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REVIEW

Retinal vein occlusion and macular edema – critical evaluation of the clinical value of ranibizumab

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Abstract: Retinal vein occlusions (RVOs) constitute the second most common cause of retinal vascular disease after diabetic retinopathy, with a prevalence of between 1% and 2% in persons older than 40 years of age. Despite the existence of numerous potential therapeutic options, none is entirely satisfactory, and many patients with RVO suffer irreversible visual loss. Fortunately however, the recent introduction of antivascular endothelial growth factor (VEGF) agents, such as ranibizumab (Lucentis®, Genentech, South San Francisco, CA) and bevacizumab (Avastin®, Genentech), offers a potentially new treatment approach for clinicians managing this disorder. The results of the BRAVO and CRUISE trials have provided the first definitive evidence for the efficacy and safety of ranibizumab in the treatment of RVO. As a result, ranibizumab has recently been approved by the US Food and Drug Administration for the treatment of RVO-associated macular edema. In this review, we provide a critical evaluation of clinical trial data for the safety and efficacy of ranibizumab, and address unresolved issues in the management of this disorder.

Keywords: ranibizumab, retinal vein occlusion, vascular endothelial growth factor, macular edema

Introduction

The retinal circulation is ordinarily an end-artery system that does not communicate with the blood vessels of the choroid and ciliary body – blockage of the retinal venous circulation thus leads to significant retinal damage with accompanying visual loss.[1] As such, retinal vein occlusions (RVOs) constitute the second most common cause of retinal vascular disease after diabetic retinopathy, with a prevalence of between 1% and 2% in persons older than 40 years of age.[2–4] Despite the existence of numerous potential therapeutic options, none is entirely satisfactory, and many patients with RVO suffer irreversible visual loss.[5] Fortunately however, the recent introduction of antivascular endothelial growth factor (VEGF) agents, such as ranibizumab (Lucentis®, Genentech, South San Francisco, CA) and bevacizumab (Avastin®, Genentech), offers a potentially new treatment approach for clinicians managing this disorder.[6]

In this review, we begin by providing an overview of RVO pathophysiology and describing existing treatment options for associated macular edema; we continue by highlighting the role of VEGF in RVO-associated macular edema, before describing the pharmacology of ranibizumab. We conclude with a critical evaluation of clinical trial data for the safety and efficacy of ranibizumab in this disorder.

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Pathophysiology of retinal venous occlusion

RVOs typically occur as a result of arteriosclerosis and, hence, systemic cardiovascular risk factors (eg, hypertension, hyperlipidemia, diabetes mellitus) play a key pathogenic role.[7,8] In patients with arteriolosclerosis, thickening and hardening of the retinal arterial walls may lead to retinal venous narrowing and stasis, with resultant thrombosis (the distribution of the retinal venous circulation mirrors that of the retinal arterial circulation and, at crossing-points, arteries and veins share a common adventitial sheath). In younger patients, hypercoagulability may also be a factor.[8] Occlusion of the retinal vein by thrombosis then leads to elevation of venous and intracapillary pressure, with slowing of arterial blood flow – the combination of these factors leads to extravasation of serous fluid and hemorrhage, as well as varying amounts of capillary endothelial damage. The subsequent marked increase in interstitial fluid and protein leads to an increased interstitial pressure, which can act as an impediment to capillary perfusion and result in ischemia (the role of VEGF and other growth factors in this process is discussed in a later section).[1,9]

Visual loss in RVO occurs through a varying combination of three distinct mechanisms.[1,9] Firstly, serous exudation distal to the point of obstruction may result in macular edema; when the associated damage to the vascular architecture is severe, such edema may become prolonged or permanent with attendant degenerative changes (macular holes, epiretinal membranes etc). Secondly, retinal hemorrhages may be seen in the area drained by the retinal vein distal to its obstruction; in severe cases, dissection of blood beneath the retina may lead to retinal pigment epithelium (RPE) atrophy and/or scarring, often in a subfoveal location. Finally, venous obstruction may be accompanied by ischemic damage to the retina, with extensive loss of the capillary bed and post-ischemic atrophic changes. When sufficient retinal ischemia is present, pathologic retinal neovascularization may ensue, resulting in vitreous hemorrhage and/or tractional retinal detachment, while iris neovascularization may culminate in "neovascular" glaucoma.[10,11]

Current treatment of retinal venous occlusion

RVOs are typically classified according to whether the obstruction occurs in the central retinal vein (central retinal vein occlusion [CRVO]) or one of its branches (branch retinal vein occlusion [BRVO]). This distinction is important as there are significant differences in the clinical features, and response to treatment, of each entity.[12,13] For both CRVO and BRVO, the development of pathologic neovascularization is typically treated with scatter laser photocoagulation to the peripheral areas of nonperfused retina. However, the treatment of visual loss resulting from macular edema is more complex.

