.2 logMAR (greater than 2 ETDRS lines) at the 3-month F/U was achieved in 22 (42%) eyes treated with IVB/PDT, one with IVB, and none with PDT. Although this result indicates that less overall intervention may be required with combination therapy, the follow-up was brief, and conclusions regarding long-term visual acuity results cannot be extrapolated to clinical practice as IVB monotherapy rarely consists of a single injection. In another study, dual therapy with IVB and PDT led to improvement in BCVA of 2 lines or more in 67% of patients, with a mean improvement of 2 lines at 7 months. Sixty-three percent of eyes required only one injection. A study of treatment with IVB followed by PDT 2 weeks later reported that 88% of eyes needed only one treatment session over 6 months and 48% required only a single treatment over 12 months. Triple therapy with IVB, reduced fluence PDT, and intravitreal dexamethasone have been investigated. In a prospective, uncontrolled study of 104 eyes,
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<td>Spaide (236)</td>
<td>Exudative AMD treatment</td>
<td>Retrospective case series</td>
<td>251 eyes of 251 pts.</td>
<td>55% prior PDT with or without steroids, 21% prior PEG, 17% not reported</td>
<td>IVB 1.25 mg monthly × 3, repeated if leakage recurred. Mean number of inj = 2.35</td>
<td>Mean VA baseline = 20/184, 3mo = 20/109 (p &lt; 0.001); mean CRT: baseline = 340 μm, 3mo = 213 μm (p &lt; 0.001). 38.3% halved visual angle. No significant VA difference between previously treated and naïve.</td>
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<td>Avery (28)</td>
<td>IVB for exudative AMD</td>
<td>Retrospective case series</td>
<td>81 eyes of 79 pts.</td>
<td>26% prior PDT, 30% prior PEG, 22% prior PDT and PEG</td>
<td>IVB 1.25 mg monthly until ME, SRF, or PED resolved</td>
<td>Mean VA baseline = 20/200, 2mo = 20/125 (p &lt; 0.0001); mean CRT decrease of 92 μm at 4 wk; complete resolution of symptoms in 20/81 eyes (month 1) and 25/51 eyes (month 2). No difference in VA outcome between previously treated vs naïve.</td>
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<td>Rich (200)</td>
<td>IVB for exudative AMD</td>
<td>Retrospective case series</td>
<td>53 eyes of 50 pts.</td>
<td>43% prior PDT, 62% prior PEG, 30% prior PDT and PEG, 25% no prior treatment</td>
<td>IVB 1.25 mg; repeated if cystic maculopathy or SRF noted; 2.3 mean number of injections</td>
<td>Mean Snellen VA baseline = 20/160, 3mo = 20/125 (p &lt; 0.001); mean CRT baseline = 351 μm, 3mo = 261 μm (p &lt; 0.001)</td>
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<td>Emerson (75)</td>
<td>Evaluating &quot;Retreatment “as needed”</td>
<td>Retrospective case series</td>
<td>79 eyes of 74 pts</td>
<td>59% prior therapies</td>
<td>IVB 1.25mg; retreated if SRF or retinal thickening on OCT (monthly) or leakage on FA (every 2-3 months)</td>
<td>Total injections by 3 mo: 25% one inj, 56% two inj, 13% three inj, 5% four inj. Mean ETDRS BCVA: baseline = 20/100, 1mo = 20/80 (p &lt; 0.001), 3mo = 20/80 (p = 0.04); mean CRT: baseline = 304 μm, 1mo = 227 μm (p &lt; 0.001), 3mo = 237 μm (p &lt; 0.001)</td>
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<td>Yoganathan (265)</td>
<td>Naïve vs Previously treated</td>
<td>Retrospective case series</td>
<td>50 eyes of 48 pts.</td>
<td>28% no prior treatment; 72% prior PEG and/or PDT</td>
<td>IVB 1.25 mg; retreatment if SRF, IRF, or hemorrhage; mean 3.5 injections. Mean f/u 34 wks</td>
<td>Mean ETDRS VA: naïve baseline = 20/160, 24wk = 20/63 (p &lt; 0.001) 43% gained &gt;/ = 3 lines. Previously treated baseline = 20/200, 24 wk = 20/200. 17% gained &gt;/ = 3 lines. Naïve eyes had better outcome.</td>
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<td><strong>Costa (61)</strong></td>
<td>Dose escalation</td>
<td>Prospective nonrandomized case series</td>
<td>45 eyes (15 for each dose)</td>
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<td>Single inj of IVB of 1.0mg, 1.5mg, or 2.0mg, F/u at 1, 6, 12 wks</td>
<td>Improved VA at 12 wks: 1.0mg = 0.3 line, 1.5mg = 0.6 line, 2.0mg = 1.0 line (p = 0.02)</td>
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<td><strong>Bashshur (35)</strong></td>
<td>PDT vs IVB</td>
<td>Prospective case series</td>
<td>62 eyes (IVB=32, PDT=30)</td>
<td>Predominantly classic CNV lesions</td>
<td>PDT group retreated (mean 2.3) if persistent leakage on FA at 3, 6 months. IVB 1.25mg, retreated monthly (mean 2.4) if SRF, cysts on OCT, decrease VA, increased CRT, new CNV/heme. 6 months f/u</td>
<td>Baseline BCVA: PDT = 20/108, IVB = 20/119; 3 mo: PDT = 20/118, IVB = 20/89 (p = 0.09); 6 mo: PDT = 20/143, IVB = 20/68 (p&lt;0.001). Baseline CRT: PDT = 354, IVB = 352; 3mo: PDT = 300, IVB = 262 (p = 0.04); 6mo: PDT = 292, IVB = 241 (p = 0.002). Better outcome with IVB</td>
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<td><strong>Lazic (146)</strong></td>
<td>PDT vs IVB vs PDT+IVB</td>
<td>Randomized controlled clinical trial</td>
<td>156 eyes (PDT=50, IVB=54, COMB=52)</td>
<td>Minimally classic or occult CNV, no previous treatment</td>
<td>PDT once or IVB 1.25mg once or PDT+ IVB 1.25mg once</td>
<td>Baseline logMAR VA: PDT = 1.11 (20/250), IVB = 1.09 (20/250), COMB = 1.06 (20/250); change at 1 mo: PDT = 0.05, IVB = 0.17, COMB = 0.25; change at 3mo: PDT = 0.01, IVB = 0.08, COMB = 0.22 (p&lt;0.001 for IVB and Comb). CRT decreased significantly in all groups. Improvement &gt; 0.2 logMAR at 3-month F/U in 23 subjects (1 BEV, 22 COMB, and 0 PDT). Best outcome with combination treatment</td>
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<td><strong>Dhalla (70)</strong></td>
<td>Dual therapy (IVB + PDT) rate of retreatment</td>
<td>Retrospective case series</td>
<td>24 eyes of 24 pts.</td>
<td>Classic 38%; occult 62%; subfoveal 67%; juxtafoveal 33%; no previous treatment</td>
<td>IVB 1.25 mg plus PDT within a 2 wk interval; retreatment for persistent SRF or leakage on FA</td>
<td>85% (20/24) VA stable or improved; 67% improved 2 lines or more. Mean improvement of 2.04 lines at 7 mo. 63% single treatments, 33% 2 treatments; 4% 3 treatments over 7 mo</td>
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Mean BCVA improved by 1.8 lines (p < 0.01) and central retinal thickness (CRT) decreased by 182 microns (p < 0.01) during the 40-week period of follow-up. Only 17% required additional injections of bevacizumab.26

A National Eye Institute funded trial directly comparing bevacizumab versus ranibizumab monotherapy for the management of exudative AMD (CATT; Comparison of Age-related macular degeneration Treatments Trial) is currently enrolling subjects. Various treatment frequencies will be compared. Further evaluation of combination treatment versus monotherapy is needed.

