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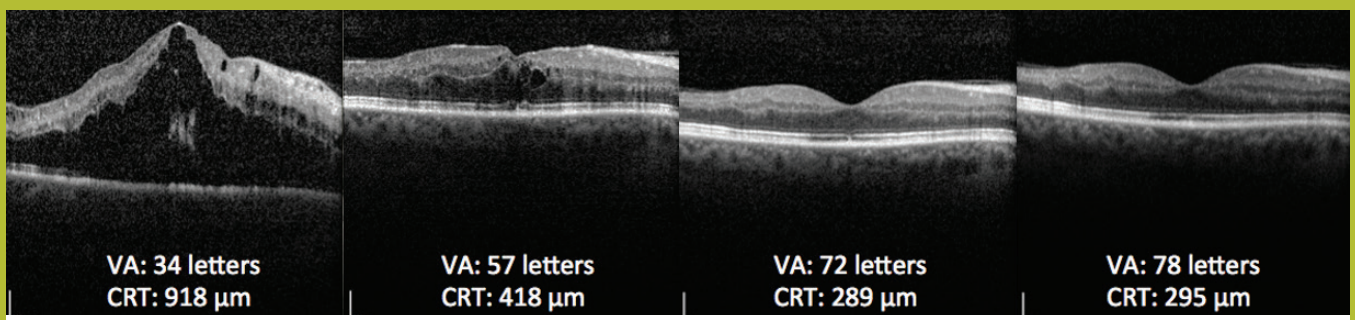

Ranibizumab:

Expanding Horizons in Retinal Vein Occlusion Management

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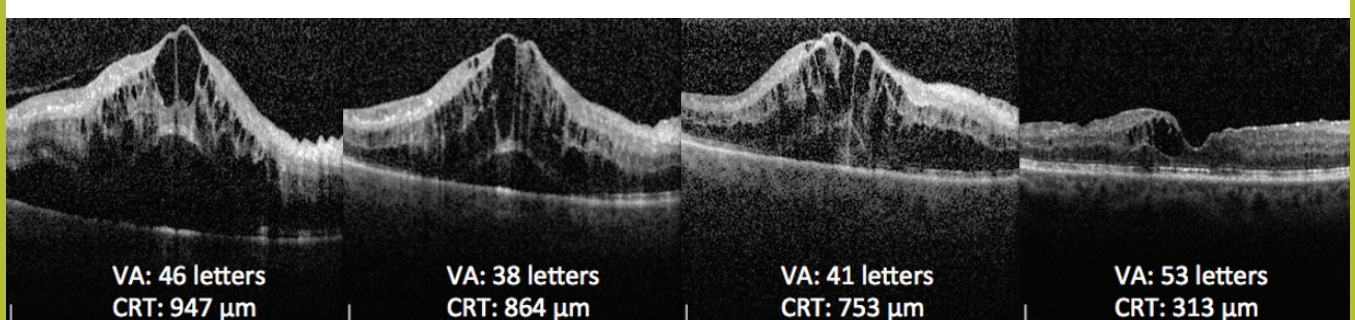

Ranibizumab:
Expanding Horizons in Retinal Vein Occlusion Management

This supplement summarizes presentations from 3 retina experts who gathered in London in September 2014 to discuss visual impairment due to macular edema secondary to retinal vein occlusion, including the latest clinical trial results of ranibizumab.

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Retinal Vein Occlusion: Disease Burden and Treatment Options

RVO patients treated with ranibizumab can expect a reduction in treatment frequency over time.

BY JORDI MONÉS, MD, PHD

As retinal surgeons, we diagnose and treat retinal vein occlusion (RVO) daily. The current treatment options offer more help than ever for our patients with this vascular disease, and a recent update in the European dosing regimen of one of the most widely recognized first-line anti-VEGF treatments, ranibizumab (Lucentis, Novartis and Roche/Genentech), supports customizing treatment based on each patient's individual prognosis and progress. This is a welcome development given the pervasiveness of this disease and its burden on patients and society.