Patients with macular edema as a result of BRVO typically present with moderately reduced visual acuity and even without intervention, the visual status of such patients frequently improves over time.[11] For those BRVO patients with persistent macular edema, and visual acuity of 20/40 or worse, grid laser photocoagulation to the area of capillary leakage within the macula – and outside the foveal avascular zone – may be of benefit. In the Branch Vein Occlusion Study (BVOS), eyes treated with grid laser photocoagulation were almost twice as likely as untreated eyes to gain 2 additional lines of visual acuity at 3 years (65% versus 37%).[14] However, in some patients, poor vision persisted despite treatment: in 40% of treated eyes, visual acuity was worse than 20/40 at 3 years, while in 12% of such eyes it remained below 20/200.

In comparison with BRVO, patients with CRVO-associated macular edema often present with more significantly reduced vision, which often deteriorates further with time, regardless of intervention.[10] However, the visual prognosis in such patients very much depends on the perfusion status of the retina at the time of occlusion.[1,15] Patients with "nonischemic" (or "perfused") CRVO often have relatively benign disease, with resolution of macular edema in approximately 30% of eyes over time (and pathologic neovascularization occurring only rarely).[10] However, in patients with "ischemic" (or "nonperfused") CRVOs, there is little chance of visual improvement, and the risk of pathologic neovascularization is high (neovascular glaucoma develops in approximately 25% of these eyes).[10] Unlike BRVO, the available evidence suggests that grid laser photocoagulation of macular edema in patients with CRVO is of no visual benefit.[12] In the Central Vein Occlusion Study (CVOS), patients with macular edema caused by CRVO, and visual acuity of 20/50 or worse, had no significant improvement in vision after 3 years of treatment with grid laser therapy (although fluorescein angiographic leakage was reduced).[16]

More recently, the role of intraocular corticosteroids in the treatment of RVO-associated macular edema has been extensively investigated. In addition to their potent anti-inflammatory effect, corticosteroids are known to

reduce vascular permeability.[17] In the Standard Care versus Corticosteroid for Retinal Vein Occlusion (SCORE) study, similar outcomes were achieved when BRVO was treated with either grid laser photocoagulation or preservative-free intravitreal triamcinolone; however, adverse events, such as increased intraocular pressure or cataract progression, were higher in those receiving triamcinolone.[18] In contrast, for patients with macular edema secondary to nonischemic CRVO, treatment with intravitreal triamcinolone led to superior outcomes than observation alone. Of subjects receiving triamcinolone 1 mg and 4 mg, 27% and 26%, respectively achieved a gain in visual acuity of 15 or more letters, versus only 7% of controls.[19]

While it is clear that grid laser photocoagulation is helpful for the treatment of BRVO, and that intravitreal triamcinolone is superior to observation alone for the treatment of some patients with CRVO, the limitations of both approaches are readily apparent. However, the isolation of VEGF in 1989, and the increasing awareness of its role in chorioretinal vascular diseases, has offered new opportunities to address these shortcomings.[19]

Vascular endothelial growth factor and ranibizumab

In the past 20 years, significant progress has been made in our understanding of angiogenesis, the process by which new blood vessel formation occurs in adults.[20] Angiogenic processes are initiated by an angiogenic stimulus, most commonly hypoxia, which leads to the upregulation of growth factor expression. Growth factor production, in turn, leads to vasodilatation and increases in vascular permeability, and ultimately to formation of a complex vascular network. Each step of the angiogenic sequence is controlled by a delicate balance between pro- and anti-angiogenic growth factors, the most important of which is VEGF-A (other important factors include fibroblast growth factor, platelet-derived growth factor, and erythropoietin).[21]

VEGF-A, first isolated in 1989 by Ferrara et al, is a glycoprotein produced by cells in response to hypoxia – cells deficient in oxygen produce a transcription factor, hypoxia inducible factor, that stimulates its production and release.[22,23] Circulating extracellular VEGF-A then binds to receptors on endothelial cells, leading to increased vascular permeability and proliferation of the endothelial cells. VEGF-A is the prototype member of a gene family (a group of genes with shared sequences and with similar biochemical functions) that also includes placental growth factor (PIGF), VEGF-B, VEGF-C, VEGF-D, and VEGF-E (prior to the discovery of others, VEGF-A was known simply as VEGF and the terms are used interchangeably in this review). VEGF-A has 4 major isoforms – different forms produced by alternative gene splicing. Isoforms 165 and 121 are freely diffusible outside the cell, whereas isoforms 189 and 206 are almost completely sequestered in the extracellular matrix.