**RETINAL ANGIOMATOUS PROLIFERATION**

Retinal angiomatous proliferation (RAP) is a variant of neovascular AMD that can exhibit intraretinal neovascularization, subretinal neovascularization, and choroidal neovascularization (CNV).262 A number of studies have evaluated the effect of IVB on eyes with CNV secondary to RAP.62,93,131 One series evaluated 23 eyes with RAP (11 with previous treatment) that were treated with IVB. At 3-month follow-up, five eyes (21.7%) had 2 or more lines improvement, five eyes (21.7%) had worse vision, and 11 (47.8%) remained unchanged. Successful combination therapy with IVB and intravitreal triamcinolone has also been reported.26

**AMD = age-related macular degeneration; BCVA = best corrected visual acuity; CNV = choroidal neovascularization; CRT = central retinal thickness; ETDRS = Early Treatment of Diabetic Retinopathy Scale; f/u = follow-up; IVB=intravitreal bevacizumab; IVT=intravitreal triamcinolone; MAR = minimal angle of resolution; ME = macular edema; OCT=optical coherence tomography; PDT = photodynamic therapy with verteporfin; PED = pigment epithelial detachment; PEG = pegaptanib; SRF = subretinal fluid; VA = visual acuity.**

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### Table: Comparison of treatment outcomes

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<th>Study</th>
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<th>Patients</th>
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<td>Augustine (26)</td>
<td>Triple therapy (IVB + IVT + PDT)</td>
<td>Prospective case series</td>
<td>104 eyes</td>
<td>All CNV lesion types included</td>
<td>Mean improvement 1.8 lines (p &lt; 0.01)</td>
<td>39.4% gained 3 or more lines, 3.8% lost 3 or more lines</td>
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<td>Jonas (125)</td>
<td>Results based on CNV lesion type</td>
<td>Retrospective case series</td>
<td>67 eyes of 66 pts.</td>
<td>42% occult with or without minimally classic CNV, 33% predominantly or purely classic CNV, 25% PED</td>
<td>No significant difference in VA outcomes based on CNV lesion type</td>
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**Baseline BCVA = 20/126, 3mo BCVA = 20/85, mean improvement 1.8 lines (p < 0.01). 39.4% gained 3 or more lines, 3.8% lost 3 or more lines.**
treatment for juxtafoveal myopic CNV found no visual benefit after 3 years of follow-up.209

Although follow-up is limited in the reported case series of pathologic myopia treated with bevacizumab, the initial results appear promising (Table 3).23,50,144,157,187,199,208,212,242,260 A prospective study of 22 eyes evaluated the results of three consecutive monthly IVB injections with an additional three monthly injections in eyes with persistent CNV leakage. All patients completed 6 months of follow-up. Only 2/20 eyes (10%) required the second series of injections. BCVA improved from 20/80 at baseline to 20/45 at 6 months. Sixty-eight percent improved 2 lines or more at 6 months.47

Another series with 14 eyes and mean baseline BCVA of 20/200 responded well with 43% improving 3 lines or more at 3 months, achieving a final mean visual acuity of 20/60.106

CNV SECONDARY TO ANGIOID STREAKS

There are numerous case reports and case series describing successful treatment of CNV secondary to angiod streaks with IVB.19,39,50,68,151,195,201,211,244 Visual acuity testing showed meaningful improvement following IVB treatment in both naïve eyes and those previously treated with PDT. One series of 16 eyes with CNV due to pseudoxanthoma elasticum were treated with IVB. Further treatments were administered depending on disease activity, with an average of 2.4 injections administered over 8 months of follow-up. Mean BCVA improved from 20/100 at baseline to 20/63 at the final visit, but this was not statistically significant (p = 0.126). Eyes with minimal morphological changes in the central macula were more likely to improve their visual acuity significantly, suggesting a better outcome with early treatment.86

CNV SECONDARY TO BEST DISEASE

A single case report described a 13-year-old boy with confirmed Best disease who presented with vision loss due to secondary choroidal neovascularization and was treated with a single IVB injection. His visual acuity improved from 20/40 to 20/20 over a period of 6 months. OCT and fluorescein angiography (FA) demonstrated regression of the CNV and resolution of the macular edema.148

CNV SECONDARY TO ADULT VITELLMIFORM DYSTROPHY

A single case report described a female patient with CNV secondary to adult vitelliform dystrophy who was treated with single injection of IVB. Despite improvement on OCT and FA, her vision remained unchanged at 10 months of follow-up.160

CNV SECONDARY TO CENTRAL SEROUS CHIORIOTRETINOPATHY

Two eyes with CNV secondary to central serous chorioretinopathy (CSCR) received monthly injections of IVB for 3 months. Both eyes had regression of the CNV and visual acuity improvement of 2 lines or more at 6 months of follow-up.46

CNV SECONDARY TO PUNCTATE INNER CHORIODOPATHY

Successful treatment of CNV secondary to punctate inner choriodopathy (PIC) has been reported.203,254 IVB was administered monthly for 3 months in four eyes with CNV secondary to PIC. Three of four eyes (75%) improved their vision by 2 or more lines at the 6-month follow-up visit.46

CNV ASSOCIATED WITH MULTIFOCAL CHOROIDITIS

A case series of 12 eyes with CNV secondary to multifocal choroiditis reported a statistically significant improvement in BCVA following IVB treatment. Mean follow-up was 58.8 weeks with a mean of 3.4 injections per eye. The data were reported in conjunction with other causes of CNV thus preventing subset reporting for multifocal choroiditis alone. A separate single case report of CNV secondary to multifocal choroiditis showed resolution of leakage on fluorescein angiography following treatment with IVB and PDT.250

CNV SECONDARY TO PRESUMED OCULAR HISTOPLASMOSIS SYNDROME

In a retrospective case series, 28 eyes with CNV secondary to presumed ocular histoplasmosis syndrome (POHS) were treated with IVB.10 The average pretreatment logMAR vision (logarithm of the minimum angle of resolution) was 0.65 (Snellen equivalent 20/88). The mean follow-up was 22 weeks with an average of 1.8 intravitreal injections. The average final logMAR vision was 0.43 (20/54). Twenty eyes (71%) improved their BCVA, four eyes (14%) were unchanged, and four eyes (14%) experienced a decrease in vision.215

CNV SECONDARY TO CHOROIDAL OSTEOMA

Two cases of CNV associated with macular choroidal osteoma and treated with IVB have been reported. A 19-year-old woman presented with visual acuity of 20/200 and improved to 20/25 6 weeks after a single treatment with IVB. This was maintained throughout 9 months of follow-up.17 Another 25-year-old woman presented with visual acuity of CF at 1.5 meters. Two treatments of IVB were given 6 weeks apart. Her visual
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<td>Chan (47)</td>
<td>Prospective case series</td>
<td>22 eyes of 22 pts</td>
<td>IVB 1.25mg given monthly x 3. Repeat series if leakage on FA</td>
<td>BCVA (ETDRS) baseline = 20/80, 6 mo = 20/45 (p &lt; 0.001). 68% improved 2 or more lines. 91% needed only one set of 3 injections.</td>
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<td>Hernandez-Rojas (106)</td>
<td>Prospective case series</td>
<td>14 eyes, 14 pts</td>
<td>IVB 2.5mg, retreatment if persistent SRF, decreased VA, or leakage on FA</td>
<td>Mean BCVA baseline = 20/200, 12 wk = 20/60 (p = .001); 45% gained &gt; 3 lines 75% improved 2 lines; mean CRT baseline = 194μm, final visit = 155μm (p = 0.027).</td>
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<td>Sakaguchi (212)</td>
<td>Prospective case series</td>
<td>8 eyes of 8 pts</td>
<td>25% prior IVT</td>
<td>IVB 1.0 mg; 38% received 2 doses</td>
<td>75% improved 2 lines; mean CRT baseline = 194μm, final visit = 155μm (p = 0.027).</td>
</tr>
<tr>
<td>Yamamoto (260)</td>
<td>Retrospective case series</td>
<td>11 eyes of 9 pts</td>
<td>45% previous PDT treatment</td>
<td>IVB 1.25mg repeated monthly if persistent SRF, 82% received 1 inj, 18% received 2 inj</td>
<td>Mean VA improvement 3.5 lines (mean f/u 153 days).</td>
</tr>
<tr>
<td>Mandal (157)</td>
<td>Prospective case series</td>
<td>12 eyes, 11 pts</td>
<td>No previous treatment</td>
<td>IVB 1.25 mg, repeat if persistent SRF</td>
<td>BCVA baseline = 20/235, 6 mo = 20/71; 75% improved 3 lines or more.</td>
</tr>
</tbody>
</table>

BCVA = best corrected visual acuity; CNV = choroidal neovascularization; CRT = central retinal thickness; ETDRS = Early Treatment of Diabetic Retinopathy Scale; FA = fluorescein angiography; f/u = follow-up; PDT = photodynamic therapy with verteporfin; SRF = subretinal fluid; IVT = intravitreal triamcinolone; VA = visual acuity.
acuity improved to 20/125 with resolution of CNV on FA and OCT. No reactivation was present at the 4-month follow-up.\textsuperscript{186}

**CNV SECONDARY TO TOXOPLASMOSIS**

Three cases of CNV secondary to ocular toxoplasmosis were reported to resolve after a single IVB treatment.\textsuperscript{103} Follow-up over 12 months showed improved visual acuity and no recurrence of CNV.\textsuperscript{37}

**CNV SECONDARY TO UVEITIS**

IVB treatment for CNV secondary to uveitis has been reported.\textsuperscript{158} Ten eyes were treated with a mean of 2.5 injections of IVB. Complete resolution of leakage was noted in three of 10, and an improvement was found in the remaining seven. The logMAR vision improved from 0.62 (20/55) to 0.45 (20/40) (p = 0.01).\textsuperscript{248} Another series reported that the CNV resolved completely in nine (100\%) of nine affected eyes. At the last examination, visual acuity was improved in eight eyes (88.8\%), and stable in one (11.2\%) over a mean follow-up of 7.1 months. Seven eyes received one injection, one eye required two injections, and one eye required three injections.\textsuperscript{9} The etiology of the uveitis in these reports has been variable. There are single reports where IVB was successfully used to treat uveitis-related neovascularization associated with sarcoidosis, and with lupus.\textsuperscript{141}

**CNV SECONDARY TO PSEUDOTUMOR CEREBRI**

A single case of CNV secondary to pseudotumor cerebri treated with IVB has been reported. A single injection of IVB resulted in a return to baseline visual acuity and regression of the CNV.\textsuperscript{120}