RVO OVERVIEW

RVO is the second most common retinal vascular disease globally. Approximately 16 million people have RVO in 1 or both eyes.[1] Occlusion can occur in the central retinal vein (CRVO) or it can occur in one of the retinal branches (BRVO). Retinal ischemia can result, and if ischemia is present, the visual acuity outcome is likely to be worse than it is for patients without ischemia.[2]

The incidence of RVO is highest among elderly patients.[3] The 10-year incidence of RVO is 1.6% in people aged 49 and older, and 70% of these RVO patients have BRVO (with a prevalence of 0.44%); about 30% have CRVO (with a prevalence of 0.08%).[3-5]

Given its frequency among older patients, as well as the widespread demographic trend toward longer life expectancy, long-term management of RVO must be a consideration for physicians.[3,4]

The prognosis for untreated RVO patients is generally poor. Visual acuity is compromised at baseline and it typically decreases further over time in patients with CRVO. Greater than 30% of eyes with nonischemic CRVO convert to ischemic CRVO within 3 years, and in ischemic CRVO cases, neovascular glaucoma develops in greater than 25% of eyes within 15 months.[6]

Similarly, BRVO is not a mild disease. Only about 25% of these patients resolve spontaneously and clinically significant improvement beyond 20/40 is rare in untreated eyes. The literature shows that during a 12-month period, 5% to 15% of eyes with BRVO will develop macular edema.[7]

> Effective overall management of RVO requires attention to ophthalmic causes of impairment, as well as systemic elements of the disease.

Although the incidence of RVO is more prevalent among older people, 20% to 41% of patients are of working age at the time of RVO diagnosis.[3] This has implications both for the patients themselves with respect to their quality of life, as well as the socioeconomic climate of their environment if the condition affects their ability to work and contribute to the economy.

RVO patients typically have a complex range of comorbidities, such as diabetes and hypertension, along with RVO-related disease presentations such as retinal ischemia.[2,8] Effective overall management of RVO requires attention to ophthalmic causes of impairment, such as edema, ischemia, and neovascularization, as well as systemic elements of the disease such as hypertension and high cholesterol, among others.[2,9,10] These are important factors to consider when deciding on the optimal treatment for individual patients (Figure1).

RVO TREATMENT OPTIONS

There are a variety of options for managing this disease, including anti-VEGF therapies, steroids, and grid-pattern laser photocoagulation. An established body of evidence supports the use of ranibizumab as a first-line treatment for BRVO and CRVO.[11]

The BRAVO and CRUISE studies were key in defining a new treatment paradigm for patients with BRVO and CRVO, respectively. These two studies provided pivotal