For both CRVO and BRVO, the extent of associated retinal ischemia is dependent on the severity and location of the obstruction (although CRVO is typically classified as ischemic or nonischemic, a degree of retinal ischemia is present in both subtypes).[1,24] As VEGF is produced in response to hypoxia, it is not surprising that increased levels of this growth factor have been found in the ocular fluids of patients with RVO. In fact, intravitreal levels of VEGF in CRVO are the highest of those measured among all retinal vascular disease.[25] Upregulation of retinal VEGF mRNA expression has also been demonstrated in patients with RVO;[26] and correlations have been detected between aqueous concentrations of VEGF and the onset of iris neovascularization.[27] Furthermore, in primate models, almost all the features of CRVO can be replicated by intravitreal injection of VEGF.[28] Thus, for patients with RVO, strategies aimed at VEGF inhibition represent an attractive therapeutic approach, although, for RVO-associated macular edema, the relative contribution of hydrodynamic changes secondary to obstruction versus growth factor upregulation remains unclear. Furthermore, VEGF may be critical to the formation of retinal collateral circulations and the establishment of a new retinal blood flow equilibrium. Currently, one of the most effective methods for the inhibition of VEGF is through the intravitreal administration of ranibizumab.

Ranibizumab is an antibody fragment that binds and inhibits all isoforms of VEGF-A.[29] It is a chimeric molecule, consisting of an antigen-binding murine component, and a nonbinding human component that serves to make it less antigenic (in Greek mythology, the chimera was a monster with a lion's head, a goat's body, and a serpent's tail). Ranibizumab was developed by alteration of trastuzumab which is also similar to bevacizumab (Avastin), a humanized version of a murine full-length monoclonal antibody first derived in 1996, and used in the treatment of colorectal carcinoma.[22] The need for herceptin alteration was driven by preclinical studies suggesting that a full-size antibody would be unable to penetrate the retina (in apparent conflict with these findings, Shahar et al recently reported that, in rabbit eyes, intravitreal injection of bevacizumab resulted in penetration throughout the retina, but

not within the RPE or choroid).[30,31] Substitution of targeted amino acids was also performed in a bid to maximize the binding affinity of ranibizumab for VEGF, in the hope that this change would lead to improved outcomes (the VEGF binding affinity of ranibizumab is approximately 100 times that of bevacizumab).[22] In 2006, ranibizumab was licensed by the US Food and Drug Administration (FDA) for use in the United States to treat neovascular age-related macular degeneration (AMD) (www.gene.com/gene/products/information/tgr/lucentis; accessed February 18th, 2011).

Use of ranibizumab in retinal vein occlusions

The potential of anti-angiogenic therapy – pegaptanib, bevacizumab, and ranibizumab – for the treatment of RVO was recognized at an early stage; in fact, the first use of bevacizumab in CRVO was described prior to the FDA clearance of ranibizumab for neovascular AMD.[32] More recently, a number of prospective studies have evaluated the role of ranibizumab in this context.[33]

Initial prospective ranibizumab studies

In a small, single-center trial, Pieramici et al evaluated the role of intravitreal ranibizumab for the treatment of CRVO-associated macular edema (www.clinicaltrials.govNCT00406796).[34] In this study, 10 patients with perfused CRVO were randomized to receive either 0.3 mg (n = 5) or 0.5 mg (n = 5) of ranibizumab. Subjects initially received ranibizumab at baseline, and then monthly for 2 additional doses, with subsequent quarterly retreatment as required for recurrent or persistent edema. After the initial loading phase, 40% of patients gained 15 or more letters of visual acuity, with a mean increase of 12 letters, and a reduction in optical coherence tomography (OCT)-derived central retinal thickness (CRT) of 272 μm. After 9 months however, these benefits had lessened – 30% of participants gained 15 or more letters of visual acuity, with a mean increase of only one letter, and a reduction in CRT of 119 μm. As a result of these findings, the trial protocol was amended in its second year, with subjects being reviewed monthly and receiving ranibizumab retreatment (0.5 mg) as required.[35] In addition, a second cohort of patients (n = 10) was recruited and, following a similar loading phase, also received monthly, as required, ranibizumab retreatment. In the first cohort of patients, initial gains in visual acuity were lost with quarterly retreatment – these gains returned when the potential for monthly retreatment was provided in the second year. For the second cohort, the visual gains attained during the loading phase were maintained until the conclusion of the study at 2 years. A number of anatomic parameters other than CRT were also evaluated: for 19 of the 20 participants, ranibizumab resulted in reductions in intraretinal hemorrhage, optic nerve swelling, and/or venous diameter. Finally, no serious ocular adverse events were reported, although, over the 2-year period, one subject suffered from a myocardial infarction and one from a cerebrovascular event.