**PERIPAPILLARY CNV**

Treatment of peripapillary CNV with IVB has also been effective.\textsuperscript{193,292,298} In one case series, five of six eyes resolved their leakage on FA and OCT after monthly IVB treatments for 3 months. Visual acuity improved an average of 4 lines in those five eyes.\textsuperscript{82}

**IDIOPATHIC CNV**

Ten eyes with idiopathic CNV, mean BCVA of 20/43, and mean CRT of 270 microns were treated with IVB.\textsuperscript{50,155} The visual acuity improved to 20/29 (p = 0.003) at the 3-month assessment. Six eyes required only one injection, and the other four received a second injection after FA revealed persistent leakage. The follow-up period ranged from 5 to 12 months (mean 6.8 months).\textsuperscript{97} Another study included nine eyes, treated with a series of three injections. At 6-month follow-up, the mean gain in visual acuity was 2.2 lines, with 67\% gaining 2 or more lines.\textsuperscript{46}

Intravitreal bevacizumab has become a first-line agent in the treatment of exudative AMD. The efficacy of bevacizumab will be compared to ranibizumab in a randomized clinical trial. Optimal treatment regimens and the potential of combination therapy are still to be elucidated. CNV associated with other retinal disorders appears to respond favorably to IVB as well, often requiring a shorter duration of treatment to elicit involution and cessation of leakage.

**Retinal Neovascularization**

Retinal neovascularization is a potential sequelae of vascular compromise of the retina in a multitude of diseases. Neovascularization can lead to vision loss from vitreous hemorrhage (VH) or tractional retinal detachment (TRD).

**PROLIFERATIVE DIABETIC RETINOPATHY**

The standard of care for the management of neovascularization due to diabetic retinopathy is panretinal photocoagulation (PRP) with argon laser, which reduces the chance of severe vision loss by 50\%.\textsuperscript{7} However, some patients will have persistent neovascularization despite PRP. Others have media abnormalities precluding the administration of PRP (e.g., corneal edema, VH, cataract). Many case reports and series have shown rapid regression of neovascularization of the iris, disk, and retina following IVB treatment.\textsuperscript{29,31,115,164,166,176,182,189} Most report extensive, if not full, regression of the neovascularization between 1 and 3 weeks after injection with some reporting regression as early as 24 hours after treatment. A large series reported 44/44 eyes had complete or partial regression of neovascularization at 1 week.\textsuperscript{27} Complete resolution of leakage of the disk was noted in 19/26 (73\%) and iris neovascularization resolved in 9/11 (82\%). Recurrence occurred as early as 2 weeks whereas others had no recurrence at the 11-week follow-up visit. Treatment with IVB has also been shown to be effective in causing regression of persistent neovascularization despite prior extensive PRP in proliferative diabetic retinopathy (PDR).\textsuperscript{127}

IVB treatment in conjunction with PRP for PDR has been evaluated. One retrospective study reviewed 30 patients with symmetrical bilateral severe PDR. One eye was used as the control and the other eye served as the treatment eye. The control eye underwent PRP in two sessions separated by 2 weeks. The treatment eye received the same laser protocol, preceded by an IVB injection 1 week earlier. Baseline BCVA and CRT were
similar between the two groups (IVB group logMAR BCVA = 0.073 [20/24], CRT = 279 microns, control group VA = 0.069 [20/24], CRT = 273). However, at the 24-week follow-up, the IVB-pretreated group had a statistically significant improvement in BCVA and CRT (VA = 0.039 [20/22], CRT = 264 microns) when compared to the control group (VA = 0.149 [20/28], CRT = 298 microns) (p < 0.001). Twenty-three percent of the control eyes had a decrease in BCVA by 2 lines or greater at 24 weeks, whereas none of the IVB group had worsening of vision. It was postulated that pretreatment with IVB may prevent secondary macular edema that is occasionally associated with PRP administration. In another study, 30 eyes were prospectively randomized to either PRP alone or PRP with IVB given after the second PRP session. This study found no difference in visual acuity; however, the total area of leakage from NV was less in the combination-treatment group. A third prospective, fellow-eye sham controlled clinical trial included 80 eyes of 40 patients with high-risk PDR. All eyes received PRP with the study eyes receiving IVB at the time of the first of two PRP sessions. After 6 weeks, 87.5% of the IVB group showed complete regression of proliferation by FA compared to 25% of sham. However, by week 16, PDR recurred in a sizable number of the IVB group with the complete regression rate in the two groups becoming identical (25%). IVB has been used successfully as initial treatment in eyes with vitreous hemorrhage preventing treatment with photocoagulation. One interesting case describes a 76-year-old woman with posterior capsule opacification due to capsular neovascularization despite previous PRP. Her baseline BCVA measured 20/200. After a single injection of IVB, she had nearly complete resolution of the posterior capsule neovascularization, allowing a YAG capsulotomy to be performed, which resulted in final vision of 20/40.

Preoperative intravitreal bevacizumab has been administered prior to pars plana vitrectomy (PPV) to assist in the management of PDR-related complications such as vitreous hemorrhage and tractional retinal detachment. The goal of pretreatment is to induce vessel regression and thereby reduce intraoperative bleeding and facilitate membrane peeling. One series evaluated 22 eyes with severe PDR scheduled for vitrectomy. Eleven eyes received IVB 5–7 days prior to surgery while the control group received no pretreatment. The average complexity scores were the same for the two groups prior to treatment. The study reported shorter surgical time (57 vs 83 minutes), fewer tool exchanges (27 vs 53), less intraoperative bleeding episodes (5 vs 15), and fewer endodiathermy uses (2 vs 9) in the eyes with preoperative IVB versus those without pretreatment. Visual acuity outcomes differed greatly between the groups with the mean BCVA improving from logMAR 1.87 (CF) to logMAR 0.88 (20/150) in the bevacizumab group at 6 months while the control group did not improve (logMAR 2.04 [CF] at baseline and 2.01 [CF] at 6 months) (p = 0.01 comparing groups). It is uncertain why the control group did not have improved visual acuity at final follow-up. Another series showed improved vitreous clear up time (7.2 vs 15.2 days) following PPV and octafluoropropane gas (C8F8) in eyes with severe PDR pretreated with IVB 1 week prior to surgery compared to those not pretreated. The timing for IVB pretreatment is not clear. Tractional changes may occur or worsen after IVB treatment and prior to surgery. In one large series, 11 out of 211 (5.2%) eyes with PDR refractory to PRP developed or had progression of TRD following IVB treatment. The mean time from injection to TRD development or progression was 13 days (range: 3–31 days). Currently, many surgeons administer the injection within the week prior to surgery in an effort to avoid this complication.

Panretinal photocoagulation remains the gold standard treatment for proliferative diabetic retinopathy given its long-term effectiveness. There are conflicting data on whether adjunctive IVB is helpful in the routine treatment of PDR. As the benefits of adjunctive IVB appear to be short term, routine use is not recommended at this point. However, in cases where laser treatment is not possible due to media opacity, or in cases of persistent neovascularization despite extensive laser treatment, then using bevacizumab as adjuvant treatment is reasonable. This may allow time for more definitive treatment to be administered at a later date. There is growing evidence that preoperative bevacizumab can improve intraoperative surgical conditions, including a surgeon’s ability to dissect fibrovascular membranes without extensive bleeding. If utilized, a reasonable timeframe for administration would be 2 to 7 days prior to surgery.

SICKLE CELL NEOVASCULARIZATION

In one case report, a 36-year-old man with sickle cell retinopathy developed retinal neovascularization with subsequent VH and his BCVA decreased to 20/60. FA demonstrated an area of non-perfusion adjacent to the “sea-fan” neovascularization. The VH precluded application of adequate sectoral laser photoacoagulation. Intravitreal bevacizumab was administered, resulting in regression of the retinal neovascularization, resolution of the hemorrhage, and visual acuity improvement to 20/20 over the next 4 weeks. Sectoral laser photoacoagulation was subsequently applied to the area of non-perfusion.
similar case was reported with a single IVB treatment, resulting in long-term regression of retinal neovascularization.220

Future evidence may further support the value of IVB for sickle cell neovascularization if vitreous hemorrhage precludes sectoral PRP or for persistent neovascularization despite complete PRP.

**RETNOPATHY OF PREMATURITY**

Thirty-one percent of infants with stage 3, zone 1 retinopathy of prematurity (ROP) have unfavorable visual outcome, despite early cryotherapy treatment.193 Oxygen-induced retinopathy models show an association of elevated intraocular levels of VEGF with pathologic retinal neovascularization.71,170,196,242 The standard treatment for ROP involves either sectoral laser photocoagulation or cryotherapy. Treatment of ROP with IVB has been reported.30,67,142,213,218,249 A retrospective, consecutive case series describes 22 eyes of 11 infants without previous treatment with moderate and severe stage 3 ROP in zone I or posterior zone II, treated with bilateral IVB at 9 to 15 weeks of age (mean 11 weeks). Follow-up varied from 13 to 85 weeks (mean 48.5 weeks). All 22 eyes were treated successfully with only one injection resulting in regression of tunica vasculosa lentis, reduction of iris vessel engorgement, decreased plus disease (reduction of retinal vascular engorgement), and regression of peripheral retinal neovascularization. Potential complications such as retinal detachment did not occur,177 but have been described following IVB treatment in this setting.107 Successful treatment of ROP with IVB combined with laser has also been reported.55

There is extensive uncertainty regarding potential ocular and systemic side effects of IVB in premature infants. These concerns may preclude routine use of IVB in the treatment of ROP. Photocoagulation or retinal cryotherapy remains the standard treatment choice. IVB may be considered for salvage treatment in cases progressing despite standard therapy.