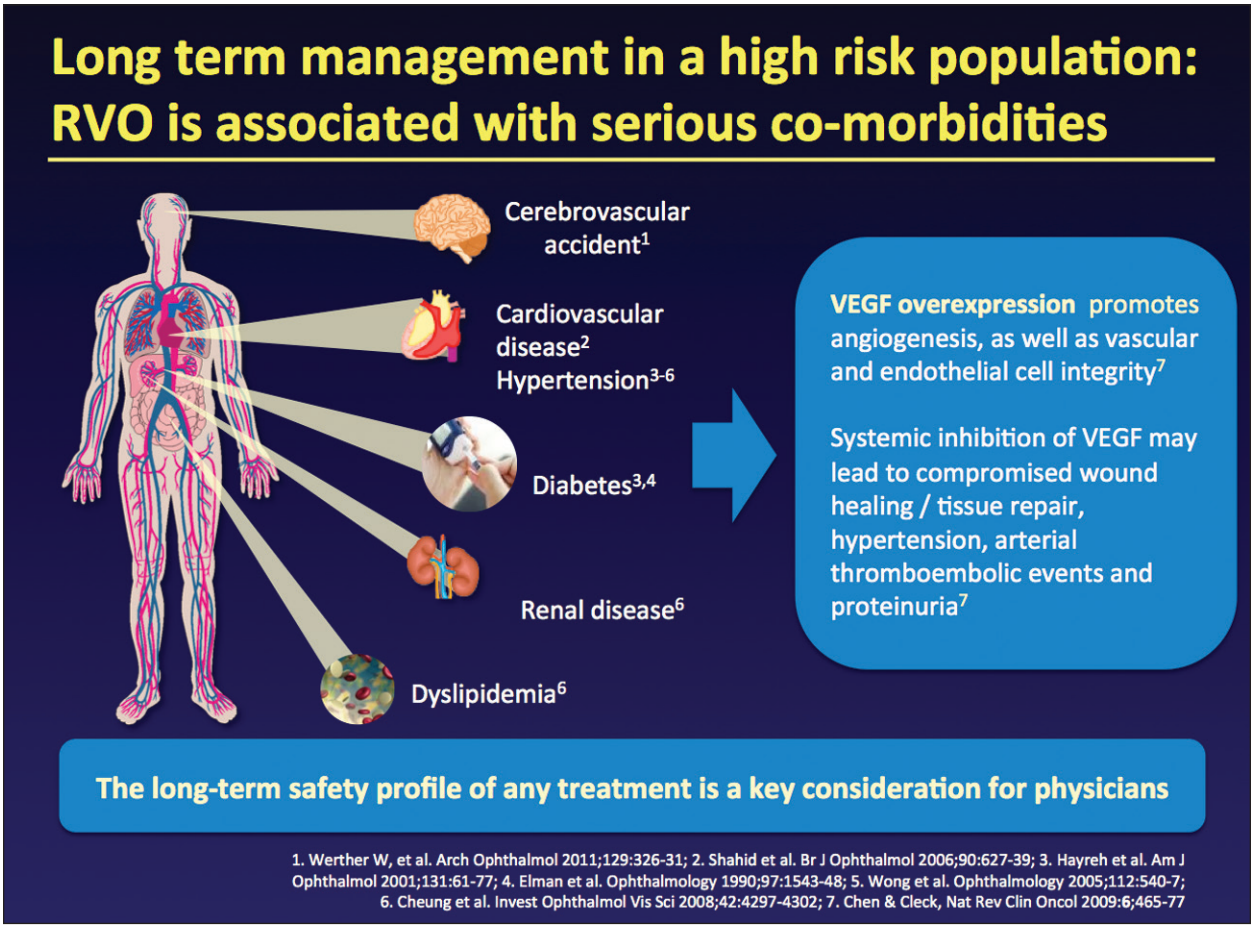

Figure 1. Underlying risk factors driving RVO include hypertension, high cholesterol, and vasculopathies. Patients typically present with a range of cardiovascular-related comorbidities.

data and a turning point for RVO patients, demonstrating the efficacy and established safety profile of ranibizumab for both BRVO and CRVO.[12,13] In these studies, ranibizumab treatment was associated with significant improvements in BCVA, which were sustained over 12 months of treatment (Figure 2).[14]

Follow up studies, including HORIZON and RETAIN,[15,16] have since demonstrated that rapid improvements in visual acuity associated with ranibizumab therapy can also be sustained in the long term.

A wealth of long-term evidence has demonstrated that administering injections of ranibizumab as needed (PRN) improves and sustains significant BCVA gains for several years. The RETAIN study showed that PRN ranibizumab led to sustained gains in BCVA for at least 4 years.[16] There was a small number of patients in the RETAIN study, and an admittedly a high dropout rate; however, it did show a long-term benefit.[16]

The SHORE[17] study examined monthly versus PRN dosing. In this study, a durable response was achieved from 7 through 15 months with a low number of injections. Findings from this study suggest a flexible, individualized regimen may be enough for stable vision, and proved that there was no long-term difference for patients who received either PRN or monthly injections.