In a further small, single-center trial (www.clinicaltrials.gov NCT00407355), Campochiaro et al evaluated the role of ranibizumab in the treatment of macular edema in both CRVO (n = 20) and BRVO (n = 20).[36] Again, participants were randomized to 0.3 or 0.5 mg of ranibizumab, with a loading phase of three injections. For the remainder of the first year, attempts were then made to wean subjects off ranibizumab (in the hope that collateral formation and/or venous recanalization would render prolonged treatment unnecessary). In the second year, however, subjects were seen every 2 months, and received ranibizumab (0.5 mg) as required for recurrent edema.[37] Seventeen of 20 patients with BRVO completed 2 years of follow-up in this study, with a mean visual acuity increase of 17.8 letters (18% gained 6 or more lines of visual acuity, 59% gained 3 or more lines, and 76% gained 2 or more lines). On OCT, CRT decreased from an average of 481.5 μm at baseline, to 245.8 μm at month 24, with patients requiring an average of 2 ranibizumab retreatments in their second year. Fourteen of 20 patients with CRVO completed 2 years of follow-up, with a mean visual acuity increase of 8.5 letters – versus 12 letters following the loading phase (14% gained 6 or more lines of visual acuity, 21% gained 3 or more lines, and 43% gained 2 or more lines). On OCT, CRT decreased from an average of 533 μm at baseline, to 338 μm at month 24, with patients requiring an average of 3.5 injections in their second year. Additional analyses revealed that when the occlusion was present for more than a year prior to enrollment, or that 360-degree nonperfusion of the parafoveal capillaries was present, less favorable visual outcomes were achieved.

Spaide et al have also reported the outcomes of a small, prospective trial of ranibizumab for treatment of CRVO (FDA Investigator Investigational New Drug number 100,240).[38] In this study, patients with CRVO-associated macular edema (n = 20: visual acuity between 20/40 and 20/200, CRT > 250 μm) received ranibizumab at baseline (0.5 mg) and then monthly for 2 additional doses. Patients were then reviewed monthly and received ranibizumab retreatment

when either macular edema, or new intraretinal hemorrhage, were detected. Of note, many of the patients enrolled in this study were not treatment-naïve: 5 had previously received intravitreal triamcinolone, while 11 had received intravitreal bevacizumab. At 12 months of follow-up, participants had received an average of 8.5 ranibizumab injections – these injections led to an improvement in mean visual acuity of 18.5 letters, accompanied by a mean reduction in CRT of 388.6 μm (although reductions in CRT were not correlated with improvements in visual acuity). In one patient, with a history of transient ischemic attack, a cerebrovascular event was reported; in another, vitreomacular traction developed, although the patient's visual acuity remained improved relative to baseline.

The results of these initial, small, prospective studies have provided much valuable information for clinical practice and for the design of clinical trials; moreover, a number of subsequent case series have corroborated their findings.[39–42] For patients with RVO-associated macular edema, ranibizumab therapy appears to provide significant visual benefits, with visual acuity gains comparable to, or potentially better than, other therapeutic approaches. In addition to functional gain, ranibizumab therapy results in significant reductions in excess retinal thickening as determined using OCT (although the exact nature of the relationship between anatomic gains and visual benefit remains unclear). For patients with CRVO, it appears that frequent – potentially monthly – monitoring may be required for extended periods, coupled with aggressive retreatment of recurrent or persistent edema; for patients with BRVO, less frequent retreatment may be sufficient. While these results are promising, the nature of the studies precludes the drawing of firm conclusions regarding efficacy, and comparison with other therapies should be made with caution. Furthermore, the small numbers enrolled in these studies do not allow conclusions to be drawn regarding the safety of this approach. Fortunately, a number of large, randomized, controlled, multi-center, clinical trials have been undertaken – both for BRVO and for CRVO – and their initial findings have been reported.

CRUISE

Treatment of CRVO-associated macular edema was evaluated in the phase III, Central Retinal Vein OcclUsIon Study: Evaluation of Efficacy and Safety trial (CRUISE – www.clinicaltrials.gov NCT00485836).[43] The CRUISE trial was a 6-month, multi-center, randomized, sham injection-controlled study, with an additional 6 months of follow-up (total 12 months). The study included a 6-month treatment period, during which subjects received monthly intraocular injections of 0.3 mg or 0.5 mg ranibizumab, or sham injections; and a 6-month observation period, during which all patients could receive monthly ranibizumab retreatment if they met prespecified functional and anatomic criteria (visual acuity ≤20/40 or OCT-derived CRT ≥ 250 μm). Study visits, including OCT imaging, were also carried out 7 days after baseline treatment.