**Macular Edema**

**DIABETIC MACULAR EDEMA**

Diabetic macular edema (DME) is the leading cause of vision loss in the working-aged population in the United States. The Early Treatment Diabetic Retinopathy Study (ETDRS) demonstrated that immediate focal photocoagulation reduced moderate vision loss by 50% at 3 years of follow-up. At 9 months, approximately 40% gained 1 line or more on ETDRS visual acuity testing. Only 3% gained 3 or more lines of vision and 12% of treated eyes lost 15 or more ETDRS letters at the 3-year follow-up interval.3

There has been interest in finding other treatments for DME, particularly central edema, in an effort to improve the ability to regain vision. Laser treatment has the potential to cause vision loss from inadvertent foveal burns or spread of laser scars over time. Patients with leaking microaneurysms situated too close to the fovea are especially at risk. Despite laser treatment, some patients have persistent DME. For these reasons, alternate therapies have been attempted, including trials of intravitreal triamcinolone, fluocinolone implants, and vitrectomy.109,150,163

A phase II prospective controlled randomized trial using pegaptanib for DME was the first to demonstrate the potential of anti-VEGF medications to be effective for this disease.65 With 182 subjects enrolled, central retinal thickness decreased modestly by a mean of 68 microns in the 0.3-mg treatment group compared to no change in the control groups (observation only or laser treated). Visual acuity improved by 2 or more lines in 34% versus 10% in the control group (p < 0.01).

Intravitreal bevacizumab has been studied for the treatment of DME. A multicenter, multinational retrospective study evaluated 78 eyes of 64 patients with DME with a minimum follow-up of 6 months. Patients were treated with at least one injection of either 1.25 mg or 2.5 mg of IVB and underwent ETDRS visual acuity testing. Approximately 20% required a second injection at a mean of 13.8 weeks and 8% needed a third injection at a mean of 11.5 weeks later. Final visual acuity analysis demonstrated that 41.1% of eyes remained stable, 55.1% improved 2 or more lines, and 3.8% decreased 2 or more lines. Mean CRT at baseline was 387 microns and decreased to a mean of 275 microns at the end of follow-up (p < 0.0001).20

Another study reported on 51 patients with refractory DME, with prior interventions including...
focal laser (35%), panretinal laser (37%), vitrectomy (12%), or intravitreal injection of triamcinolone (33%). Twelve weeks following IVB treatment, there was a statistically significant decrease in the mean CRT on OCT (501 microns at baseline to 377 microns), but no significant change in mean visual acuity (logMAR 0.84 [20/145]) compared to baseline (0.86 logMAR [20/145]). Another series of 11 eyes previously vitrectomized for DME did not show any visual acuity improvement after treatment with IVB. The lack of improvement could be a result of permanent photoreceptor damage from the duration of disease or from extensive previous treatments.

Attempts have been made to compare IVB to intravitreal triamcinolone acetonide (IVT) in the treatment of DME. Although both treatment modalities have shown short-term benefits in terms of reduced retinal thickening and improved visual acuity, long-term results are unknown. The superiority of one treatment over the other or in combination with the other is uncertain.

Although many reports show at least a short-term benefit of IVB in the treatment of DME, fewer studies directly compare IVB to laser photocoagulation. Two randomized, controlled, clinical trials have been reported. One study found superior visual acuity results for IVB when compared to laser at 12 weeks. A separate arm of the study showed no additional benefit of IVT in addition to IVB. The Diabetic Retinopathy Clinical Research Network (DRCR.net) reported phase II findings comparing IVB and standard laser treatment for center-involving DME in 121 subjects. Differing doses of IVB (1.25 mg and 2.5 mg), differing interval dosing (once vs twice), and combined treatment (IVB followed by focal laser at 3 weeks followed by IVB at 6 weeks) were evaluated. Twelve-week results showed greater improvement in visual acuity with IVB (both 1.25 mg and 2.5 mg), with an average 1 line gain, compared with no vision difference in the laser treated groups. However, the study was not powered to determine superiority of treatment groups. Whereas the CRT improved more quickly in the IVB only groups, the improvement found at 12 weeks was matched by the laser group. There were no meaningful differences between IVB 1.25 mg and 2.5 mg in CRT reduction or visual acuity improvement. Combined focal laser and IVB did not achieve results equal to IVB monotherapy, but follow-up was too limited to make conclusions regarding combination therapy. Of interest, the effects of IVB on retinal thickening appeared to plateau at 3 weeks, indicating that injections may need to be administered every 4 weeks rather than every 6 weeks in future clinical trials. Electrophysiology testing in eyes with DME treated with IVB found an improvement in the multifocal electroretinography tracings 2 months following IVB treatment.

Although the initial results of IVB for the treatment of DME have thus far been encouraging (Table 4), it is difficult at this time to compare to the focal laser results from the ETDRS study. The results of the DRCR study suggest a more rapid reduction in retinal thickening and greater visual acuity benefit with intravitreal bevacizumab treatment compared to focal laser treatment for diabetic macular edema. However, the duration of follow-up was brief. Future studies will elucidate optimal treatment regimens, and the duration of treatment required to achieve a long-lasting response. At this juncture, IVB is reasonable as an adjunct to focal laser treatment for refractory cases, or for use in situations that preclude focal laser (e.g., microaneurysms too close to fovea, media opacity).

### CENTRAL RETINAL VEIN OCCLUSION

No proven therapy exists for patients with macular edema from central retinal vein occlusion (CRVO). The Central Retinal Vein Occlusion Study (CVOS) showed that laser treatment was not effective in treating macular edema following CRVO. Intraocular triamcinolone acetonide injection is one treatment option that, despite associated adverse events such as intraocular pressure elevation and cataract progression, has demonstrated promising short-term results for the management of macular edema associated with retinal vein occlusions. A multicenter, randomized, controlled clinical trial (the Standard Care Versus Corticosteroid for Retinal Vein Occlusion Study) evaluating intravitreal triamcinolone treatment for macular edema in CRVO is currently under way.

The first report of IVB for the treatment of macular edema secondary to CRVO was published in 2005. Within 1 week of IVB treatment, BCVA improved from 20/200 to 20/50 and OCT showed resolution of the cystic retinal edema. Improvements were maintained for at least 4 weeks. Subsequent reports have been published regarding successful experiences with this treatment. One noted advantage of IVB was the avoidance of cataract progression and glaucoma commonly associated with intravitreal triamcinolone.

Most case reports lack controls and in some cases, improvement in visual acuity may be due to the natural course of the disease. One case series evaluated seven eyes with ischemic CRVO or hemiretinal vein occlusion with a mean duration of 7 months prior to treatment with IVB. Such eyes were unlikely to improve spontaneously given the duration of disease. At the baseline examination, the
### TABLE 4