An important consideration in evaluating these data is RVO is associated with serious comorbidities, including cerebrovascular events and vascular comorbidities. VEGF overexpression is the body's defense mechanism against several manifestations of these comorbidities, particularly vasculopathy and ischemia. Systemic inhibition of VEGF may lead to compromised wound healing and tissue repair, hypertension, arterial thromboembolic events, and proteinuria. Therefore, the more dosing can be customized, and the greater the reduction in number of injections, the better off these patients will be.

EXPERT PANEL RECOMMENDATIONS

An independent European expert panel recently convened to discuss the available evidence from clinical

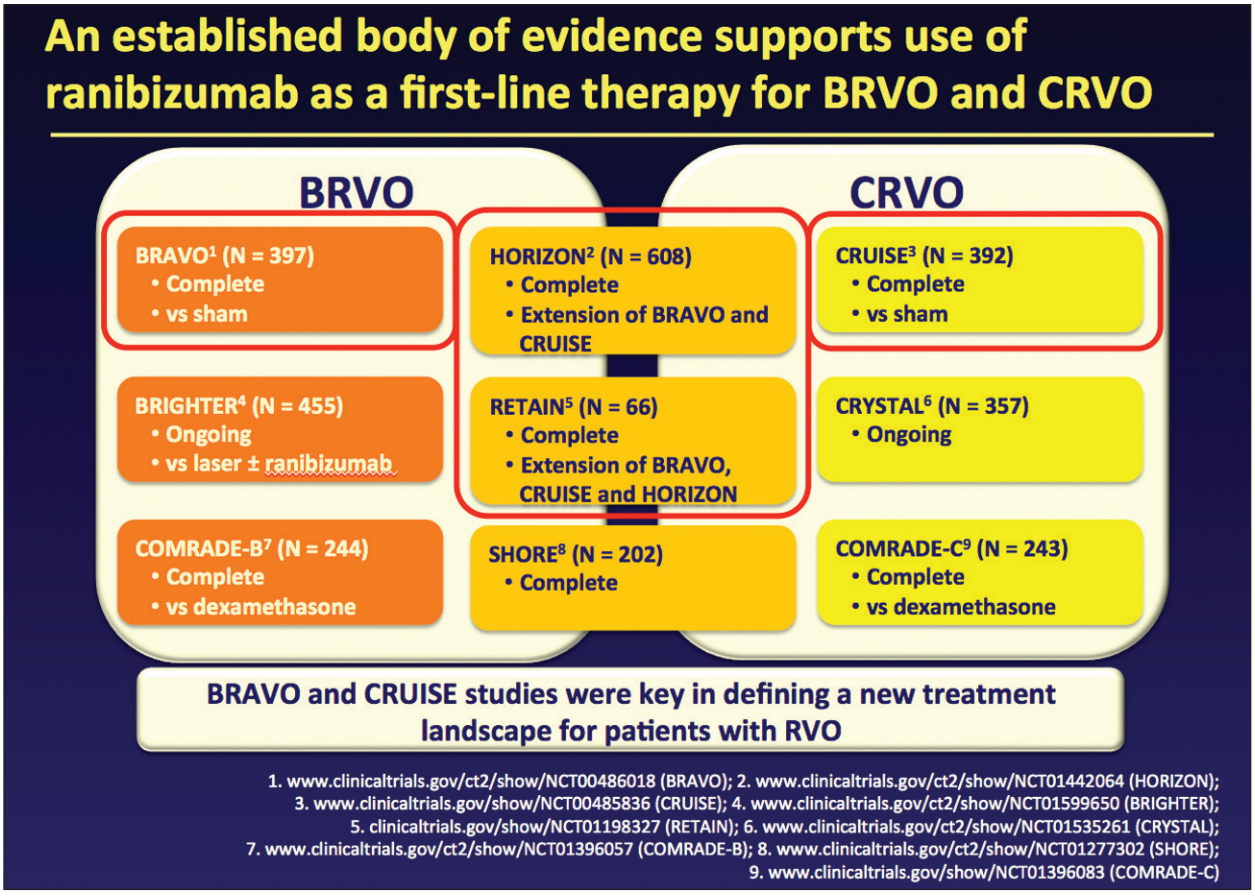

Figure 2. Ranibizumab has proven efficacy supported by a large body of clinical evidence as a flexible treatment for both BRVO and CRVO.