392 subjects with CRVO-associated macular edema were enrolled.[43] Key inclusion criteria included: CRVO-associated macular edema diagnosed within 12 months of study initiation, best-corrected visual acuity between 20/40 and 20/320, and OCT-derived CRT ≥ 250 μm (mean value obtained from 2 measurements using Stratus OCT [Carl Zeiss Meditec, Dublin, CA]). Of note, the presence of an "obvious and unequivocal" afferent pupillary defect, or previous RVO, were among the exclusion criteria. The primary efficacy outcome measure was mean change from baseline visual acuity at month 6. Secondary efficacy outcome measures included percentage of patients who gained ≥15 letters from baseline visual acuity at month 6. Additional, exploratory, efficacy outcomes included mean change from baseline NEI VFQ-25 (National Eye Institute Visual Functioning Questionnaire-25) composite score at month 6, and percentage of patients with visual acuity ≥20/40 at month 6. Safety outcomes included the incidence and severity of ocular and nonocular adverse events and serious adverse events.

Mean change from baseline visual acuity at month 6 – the primary endpoint of the study – was +12.7 letters and +14.9 letters in the 0.3 mg and 0.5 mg ranibizumab groups respectively, and +0.8 letters in the sham group ($P < 0.0001$ for each ranibizumab group versus sham).[43] The percentage of patients who gained ≥15 letters in visual acuity at month 6 was 46.2% (0.3 mg) and 47.7% (0.5 mg) in the ranibizumab groups, and 16.9% in the sham group ($P < 0.0001$ for each ranibizumab group versus sham). At month 6, significantly more ranibizumab-treated patients (0.3 mg = 43.9%; 0.5 mg = 46.9%) had BCVA of ≥ 20/40 compared with sham patients (20.8%; $P < 0.0001$ for each ranibizumab group versus sham), and OCT-derived CRT had decreased by a mean of 434 μm (0.3 mg) and 452 μm (0.5 mg) in the ranibizumab groups and 168 μm in the sham group ($P < 0.0001$ for each ranibizumab group versus sham). An improvement from baseline in the mean NEI VFQ-25 score was observed as early as month one in ranibizumab-treated patients. At month 6, the mean change from baseline score

was 7.1, 6.2, and 2.8 points in the 0.3 mg, 0.5 mg, and sham groups respectively ($P < 0.05$ for each ranibizumab group versus sham). Finally, the safety profile was consistent with previous phase III clinical trials of ranibizumab, and no new safety events were identified in patients with CRVO.

Significant reductions in macular edema were seen in both patient groups receiving ranibizumab at study visit Day 7; these changes were accompanied by significant visual improvements.[43] Thus, the majority of CRVO-associated macular edema appears to be VEGF mediated, rather than occurring secondary to increased venous pressure. The findings of the CRUISE trial also suggest that retinal ischemia is present even in patients traditionally described as having nonischemic CRVO. Of further note, patients in the CRUISE sham injection arm demonstrated similar outcomes to those of the natural history cohort in the CVOS study; but these outcomes differed from those described in the SCORE study.[16,19,43] Although the baseline visual acuity of CRUISE patients was slightly worse than that of SCORE CRVO patients (48.3 letters versus 51.0 letters respectively), CRUISE had fewer patients with large areas of capillary nonperfusion. This difference may have come about due to the exclusion of patients with an afferent pupillary defect from the CRUISE study, thus eliminating those patients with extensive capillary nonperfusion.

BRAVO

Treatment of BRVO-associated macular edema was evaluated in the phase III, *BRA*nch Retinal *V*ein *O*cclusion: Evaluation of Efficacy and Safety trial (BRAVO – www.clinicaltrials.gov NCT00486018).[44] The BRAVO trial was a 6-month, multicenter, randomized, sham injection-controlled study, with an additional 6 months of follow-up (total 12 months). The study included a 6-month treatment period, during which subjects received monthly intraocular injections of 0.3 mg or 0.5 mg ranibizumab, or sham injections; and a 6-month observation period, during which all patients could receive monthly ranibizumab retreatment if they met prespecified functional and anatomic criteria (visual acuity ≤20/40 or OCT-derived CRT ≥ 250 μm). Study visits, including OCT imaging, were also carried out 7 days after baseline treatment.