**Literature Summary: Diabetic Macular Edema**

<table>
<thead>
<tr>
<th>Author (Ref. No.)</th>
<th>Study Design</th>
<th>n</th>
<th>Population</th>
<th>Treatment Regimen</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arevalo (20)</td>
<td>Retrospective case series</td>
<td>78 eyes in 64 pts</td>
<td>No previous focal laser, IVT, or macular ischemia. 6 mo f/u</td>
<td>IVB 1.25 mg (19%) or 2.5 mg (81%), 20.5% required 2 inj, 7.7% required 3 inj</td>
<td>BCVA improved from logMAR 0.87 (20/160) to 0.6 (20/80) at 1.3, 6 mo f/u. (p&lt;0.0001); 55% improved &gt;/ = 2 lines (ETDRS), 4% worsened &gt;/ = 2 lines at 6 mo, mean CRT decreased from 387 to 267 μm (p&lt;0.0001).</td>
</tr>
<tr>
<td>Haritoglou (104)</td>
<td>Prospective case series</td>
<td>51 pts.</td>
<td>All previous treatment: focal laser (35%), panretinal laser (37%), vitrectomy (12%), IVT (33%)</td>
<td>IVB 1.25 mg; retreatment in pts. with limited response, recurrent edema, or decrease in VA. 70% received 2 or more injections</td>
<td>logMAR VA baseline = 0.86 (20/160), 6 wk = 0.75 (20/100) (p = 0.001), 3mo = 0.84 (20/125) (not significant); mean CRT baseline = 501 μm, 3mo = 377μm (p = 0.001).</td>
</tr>
<tr>
<td>Yanyali (263)</td>
<td>Retrospective case series</td>
<td>11 eyes of 10 pts</td>
<td>100% previous vitrectomy</td>
<td>IVB 1.25 mg monthly x 3</td>
<td>No improvement in VA or CRT.</td>
</tr>
<tr>
<td>DRCR.net (2)</td>
<td>Randomized clinical trial</td>
<td>109 eyes of 109 pts</td>
<td>69% previous treatment</td>
<td>Focal laser (19) vs IVB 1.25 mg (22) (baseline + 6 wks) vs IVB 2.5 mg (24) (baseline + 6 wks) vs IVB 1.25 mg (22) (baseline + sham) vs combined (22) (IVB 1.25 mg + focal (3 wks) + IVB 1.25 mg (6 wks))</td>
<td>CRT &lt; 250μm or &gt;/ = 50% reduction at 12 wks: laser (21%), IVB 1.25 (33%), IVB 2.5mg (33%), IVB 1.25 once (14%), combined (25%). 2 or more ETDRS VA lines improvement at 12 wks: laser (16%), IVB 1.25 (33%), IVB 2.5 (25%), IVB 1.25 once (9%), combined (20%).</td>
</tr>
<tr>
<td>Ahmadieh (12)</td>
<td>Randomized clinical trial</td>
<td>115 eyes of 101 pts</td>
<td>All with previous treatment</td>
<td>IVB 1.25 mg x3 at 6-week intervals vs IVB 1.25 mg + IVT 2 mg followed by IVB x2 at 6-week intervals vs sham injection (control group).</td>
<td>Change in logMAR VA at 12 wks compared to baseline: IVB = -0.15, IVB+IVT = -0.21; 24 wks: IVB = -0.18, IVB+IVT = -0.21. Change in CRT 12 wk: IVB = -71μm, IVB+IVT = -102μm; 24wk: IVB = -96μm, IVB+IVT = -92μm. (VA and CRT statistically significant compared to controls, no significant difference between IVB and IVB+IVT).</td>
</tr>
<tr>
<td>Paccola (191)</td>
<td>Randomized clinical trial</td>
<td>26 eyes</td>
<td>All with previous treatment</td>
<td>Single injection of IVB 1.5 mg, or IVT 4 mg</td>
<td>IVB and IVT both resulted in significantly decreased CRT. Effect greater and lasted longer in IVT. Both treatments significantly improved VA; more so and for longer duration with IVT. IVT had significant increase in IOP.</td>
</tr>
</tbody>
</table>

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BCVA = best corrected visual acuity; CRT = central retinal thickness; DME = diabetic macular edema; f/u = follow-up; IVB = intravitreal bevacizumab; IVT = intravitreal triamcinolone; MAR = minimal angle of resolution; PPV = pars plana vitrectomy; VA = visual acuity.
### TABLE 5

**Literature Summary: Central Retinal Vein Occlusion**

<table>
<thead>
<tr>
<th>Author</th>
<th>Study Design</th>
<th>n</th>
<th>Type</th>
<th>Total Follow-up</th>
<th>Prev Tx</th>
<th>Intravitreal Dosing Regimen</th>
<th>Baseline Data</th>
<th>Efficacy Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iturralde</td>
<td>Retrospective case series</td>
<td>16 eyes</td>
<td>CRVO; 5 non-perfused, 2 indeterminate, 9 perfused</td>
<td>Mean: 90 d (34-133 d)</td>
<td>9 with IVT</td>
<td>IVB 1.25 mg given at discretion of physician, mean # inj = 2.81</td>
<td>Mean VA: 20/600, Ave CRT: 887 μm</td>
<td>1 mo f/u: VA: 20/200 (p = 0.001), CRT 372 μm (p = 0.001), at 3 mo: 87.5% had halving of visual angle; 12.5% no change in VA.</td>
</tr>
<tr>
<td>Costa</td>
<td>Retrospective case series</td>
<td>7 eyes</td>
<td>CRVO (5), HRVO (2); nonperfused only, mean duration prior to tx 7 mo</td>
<td>25 weeks</td>
<td>?</td>
<td>IVB 2.0 mg, repeated every 12 weeks if ME present on OCT and FA</td>
<td>VA 20/320, CRT 730 μm</td>
<td>Mean change in VA ETDRS lines 3.34 lines, 4/7 improved = /&gt;3 lines at week 12, 4/6 at week 25 (2/4 for CRVO), CRT 260 μm at 25 weeks: VA 20/227 (p = 0.169), CRT 229 μm; 12 weeks: VA 20/278 (p = 0.193), CRT 252 μm (p = 0.05)</td>
</tr>
<tr>
<td>Pai</td>
<td>Prospective case series</td>
<td>9 eyes</td>
<td>CRVO</td>
<td>12 weeks</td>
<td>None</td>
<td>IVB 1.25 mg x 1</td>
<td>VA 20/468, CRT 614 μm</td>
<td>4 mo: VA = 20/80, CRT = 323 μm, VA gain similar for nonischemic and ischemic CRVO</td>
</tr>
<tr>
<td>Pringlinger</td>
<td>Prospective case series</td>
<td>46 eyes</td>
<td>CRVO</td>
<td>6 months</td>
<td>None</td>
<td>IVB 1.25 mg</td>
<td>VA 20/250, CRT 535 μm</td>
<td>6 mo: VA = 20/53, CRT = 190 μm (p &lt; 0.05)</td>
</tr>
<tr>
<td>Ferrara</td>
<td>Retrospective case series</td>
<td>6 eyes</td>
<td>CRVO</td>
<td>Mean 12 months</td>
<td>None. IVB within 3 mo of onset.</td>
<td>IVB 1.25 mg, mean total 5.8 injections</td>
<td>VA 20/428, CRT 809 μm</td>
<td>VA final visit (mean 12 mo) = 20/53 (p = 0.035), CRT 6 mo = 190 μm (p &lt; 0.05)</td>
</tr>
</tbody>
</table>

**Literature Summary: Branch Retinal Vein Occlusion**

<table>
<thead>
<tr>
<th>Author</th>
<th>Study Design</th>
<th>n</th>
<th>Type</th>
<th>Total Follow-up</th>
<th>Prev Tx</th>
<th>Intravitreal Dosing Regimen</th>
<th>Baseline Data</th>
<th>Efficacy Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pai</td>
<td>Prospective case series</td>
<td>12 eyes</td>
<td>BRVO</td>
<td>12 weeks</td>
<td>None</td>
<td>IVB 1.25 mg x 1</td>
<td>VA 20/333, CRT 672 μm</td>
<td>4 weeks: VA 20/91 (p = 0.169), CRT 341 μm; 12 weeks VA 20/126 (p = 0.193), CRT 372 μm (p = 0.03)</td>
</tr>
<tr>
<td>Rabena</td>
<td>Retrospective case series</td>
<td>27 eyes</td>
<td>BRVO; 13 perfused, 11 partial or non-perfused.</td>
<td>5.3 mo (3-8 mo)</td>
<td>Grid laser, IVT (5 with no previous tx)</td>
<td>20 mo average prior to IVB (0-49 mo). IVB 1.25 mg, ave total injection 2</td>
<td>VA: 20/200, CRT 478 μm</td>
<td>1mo, 5mo, final VA 20/100 (p = 0.001), at 12 weeks 44% halved visual angle, CRT 332 μm at 12 weeks (p &lt; 0.001)</td>
</tr>
</tbody>
</table>

BRVO = branch retinal vein occlusion, CRT = central retinal thickness, 'CRVO = central retinal vein occlusion, ETDRS = Early Treatment of Diabetic Retinopathy Scale; f/u = follow-up; HRVO = hemiretinal vein occlusion, IVB = intravitreal bevacizumab, IVT = intravitreal triamcinolone, ME = macular edema, VA = visual acuity.
The optimal timing to initiate treatment with IVB is another issue requiring further study. One retrospective series studied 23 eyes treated with IVB within 3 months of diagnosis compared to another 23 eyes treated after 3 months of diagnosis. The study showed no statistical significant difference in the mean number of ETDRS letters gained between the two groups at 6 months (<3 months = 15.8 letters; >3 months = 13.4 letters). However, the <3-month group had a better baseline visual acuity and post treatment outcome. It is uncertain whether the baseline difference in BCVA was due to duration of disease. The same study also indicated that there was no statistical difference in the number of letters gained for ischemic versus nonischemic CRVO (ischemic = 13.1 letters; nonischemic = 13.9 letters). However, the baseline visual acuity was worse in the ischemic group. An average of three injections were needed over the course of 6 months for all patients. No eyes needed PRP for neovascularization.197

Limited data exist regarding electrophysiologic changes after IVB treatment for CRVO. One study of 10 eyes reported a significant improvement on multifocal electroretinogram readings at 1 and 3 months post IVB treatment.184

Case series indicate that IVB may be beneficial in the treatment of macular edema caused by CRVO (Table 5) without the risks of increased intraocular pressure and cataract formation that are associated with intravitreal triamcinolone. Even eyes with ischemic CRVO, long-standing disease, and poor visual prognosis may respond favorably to IVB treatment. The timing of initial treatment and the duration of treatment required to achieve long-term results require further evaluation. Multiple consecutive treatments may be required. Ischemic damage may preclude visual acuity improvement in some cases even if the macular edema responds. The management of neovascular complications of CRVO with IVB are discussed in a later section.