RVO patients being treated with ranibizumab can expect a reduction in treatment frequency over time.

studies of ranibizumab in patients with RVO.[10] The panel recommended early treatment to optimize long-term visual acuity benefits and stated that delays in anti-VEGF treatment may result in lower net improvements in BCVA and vision-related quality of life, as well as slower overall anatomic improvements. Other recommendations included initiating individualized ranibizumab treatment with monthly injections and continuing until visual acuity is stable for 3 consecutive monthly assessments. Although the safety of ranibizumab has been proven, the panel stated that long-term injections should be avoided if possible, and individualized treatment should be used more frequently to reduce associated risk and maximize outcomes.

These recommendations are reflected in the new European Union label for ranibizumab, which supports a personalized treatment approach. The label provides for flexibility in monitoring, retreatment intervals, and treatment criteria. Initial treatment entails 1 injection per month until maximum visual acuity is achieved and/or there are no signs of disease activity. Monitoring and treatment intervals are based on disease activity as assessed by visual acuity and/or anatomical parameters, and retreatment criteria is based on disease activity, as assessed by visual acuity and/or anatomical parameters based on optical coherence tomography or fluorescein angiography. This gives us the opportunity to individualize treatment as much as possible, which is the best regimen to obtain both efficacy and safety.

Evaluation of the vast body of evidence supporting the proven efficacy of ranibizumab, as well as consideration of the expert European panel's RVO treatment recommendations, and the drug's new European Union label,

suggest that RVO patients being treated with ranibizumab can expect a reduction in treatment frequency over time, as well as sustained visual gains and a well established safety profile. ■

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Identifying Optimal Treatment Pathways for BRVO

Results from pivotal studies suggest what could become a new standard treatment paradigm for BRVO.

BY LARS-OLOF HATTENBACH, MD

Branch retinal vein occlusion (BRVO) is 4 times more common than central retinal vein occlusion (CRVO),[1] and often leads to reduced visual acuity. Laser therapy was once the only treatment option supported by data from high-quality clinical trials, but this has changed since the development of anti-VEGF intravitreal injection therapy.[2-4]

PIVOTAL STUDIES

The efficacy and safety profile of the anti-VEGF agent ranibizumab (Lucentis, Novartis and Roche/Genentech) in patients with BRVO was established in the pivotal randomized, controlled clinical trial BRAVO.[4] Patients who received monthly injections of 0.5 mg of ranibizumab for 6 months had a mean BCVA gain of 18.3 letters. In the subsequent 6 months, patients were treated with an individualized as needed (PRN) regimen. At 12 months, more than 60% of patients had gained 15 or more letters of visual acuity from baseline.[3] The more recent post hoc analysis shows that 71% of patients in all cohorts achieved a cumulative gain of 15 or more letters of BCVA. The BRAVO study showed us, among other things, that patients who initially received placebo injections for the first 6 months and then switched to ranibizumab never caught up to those who received early ranibizumab injections over 12 months.

Patients who completed the BRAVO study and met the inclusion criteria were enrolled in the long-term extension studies HORIZON[5] and RETAIN[6] studies. At 4 years after enrollment into the BRAVO study, the mean BCVA gain in patients continuing in these extension studies was 20.[1] letters above baseline measurements.[5] It was notable that the mean number of injections decreased over 3 years. In the first year, patients received a mean number of 8.4 injections, including mandated monthly injections during the first 6 months of BRAVO. In the third year, a mean number of 2.4 injections were administered per patient.[5]

These results demonstrated that BRVO patients who were treated with ranibizumab can achieve and maintain large visual acuity gains over a 4-year follow-up period.