392 subjects with BRVO-associated macular edema were enrolled.[44] Key inclusion criteria included: BRVO-associated macular edema diagnosed within 12 months of study initiation, best-corrected visual acuity between 20/40 and 20/400, and OCT-derived CRT ≥ 250 μm (mean value obtained from 2 measurements using Stratus OCT). The primary efficacy outcome measure was mean change from baseline visual acuity at month 6. Secondary efficacy outcome measures included percentage of patients who gained ≥15 letters from baseline visual acuity at month 6. Additional, exploratory, efficacy outcomes included mean change from baseline NEI VFQ-25 composite score at month 6, and percentage of patients with visual acuity ≥20/40 at month 6. Safety outcomes included the incidence and severity of ocular and nonocular adverse events and serious adverse events.

Mean change from baseline visual acuity at month 6 – the primary endpoint of the study – was +16.6 and +18.3 letters in the 0.3 mg and 0.5 mg ranibizumab groups respectively, and +7.3 letters in the sham group ($P < 0.0001$ for each ranibizumab group versus sham).[44] The percentage of patients who gained ≥15 letters in visual acuity at month 6 was 55.2% (0.3 mg) and 61.1% (0.5 mg) in the ranibizumab groups, and 28.8% in the sham group ($P < 0.0001$ for each ranibizumab group versus sham). At month 6, significantly more ranibizumab-treated patients (0.3 mg, 67.9%; 0.5 mg, 64.9%) had BCVA of ≥20/40 compared with sham patients (41.7%; $P < 0.0001$ for each ranibizumab group versus sham), and OCT-derived CRT had decreased by a mean of 337 μm (0.3 mg) and 345 μm (0.5 mg) in the ranibizumab groups and 158 μm in the sham group ($P < 0.0001$ for each ranibizumab group versus sham). An improvement from baseline in the mean NEI VFQ-25 score was observed as early as month one in ranibizumab-treated patients. At month 6, the mean change from baseline score was 9.3, 10.4, and 5.4 points in the 0.3 mg, 0.5 mg, and sham groups respectively ($P < 0.05$ for each ranibizumab group versus sham). Finally, the safety profile was consistent with previous phase III clinical trials of ranibizumab, and no new safety events were identified in patients with CRVO.

As the efficacy of grid laser photocoagulation for the treatment of BRVO-associated macular edema had already been demonstrated in the BVOS,[14] BRAVO participants were eligible for grid laser 3 months after study entry if they had not shown evidence of substantial visual or anatomic improvement from baseline (providing there was sufficient clearing of retinal hemorrhages).[44] As a result, in the BRAVO study, 54.5% of patients receiving sham injections received rescue laser therapy, whereas only 18.7% and 19.8% of the 0.3 mg and 0.5 mg ranibizumab groups required the same. Therefore, the modest improvements seen in the sham group may be attributable, at least in part, to the rescue therapy.

ROCC

In addition to CRUISE and BRAVO, the smaller ROCC study (randomized study comparing ranibizumab to sham in patients with macular edema secondary to central Retinal vein OCClusion) has also employed a randomized, sham-controlled, multi-center, methodology to evaluate the efficacy of ranibizumab in RVO.[45] In this 6-month trial, 32 patients with CRVO-associated macular edema were randomized to receive monthly intravitreal ranibizumab (0.5 mg) or sham injections for 3 consecutive months, with monthly retreatment as required. Twenty-nine patients completed the study and, at 6 months, the mean change in visual acuity was +12 letters for the ranibizumab group, compared with −1 letter for the sham injection group ($P = 0.067$). The mean reduction in OCT-derived CRT was 304 μm for the ranibizumab group, compared with 151 μm for the sham group.

Conclusions and future directions

FDA approval

The results of the BRAVO and CRUISE studies provided the first definitive evidence for the efficacy and safety of ranibizumab in the treatment of RVO.[43,44] Consequently, following a priority review, ranibizumab was approved by the FDA for macular edema following RVO on June 22, 2010 (www.gene.com/gene/products/information/tgr/lucentis; accessed February 18th, 2011). In essence, the BRAVO and CRUISE studies demonstrated that just under two-thirds (61%) of patients with BRVO-associated macular edema, and just under half (48%) of patients with CRVO-associated macular edema, attained significant visual improvement (ie, 15 or more letters) when treated with intravitreal ranibizumab (0.5 mg). By comparison, in the MARINA and ANCHOR studies of neovascular AMD, approximately one-third of participants demonstrated similar visual improvement (33.8 and 40.3% respectively).[46,47]