BRANCH RETINAL VEIN OCCLUSION

Macular edema is a common complication of branch retinal vein occlusion (BRVO). The standard of care at present is grid laser photocoagulation, shown to be effective in the Branch Retinal Vein Occlusion Study (BVOS).41 Recently, anti-VEGF treatments have been investigated for this disorder. A number of studies describe improved retinal thickness and visual acuity following IVB.101,118,137,138,258 In one series, BCVA improved from a baseline mean of 20/333 to 20/91 at 4 weeks after one injection. However, the effect was not sustained and at 12 weeks the visual acuity slipped to 20/126.192 In a second series 44% of 27 eyes halved their visual angle at a mean follow-up of 5.3 months, after an average of two IVB injections.183 CRT decreased from a mean of 478 microns to 332 microns.

Grid laser is generally thought to be effective in the treatment of macular edema caused by BRVO. Numerous small studies report encouraging results with IVB use (Table 5). Long-term results and the number of treatments required are unknown. A comparative study of focal laser versus IVB treatment is yet to be performed. IVB is a reasonable treatment after a 3-month period of observation in situations where standard laser treatment cannot be applied (severe retinal hemorrhages, media opacity) or when the edema is refractory to laser treatment.

PSEUDOPHAKIC CYSTOID MACULAR EDEMA

Pseudophakic cystoid macular edema (CME) following cataract removal can result in persistent decreased visual acuity despite aggressive treatment.187 However, resolution of CME often occurs without treatment. Topical nonsteroidal anti-inflammatory drugs (NSAIDS) have been shown to speed the recovery.185 The literature contains two retrospective case series of patients with persistent CME treated with IVB. The first series included 28 eyes from 25 patients, followed for a mean of 32 weeks. Twenty eyes (71.4%) had improved BCVA of 2 or more ETDRS lines, eight eyes (28.6%) remained stable, and no eyes worsened by 2 or more lines. The mean baseline BCVA was 20/160 (logMAR = 0.92) and the mean final BCVA was 20/63 (logMAR = 0.50). The mean CRT at baseline (466 microns) decreased significantly (264 microns) (p < 0.0001). Eight eyes (28.6%)
required a second injection and four (14.3%), a third injection. It is uncertain which eyes improved because of treatment and which improved as part of the natural course of the disease. A second series with 16 eyes of 16 patients showed no visual acuity benefit of IVB treatment despite repeated injections. The cause of the discrepancy in results from the two series is uncertain.

Standard treatment for persistent pseudophakic CME consists of topical NSAIDs plus topical steroids, followed by subtenons steroid injection for resistant cases. Limited retrospective case series report conflicting results for management with IVB. The potential role of IVB treatment for refractory pseudophakic CME remains uncertain.

UVEITIS-INDUCED CME

CME develops in approximately 30% of HLA B27-positive patients with anterior uveitis and is commonly found with posterior or panuveitis. Medical treatment of uveitic CME consists of topical and/or systemic NSAIDs; topical, systemic, peribulbar, or intravitreal corticosteroids; and systemic carbonic anhydrase inhibitors. One study reported on 13 patients with persistent uveitic CME treated with IVB. Eleven patients had previous medical therapy for the edema. The etiology of the uveitis varied greatly, with seven causes identified. Treatment consisted of one IVB 2.5-mg injection. Follow-up was limited to 14 weeks. Visual acuity improved by 2 lines or more in 49% of eyes at 14 weeks. Mean CRT decreased from 356 microns to 273 microns at 12 weeks. Another series of six patients with uveitic CME received IVB 1.25 mg without significant improvement in visual acuity or decrease in CRT at 1 month. Another series of 10 eyes, however, showed that IVB resulted in improved visual acuity in 4 of 10 eyes over an average of 70 days. Four eyes received two injections, and five eyes received three injections.

Considering the pathophysiology of this disorder, anti-inflammatory agents remain the mainstay of treatment. Although the visual acuity benefit following IVB treatment for uveitic CME remains controversial, it may be considered for refractory CME or in eyes with a glaucomatous steroid response.

OCCLUSIVE VASCULITIS-INDUCED MACULAR EDEMA

A case report describes one patient with mixed connective tissue disease who developed macular edema secondary to occlusive vasculitis. Visual acuity improved from 20/80 to 20/60 and CRT improved from 543 microns to 306 microns after receiving a single IVB treatment. There is insufficient evidence to recommend such treatment.

RETINITIS PIGMENTOSA MACULAR EDEMA

Two patients with persistent CME due to retinitis pigmentosa were treated with IVB. Neither patient experienced an improvement in visual acuity or retinal edema. No apparent benefit was found in this limited report.

Neovascular Glaucoma

Neovascular glaucoma (NVG) can result from numerous causes of ocular ischemia and can be a cause of significant visual morbidity. The standard treatment of NVG is retinal photocoagulation or cryotherapy, which has been reported to be effective in controlling intraocular pressure in 42–82% of cases. The CVOS found that PRP caused regression of rubeosis and angle neovascularization within 1 month in 56% (18/32) of previously untreated eyes. Concurrent treatment with topical or oral medications to lower IOP is generally necessary, and surgical pressure-lowering therapy may be required. Intravitreal bevacizumab has been utilized successfully as an initial therapy for this condition.

NVG most commonly occurs in the setting of retinal vein occlusion, but can also be induced by proliferative diabetic retinopathy or retinal artery occlusion. Numerous reports describe successful treatment of NVG secondary to these conditions. Regression of neovascular vessels and improvement in IOP has been reported within 48 hours of IVB. An early case series included four eyes with CRVO induced neovascular glaucoma with increased intraocular pressure refractory to medical treatment. These eyes were unable to have panretinal photocoagulation due to media opacities (corneal edema, vitreous hemorrhage). With intravitreal bevacizumab 1.25-mg administration, all had marked reduction of IOP within 48 hours and were able to subsequently undergo PRP laser. A retrospective, consecutive case-control study compared 11 patients receiving same-day combination therapy with IVB and PRP versus 12 patients who received PRP alone as treatment of NVG. The combination group had a significant reduction in IOP compared with the PRP-only group (–11 vs 0 mm Hg; p = 0.03) and there was a significantly higher rate and speed of neovascular regression in the combination group than in the PRP-only group (100% in 12 days vs 17% in 127 days). Other studies have shown that eyes with peripheral anterior synechia or angle closure at the time of presentation were less likely to achieve...
a lowering of their IOP with IVB, and were more likely to need glaucoma surgery. Longstanding changes in the anatomy of the trabecular meshwork preclude improvement in IOP despite the induction of regression of neovascularization.\textsuperscript{94,255}

The standard treatment for neovascular glaucoma remains PRP with IOP-lowering medications as needed. Intravitreal bevacizumab is useful in those who are unable to undergo PRP, or as bridge therapy until PRP can be performed (e.g., media opacities). In cases of severe pressure elevation despite maximal medical therapy, IVB may be administered in conjunction with PRP in an attempt to achieve rapid regression of neovascularization (Fig. 3), thereby preventing permanent angle synechiae and more quickly achieving pressure control.

**OCULAR ISCHEMIC SYNDROME**

About two-thirds of patients with ocular ischemic syndrome (OIS) present with neovascularization of the iris, with one-third of those developing NVG. Additionally, these patients can develop visual loss from macular edema. PRP causes regression of NVI in one-third of the patients.\textsuperscript{54} A case series describes two patients treated with IVB for OIS with anterior segment neovascularization. One week after treatment, both patients demonstrated regression of NVI and improvement of macular edema, with no changes in visual acuity or IOP. One eye required a second injection at 4 months. After 7 months, there was no NVI present.\textsuperscript{18}

Given the high visual morbidity associated with NVG in OIS and the relatively poor response of NVI to PRP for ocular ischemic syndrome, one may consider intravitreal bevacizumab in eyes that have persistent anterior segment neovascularization after standard PRP has been performed.

**Radiation-induced Eye Disease**

**RADIATION OPTIC NEUROPATHY**

Radiation optic neuropathy (RON) is an uncommon but destructive complication of radiation exposure to the visual pathways, occuring in patients irradiated for tumors in the choroid, retina, orbit, paranasal sinuses, and cranial fossa. RON often results in severe vision loss. Treatments have been attempted with oral corticosteroids, anticoagulation, and hyperbaric oxygen therapy, none of which have proved to be especially effective.\textsuperscript{175} Intravitreal corticosteroids have been beneficial in some eyes but cataract progression and secondary glaucoma remain potential side effects.\textsuperscript{224}

One case of IVB therapy for RON has been reported. A 69-year-old woman with a juxtapapillary choroidal melanoma was treated with a palladium-103 plaque. Eighteen months later, she developed RON with visual acuity decreased to 20/32 and symptoms of “central haze.” Ophthalmoscopy revealed optic disk neovascularization, edema, and hemorrhage. IVB 1.25 mg led to resolution of her neovascularization, edema, and cotton-wool spots, with return of visual acuity to 20/20 within 1 week. This status was maintained over 5 months of follow-up without retreatment.\textsuperscript{84}

There appears to be a possible benefit of IVB in the treatment of RON. The use of this treatment deserves further study, as the prognosis is so poor.