Unanswered questions

Despite the unprecedented findings of the BRAVO and CRUISE trials, a number of significant questions remain unanswered.[43,44] In particular, the role of ranibizumab in treatment of patients with visual acuities better than 20/40 was not addressed by these studies. This is a significant issue given that, in the natural history arm of CVOS, 29% of subjects presented with a visual acuity ≥20/40.[16] Furthermore, the efficacy of ranibizumab in the treatment of patients with severely reduced visual acuity and, potentially, advanced macular ischemia, was not evaluated (the presence of an afferent pupillary defect was an exclusion criterion for both CRUISE and BRAVO, thus eliminating many subjects with ischemic CRVO).[43,44] Ranibizumab may be of benefit in treating such patients. Caution is required, however, as VEGF has also been shown to have neuroprotective properties; such qualities may acquire increased significance in the context of significant capillary nonperfusion.[48] Campochiaro et al have also provided some evidence that complete disruption of the foveal avascular zone may correlate with poor visual outcomes.[36] Therefore, as with neovascular AMD and other macular disorders, future, cellular-based therapies may acquire an important role in certain disease phenotypes.[49]

Another unanswered question is how long therapy may be deferred. It is well known from various vein occlusion trials that some patients can experience a spontaneous improvement, suggesting that a brief course of observation may be appropriate. On the other hand, there is concern that the prospects for visual recovery could be irreversibly damaged by delaying therapy. Twelve-month data from the BRAVO and CRUISE trials suggest that even when sham-treated patients were allowed to receive open-label ranibizumab after month 6, the visual acuity never equaled those of subjects receiving ranibizumab from the outset.[50]

In addition, the relative efficacy of ranibizumab versus grid laser for BRVO has not been fully studied. Although the magnitude of benefit achieved by ranibizumab-treated patients was striking, it is unknown how the BRAVO control arm would have fared if these patients were allowed laser therapy from the outset. Comparison with the outcomes of treated patients in the BVOS study is not advisable, as the patient cohorts in the 2 studies may be very different.

While there is preliminary evidence from small prospective studies, CRUISE and BRAVO have not provided long-term (beyond one year) data on the efficacy and safety of ranibizumab in RVO.[43,44] This is of critical importance, particularly given the evidence that suggests frequent and extended retreatments are likely to be required in patients with CRVO.[37] The mechanisms underlying this requirement are unknown – venous recanalization and/or collateral formation is likely to be present after 2 years and, therefore, peripheral nonperfusion may play a critical role.[37] As such, ultra-widefield fluorescein angiography may play a role in guiding ranibizumab retreatment and/or modifying therapeutic approach.[51] Advances in Doppler OCT technology may also allow additional, noninvasive, quantification of retinal blood flow in these disorders.[52]

Bevacizumab versus ranibizumab

The initial evidence of anti-angiogenic efficacy in the treatment of RVO-associated macular edema was provided by bevacizumab.[32] A number of off-label, short-term, uncontrolled, retrospective case series have since evaluated the efficacy of intravitreal bevacizumab in RVO.[53,54] The Pan American Collaborative Retina Study Group have recently evaluated the effects of bevacizumab for both CRVO and BRVO in large, retrospective, comparative multi-center studies. For CRVO, 56.8% of eyes treated with 1.25 mg of bevacizumab gained ≥3 lines of visual acuity, while 57.1% of eyes treated with 2.5 mg of bevacizumab achieved similar gains. In the 1.25 mg dose group, OCT-derived central retinal thickness improved from 635 μm to 264 μm, versus 528 to 293 μm in the 2.5 mg dose group. For BRVO, 68% of eyes treated with 1.25 mg of bevacizumab gained ≥3 lines of visual acuity, while 72% of eyes treated with 2.5 mg of bevacizumab achieved similar gains. In the 1.25 mg dose group, OCT-derived central retinal thickness improved from 453 μm to 254 μm, versus 444 to 234 μm in the 2.5 mg dose group.

The use of bevacizumab for the treatment of RVO has also been described in a number of small, prospective studies, although there remains a lack of evidence from randomized clinical trials. Prager et al[55] have recently described the functional and anatomic changes seen in RVO-patients treated with bevacizumab (21 BRVO, 8 CRVO). In their study, mean visual acuity increased by 16 letters from baseline to month 12, and central retinal thickness decreased from 558 μm at baseline to 309 μm at month 12. Of note, fluorescein angiography revealed no progression of avascular areas and no drug-related ocular or systemic adverse effects were observed. In another prospective study, Figueroa et al[56] evaluated bevacizumab in the treatment of 18 patients with CRVO and 28 patients with BRVO. In the BRVO group, mean logMAR visual acuity improved from 0.8 ± 0.38 at baseline to 0.44 ± 0.34 at 6 months. In the CRVO group, mean logMAR visual acuity improved from 1.13 ± 0.21 at baseline to 0.83 ± 0.45 at 6 months.

In 2010, the results of ABC (Avastin [Bevacizumab] for treatment of Choroidal Neovascularization) trial provided the first level I evidence for the efficacy of intravitreal bevacizumab in neovascular AMD.[57] Other, ongoing clinical trials, such as the CATT (Comparison of Age-Related Macular Degeneration Treatments Trials) and IVAN (Inhibit VEGF in Age-related choroidal Neovascularization) studies, will provide information on the relative efficacy and safety of bevacizumab versus ranibizumab in neovascular AMD.[58,59] The results of these studies will likely be of interest for the management of RVO, particularly given the low-cost of bevacizumab relative to ranibizumab. Doses of ranibizumab greater than 0.5 mg (eg, 2.0 mg) are also being evaluated in patients with neovascular AMD – such dosages may also be of benefit in retinal vascular disease.[44,58]

Ozurdex

Until recently, the options for treatment of RVO-associated macular edema were somewhat limited – now, or in the near future, however, clinicians may have the option of multiple therapeutic approaches.[60] The use of a biodegradable dexamethasone implant (Ozurdex®, Allergan, Inc., Irvine, CA), for the treatment of RVO-associated macular edema, has recently been approved by the FDA (www.ozurdex.com; accessed February 18, 2011). In the GENEVA trials of Ozurdex, a single treatment with a dexamethasone implant produced significantly greater improvements in visual acuity than did a sham procedure – the greatest response was at day 60, where 29% of treated subjects benefited from a 15-letter gain in visual acuity, versus 11% in the sham group.[61] Just as for the SCORE trial, comparison of GENEVA trial results with the BRAVO and CRUISE data is challenging because of significant differences in the cohorts between the studies. In the GENEVA trials, among patients with CRVO, only 17% of patients had a disease duration of less than 3 months, compared with 39% in the SCORE-CRVO trial, and 69% in the CRUISE study. Given that longer duration of disease before treatment negatively impacts the chance for visual recovery, this finding complicates assessment of the magnitude of treatment efficacy between studies.[12,37,60] Nevertheless, the results of the GENEVA trial highlight the main potential benefit of Ozurdex – its extended duration of action may allow for less frequent retreatment in RVO-associated macular edema.

VEGF Trap

Another agent, VEGF Trap (Regeneron Pharmaceuticals, Tarrytown, NY), is also being evaluated for the treatment of RVO-associated macular edema.[62] VEGF Trap is a fusion protein comprising segments of the extracellular domains of human VEGF receptor-1 and VEGF receptor-2, fused to the constant region of human immunoglobulin G1. VEGF Trap binds to all isoforms of VEGF-A with a higher affinity than either bevacizumab or ranibizumab, thereby offering a theoretically longer interval between doses. The use of

intravitreal "VEGF Trap-Eye" (a formulation of VEGF Trap for intraocular delivery) is being evaluated in 2 phase III clinical trials: COPERNICUS (Controlled Phase 3 Evaluation of Repeated intravitreal administration of VEGF Trap-Eye in Central retinal vein occlusion) and GALILEO (General Assessment Limiting Infiltration of Exudates in central retinal vein Occlusion with VEGF Trap-Eye). On December 20, 2010, the results of the COPERNICUS study were announced. In this trial, 56.1% of patients receiving monthly VEGF Trap-Eye (2 mg) gained at least 15 letters of visual acuity versus 12.3% of controls. Furthermore, the mean change in visual acuity, from baseline, was +17.3 letters versus −4.0 letters for the sham injection group (www.regeneron.com; accessed February 18, 2011).

Choosing among therapies

Because of the differences in patient cohorts and trials designs, comparative analyses among the various therapeutic trials with respect to safety and efficacy is fraught with complication. In addition, safety and efficacy alone may not be the only considerations. Frequency and durability of therapy, cost, phakic status, ease of treatment, and comorbid ocular and systemic conditions (eg, glaucoma, vascular disease) may all factor into the decision-making process. In addition, the potential benefit and role of combination therapy remains unknown (eg, ranibizumab + laser for BRVO). It would appear that the best strategy at present would be careful and frequent monitoring of all patients, a thorough discussion with patients of the available therapies, and selection of therapy based on the characteristics and needs of the individual patient.

Conclusions

The introduction of anti-angiogenic therapies, such as ranibizumab, has revolutionized the treatment of neovascular AMD.[58] Recent clinical trial evidence suggests that such treatments will similarly revolutionize the treatment of both BRVO and CRVO.[43,44] However, significant gaps still remain in our knowledge of ranibizumab applicability, and use of ranibizumab is unlikely to be a panacea for the treatment of RVO. In the short term, determination of optimal retreatment regimens may further improve ranibizumab efficacy, in the longer term, integration with other therapeutic approaches may also prove fruitful. Regardless, the application of ranibizumab represents an important advance in reducing visual debility from RVO-associated macular edema.

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Disclosure

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