**RADIATION RETINOPATHY**

Radiation retinopathy can result in severe vision loss, with visual acuity diminishing to 20/200 or worse in more than 50% of patients 5 years post treatment with brachytherapy for choroidal melanoma.\textsuperscript{102} Treatment options for radiation-induced macular edema have included laser photocoagulation and intravitreal triamcinolone acetonide.\textsuperscript{223}

IVB has been used to successfully treat radiation retinopathy.\textsuperscript{24,83,165,268} Six patients with radiation retinopathy secondary to ophthalmic plaque irradiation for choroidal melanomas received a mean of 2.8 IVB injections over a mean follow-up of 4.7 months. There was an improvement in macular edema, retinal hemorrhage, cotton-wool spots, and microaneurysms. Two patients had improved vision (20/320 to 20/100 and 20/32 to 20/20) and none had further deterioration.\textsuperscript{38} In the largest series to date, 21 patients with radiation retinopathy were treated with IVB every 6–12 weeks. Visual acuities remained stable or improved in 86% (n = 18). Three patients (14%) regained 2 or more lines of visual acuity.\textsuperscript{85}

There appears to be a possible benefit of IVB in the treatment of radiation retinopathy in limited reports. The most suitable timing for administration is unknown. It is reasonable to consider treatment with IVB for secondary neovascularization or macular edema, particularly if laser application is precluded or ineffective.
Other

BREAST CANCER WITH CHOROIDAL METASTASIS
A 57-year-old woman with breast cancer metastatic to bone and lungs developed rapidly decreasing vision in her right eye. BCVA measured 20/200. Fundus evaluation revealed a solitary elevated choroidal mass in the posterior pole with subretinal fluid accumulation involving the fovea. Choroidal metastasis secondary to breast cancer was diagnosed. IVB 1.25 mg was administered and her visual acuity improved to 20/60 as the associated subretinal fluid reduced markedly. Both fundus evaluation and ultrasonography revealed a dramatic (50%) decrease in the size of the tumor.17

This case is of interest but provides insufficient evidence to recommend treatment at this time. Radiation therapy is very effective for managing such choroidal lesions. The reduction in tumor size deserves further study.

MELANOMA-ASSOCIATED NEOVASCULARIZATION
A 68-year-old man with skin melanoma developed epiretinal and vitreous metastasis and iris neovascularization. He was treated with vitrectomy combined with IVB. Iris neovascularization resolved within 4 days of treatment but recurred after 6 weeks. Further IVB treatment resulted in resolution of neovascularization. Epiretinal tumor plaques continued to increase in size throughout the treatment period, apparently unresponsive to the IVB therapy.119

IVB treatment for metastatic skin melanoma did not provide an antiproliferative affect on tumor growth in a single case report.

MACROANEURYSM
A single case report of a macroaneurysm in a type 2 diabetic treated with IVB has been reported. The macroaneurysm resolved along with the associated macular edema and hard exudates 2 weeks after the second of two injections of IVB delivered 1 month apart. BCVA improved from 20/400 to 20/50. The duration of effect was not reported.49

The effect in this case report is similar to that described for other causes of macular edema. Standard therapy for macroaneurysm remains observation or photocoagulation if visual acuity is threatened.

VASOPROLIFERATIVE TUMOR
A 59-year-old with a vasoproliferative tumor, previously treated with laser photocoagulation and cryotherapy presented with CME and visual acuity of 20/200. FA showed early hyperfluorescence and leakage of tumor vessels. IVB 2.5 mg was administered. Twenty-four days after treatment, the visual acuity improved to 20/20−1, the tumor thickness decreased to 1.0 mm and the macular edema resolved.134 A single report limits the ability to provide a recommendation.

COATS DISEASE
A 14-year-old boy with Coats disease unresponsive to laser treatment was treated with IVB and intra-vitreal triamcinolone acetonide. Following treatment, the superior bullous exudative retinal detachment and subfoveal serous fluid collection dramatically improved. The visual acuity improved from 20/400 to 20/125 and remained stable 6 months after injection.43 A separate article reported treatment of unilateral Coats with IVB in two girls, 14 and 16 years old, respectively. Both had macular edema and exudates of more than 6 months’ duration. One showed improvement of macular edema and exudates, confirmed with FA and OCT, with a modest visual acuity improvement. The other girl did not improve.252

Limited case reports show modest improvement in two of three eyes treated with IVB. Further study in cases that have failed standard therapy is required prior to making treatment recommendations.

JUXTAPAPILLARY CAPILLARY HEMANGIOMA
A 58-year-old patient presented with a right peripapillary hemangioma and visual acuity of 20/200. FA showed early hyperfluorescence and leakage of tumor vessels. IVB 1.25 mg was administered. Two days later a decrease in exudation was observed and visual acuity improved to 20/40. Two weeks later, PDT was administered. Within 1 month, the tumor regressed markedly and visual acuity improved to 20/25. One year after therapy, the macula remained free of edema and visual acuity was 20/25.269 In contrast, a second case report of a 23-year-old man with a Von Hippel-Lindau-associated capillary hemangioma of the optic nerve received three treatments of IVB with no effect on tumor size or exudation.66

Conflicting results exist in two case reports. The eye that derived a benefit received PDT following the IVB. There was no apparent benefit from IVB monotherapy in this condition.

IDIOPATHIC MACULAR TELANGIECTASIA
Idiopathic macular telangiectasia (IMT) is a developmental retinal vascular abnormality associated with incompetence and ectasia of perifoveal capillaries.91 Associated macular edema and subretinal neovascularization are the most common causes of visual loss. Type I is typically found in men and usually involves only one eye. Type II is found in both men and women and typically involves both eyes. Laser
Several case reports describe regression of retinal and subretinal neovascularization due to IMT when treated with IVB. In one series, six eyes of six patients with subretinal neovascularization were treated with IVB. Mean BCVA improved from 20/200 to 20/100, with a mean follow-up of 4.2 months. At the final visit, visual acuity had improved 2 or more lines in five eyes (83%) and remained the same in one eye (17%). Mean CRT improved from 263 microns to 201 microns. Only one eye received more than one (two) IVB injection. The effect of IVB on retinal thickening due to IMT has also been explored. One case report described a patient with associated macular edema refractory to focal laser treatment who was treated with IVB 1.25 mg. Within 1 week, visual acuity improved from 20/50 to 20/25 and OCT demonstrated complete resolution of macular edema. The edema recurred after 3 months, and resolved once again with a repeat treatment. Another report showed that a patient with type 1 IMT had improvement of BCVA (20/50 to 20/20) after a single injection of IVB. This was sustained over the 12-month follow-up period without need for retreatment. The same series also reported two cases of type 2 IMT, neither of which had improvement of BCVA after three injections of IVB despite reduced leakage on FA. A second series of six eyes with IMT found an average of 8.7 ETDRS letters improvement at the final 18-month follow-up period. Patients required an average of 3.5 injections of IVB over the course of the study to manage recurrences of retinal edema.

Limited case reports suggest a possible benefit of treatment with IVB for both macular edema and subretinal neovascularization in patients with idiopathic macular telangiectasia. The duration of treatment required to achieve lasting results is unknown.

POLYPOIDAL CHOROIDAL VASCULOPATHY

An initial case report appeared to show marginal benefit of IVB in the treatment of polypoidal choroidal vasculopathy (PCV). A retrospective comparative series of 15 eyes showed a logMAR BCVA improvement from 0.61 (20/81) to 0.51 (20/65) (p = 0.014) and CRT improvement from 347 to 247 microns after 3 months of monthly IVB treatment. The underlying polypoidal vascular abnormalities persisted on ICG testing. The study suggested that patients receiving subsequent PDT were less likely to have persistent polypoidal lesions. A second retrospective series confirmed the visual acuity improvement of the previous study, but reported no benefit of adding PDT to IVB treatment. 58% of eyes had an improvement of BCVA of 2 lines or greater after an average of 15 weeks (average 2.2 injections). However, another retrospective series of 11 eyes found no visual acuity benefit of IVB treatment after 3 months.

Initial reports suggest a positive effect on vascular leakage due to PCV but minimal effect on the choroidal vascular abnormality. In patients with increased central retinal thickness associated with PCV lesions that are eccentric to fixation, one might expect a more favorable outcome. Further experience with IVB monotherapy for this condition is necessary before making a recommendation.

CENTRAL SEROUS CHORIORETINOPATHY

IVB has been studied in the treatment of CSCR for treatment of subretinal fluid accumulation caused by the primary process itself. A series of five eyes with CSCR (without CNV) were treated with a single injection of IVB. All eyes had improved visual acuity, decreased leakage on FA, and diminished neurosensory detachment on OCT. Due to the limited series and lack of controls, it is difficult to distinguish between the effect of the treatment versus the natural course of the disease. However, a separate report of a patient with CSCR persistent for more than 4 months and visual acuity reduction to 20/40 showed complete resolution of the serous detachment and improved vision of 20/20 2 weeks following IVB treatment. This improvement persisted at the 6-month follow-up. The standard of care for CSCR is observation, as the great majority resolve without intervention. There is currently more evidence to support the use of focal laser or PDT for refractory cases, but potential treatment with IVB for persistent subretinal fluid with diminished visual acuity deserves further study.

EALES DISEASE

Eales disease is an idiopathic oblitative peri-vascularitis of unknown etiology with extensive retinal nonperfusion, perivascular sheathing, and neovascularization of the disk and retina that affects mainly healthy young adults. A 27-year-old man with Eales disease had a vitreous hemorrhage that resolved spontaneously over 6 months. FA revealed multiple areas of retinal neovascularization for which PRP was performed. Despite the laser, further disk and retinal neovascularization developed over the next 6 months. IVB 1.25mg was administered. At 1 month, both the disk and retinal neovascularization had regressed. Follow-up at 4 months revealed...
no recurrence of neovascularization. Another case reported dramatic regression of persistent post-laser neovascularization 1 week following a single IVB treatment. No recurrence was observed after 1 year of follow-up.

The neovascularization associated with Eales disease appears to respond to intravitreal bevacizumab in a similar manner to retinal neovascularization associated with other etiologies (PDR, Sickle cell retinopathy). Although panretinal laser remains the treatment of choice for this complication, IVB can be considered for refractory cases or for those with media opacity precluding laser. IVB is not reported to influence the vasculitic process.

NONARTERITIC ANTERIOR ISCHEMIC OPTIC NEUROPATHY

In a single case report, an 84-year-old woman with a 3-week history of nonarteritic anterior ischemic optic neuropathy (NAION) and visual acuity of count fingers at 1 foot received IVB. Ten days later she had marked reduction of nerve swelling, the visual field had improved, and her visual acuity improved to 20/70. Her vision remained stable for more than 24 weeks postinjection.

It is not uncommon for mild visual improvement to occur following NAION; however, the rapidity and extent described in the report is uncommon. Further experience with IVB in this condition will be necessary to draw conclusions.

TOPICAL BEVACIZUMAB FOR CORNEAL NEOVASCULARIZATION

Topically administered bevacizumab limits corneal neovascularization following chemical injury in a rat model. However, clinical evidence is limited. Topical bevacizumab 1% (10 mg/ml) has been used to treat corneal neovascularization due to herpes in one case and ocular cicatricial pemphigoid in another. Both eyes had corneal neovascularization resistant to topical corticosteroid treatment for many months. Within 1 month of q.i.d. application of topical bevacizumab, the superficial and deep stromal neovascularization had subsided markedly. Subconjunctival injection of bevacizumab also led to regression of corneal neovascularization due to dry eye and corneal graft failure.

Early reports show a possible clinical benefit of IVB for corneal neovascularization. The limited reports make it difficult to give a recommendation regarding treatment for this condition. Consideration should be given to the duration of treatment and uncertainty regarding systemic absorption.

BLEB REVISION

Bleb failure is a major factor limiting the long-term success of trabeculectomy surgery. The process of bleb failure involves vascularization with fibroblast migration and eventual scarring of the fistula tract. One case report describes the use of bevacizumab in bleb needling revision in a patient with a failing bleb. A 64-year-old patient presented 2 months following trabeculectomy with mitomycin C (MMC) with increasing intraocular pressure (IOP) and a vascularized bleb. Visual acuity was 20/100 and IOP was 26 mm Hg. He underwent needle bleb revision with 0.04 mg MMC twice without sustained benefit. The IOP remained at 25 mm Hg. A third needling procedure was performed with 1 mg of bevacizumab injected at the temporal base of the bleb at the end of the procedure. At the next visit, the IOP measured 7 mm Hg with evidence of a more diffuse bleb and decreased vascularization of the bleb. Two weeks later, the IOP increased to 16 at which time a second bevacizumab needling was performed. After 6 weeks of follow-up, the patient had a mildly vascularized bleb and IOP remained controlled at 6 mm Hg. Further investigation is warranted after this encouraging case report.

FILTERING SURGERY

Adjunctive IVB at the time of trabeculectomy and valve implant surgery for neovascular glaucoma has been reported. All surgeries were reported to be successful without adverse events. It is uncertain what, if any, effect the IVB had on surgical outcome. Early limited reports do not clarify the clinical benefit of IVB in filtering surgery. In cases of neovascularization, IVB may be considered as adjunctive treatment at the time of surgery or prior to surgery (see the section on neovascular glaucoma).

Safety

Both ocular and systemic side effects have been an area of debate for intravitreal anti-VEGF medications, especially so for the off-label use of bevacizumab. Intravenous use of bevacizumab for the management of colorectal cancer is associated with severe systemic side effects including arterial thromboembolism, gastrointestinal perforation, hemorrhage, hypertensive crisis and nephrotic syndrome. Of note, these patients were receiving concurrent chemotherapy. Initial studies using this therapy intravenously for ocular disease in a healthier population did not find nearly the same risks. IVB is administered at 1/400th of the dose used for intravenous treatment and has not been found to result in unexpected systemic side effects.
Pegaptanib and ranibizumab have been rigorously evaluated for safety during the FDA approval process, which ensures comparison with control groups. For ranibizumab, the combined rate of myocardial infarction and stroke during the first year of the ANCHOR and MARINA trials was higher in the 0.5 mg arm than in controls (2.9% and 1.3% respectively), but these differences were not statistically significant and were not evident at 2-year follow-up. The safety data for bevacizumab do not include controls, with the exception of a few clinical trials. In these, the follow-up is too short to make firm conclusions regarding safety. There has been no apparent systemic safety concerns related to the administration of IVB in these studies.

A safety study evaluating ocular and systemic side effects of IVB followed 1,173 patients for 12 months. Systemic adverse events were reported in 18 (1.5%) patients. These included seven (0.59%) cases of an acute elevation of blood pressure, six (0.5%) strokes, five (0.4%) myocardial infarctions, and five (0.4%) deaths. Ocular complications included seven (0.16%) bacterial endophthalmitis, seven (0.16%) tractional retinal detachments, four (0.09%) uveitis, and a case (0.02%) each of rhegmatogenous retinal detachment and vitreous hemorrhage. These results are similar to those found for the other anti-VEGF agents in registration trials. Of note, the series is retrospective and 92 patients were lost to follow-up. Also, there was no standard dosing regimen in terms of volume of administration or frequency of injection. An international Internet-based safety survey of 7,113 injections of IVB reported similar findings. The incidence of adverse events during a mean follow-up of 3.5 months included the following: 0.01% endophthalmitis, 0.21% acute blood pressure rise, 0.07% stroke, 0% myocardial infarction, and 0.03% death. Fluorophotometry has been used to demonstrate the potential risk of compounding individual doses of bevacizumab has garnered much attention. Reported series have not substantiated this concern. One study evaluated the rate of inflammatory reaction, infectious, and noninfectious endophthalmitis following 1218 injections of IVB. Infectious endophthalmitis was reported in one patient and in no patients was a noninfectious response noted. There were no reported cases of cellular infiltration or amorphous opacification of the vitreous.

The National Eye Institute is sponsoring a study to assess the safety and efficacy of IVB in a comparative trial of bevacizumab and ranibizumab for the treatment of exudative AMD. This will provide the best level of evidence regarding safety of bevacizumab.
Specifically, studies of IVB for exudative AMD have found visual acuity and morphology results similar to those of the ranibizumab registration trials. This has led to the use of IVB as a first line therapy by many retina specialists, accounting for more than 50% of anti-VEGF administrations in the United States. Its markedly lower cost has led to the adoption of IVB treatment for exudative AMD throughout the world.

The use of IVB in other conditions that can result in choroidal neovascularization (idiopathic, histoplasmosis, CSR, Bests disease, etc.) has also been expanding. The results of AMD studies with larger numbers have been extrapolated to these conditions and case series confirm positive results. CNV associated with non-AMD conditions appear to respond more favorably, requiring fewer administrations of bevacizumab to achieve lasting regression. In situations such as proliferative diabetic retinopathy and neovascular glaucoma, there is a good standard therapy. Adjunct treatment with IVB is reasonable for cases of treatment failure or when first line therapy cannot be provided. If the IVB treatment is effective, then standard treatment with photocoagulation can then be applied or supplemented for more definitive control.

For the management of macular edema due to various conditions, intravitreal bevacizumab also shows promise. Once again, standard treatment with laser takes precedence, but IVB has found a role as adjunct management for refractory cases or for cases in which laser cannot be applied. Studies comparing various monotherapies and combination therapy are underway. A randomized controlled trial studying IVB for diabetic macular edema found initial positive visual acuity results and recommended Phase 3 trials. Not only would such trials provide superior evidence on which to base management decisions, but they would also provide more clear safety data.

This paper outlines many conditions that are sufficiently rare to have limited case reports describing bevacizumab treatment. As a summary for such conditions, IVB is reasonable to use for salvage therapy of neovascularization that has not responded to standard treatment. There are a few conditions in which no significant beneficial effect has been identified, notably center-involving polypoidal vasculopathy and CME in retinitis pigmentosa.

Further safety data continue to accumulate, ranging from histology to functional retinal testing to adverse event reporting in larger trials. There is no current evidence that bevacizumab differs from the other injectable anti-VEGF agents in its safety profile. In the next few years the role of bevacizumab treatment for multiple conditions will undergo more rigorous study, allowing more refined recommendations regarding the care of patients.

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