The recently published SHORE study[7] has further added to the body of evidence in support of ranibizumab for the treatment of BRVO patients. Randomized patients in the as-needed (PRN) and monthly treatment arms of the study both demonstrated good visual acuity gains over the course of the study, with the PRN arm yielding a higher numerical visual acuity gain than the monthly arm, although this was not statistically significant.

NEW DATA: BRIGHTER STUDY

Questions regarding the optimal treatment pathway for patients with BRVO remained, such as which of the currently approved therapies produced the best gains in BCVA? What effect does the dosing schedule have on outcomes, and how should patients with retinal ischemia be treated compared with those without ischemia?

The latest results from head-to-head trials, such as the BRIGHTER[8] and COMRADE-B[9] studies, have the potential to answer these questions and to help inform physicians' future treatment decisions. The BRIGHTER study was a randomized, controlled trial comparing ranibizumab with laser therapy in patients with BRVO. The study's primary objective was to evaluate the efficacy of a PRN dosing regimen with a 0.5-mg dose of ranibizumab, as assessed by the mean BCVA change, at month 12 compared with baseline. Broader inclusion/exclusion criteria allowed patients with ischemia and longer disease duration to be included in this study.[8]

The BRIGHTER study comprised 3 treatment groups: ranibizumab monotherapy; a combination of ranibizumab and adjunctive laser; and laser monotherapy. All patients who received ranibizumab were treated according to a PRN plan, with monthly monitoring from month 1 to month 6. This is an ongoing 24-month study. The primary analysis took place at 6 months.

The open-label, multicenter study involved 455 patients with visual loss from macular edema secondary

In BRIGHTER, superior improvement in BCVA occurred among patients treated with ranibizumab, either as monotherapy or in combination with laser treatment.

to BRVO. After screening, 183 patients were assigned to treatment with ranibizumab, 180 were assigned to treatment with ranibizumab plus adjunctive laser photocoagulation, and 92 were assigned to treatment with laser alone. Patients assigned to ranibizumab underwent monthly intravitreal injections in the study eye until stable visual acuity was achieved for 3 consecutive months. Patients assigned to laser therapy underwent treatment as soon as indicated, which was repeated at minimum intervals of 4 months. Laser treatments were not administered if no macular edema was present or if the patient had a BCVA of at least 79 letters.

Patients in the ranibizumab monotherapy group had better baseline visual acuity; 60% had a BCVA of at least 60 letters, compared with approximately 47% in the other 2 groups. At 6 months, ranibizumab monotherapy was associated with a mean gain in BCVA of 14.8 letters, and the combination was associated with a mean gain of 14.4 letters. In contrast, laser monotherapy was associated with a mean gain of 6.0 letters, a difference that was statistically significant, compared with the 2 ranibizumab groups.

The proven efficacy of ranibizumab in BRVO was further supported by the BRIGHTER results. In BRIGHTER, superior improvement in BCVA occurred among patients treated with ranibizumab, either as monotherapy or in combination with laser treatment. This finding is particularly noteworthy, given that laser monotherapy has been the standard of care for decades.

Other noteworthy outcomes included the finding that ranibizumab treatment provided similar BCVA gains in both ischemic and nonischemic patients over 6 months.[3] For the purpose of this study, retinal ischemia was defined as present if there was capillary loss in the macular (mild, moderate, or severe) detected by fluorescein angiography. In this study, ischemia did not affect the treatment efficacy; patients with and/or without ischemia had comparable visual outcomes over 6 months.

NEW DATA: COMRADE-B STUDY

COMRADE-B[9] supports ranibizumab as a first-line therapy for patients with BRVO. Safety data confirm the well-established safety profile of ranibizumab. COMRADE-B is the first head-to-head trial comparing ranibizumab injections with a 0.7-mg dexamethasone

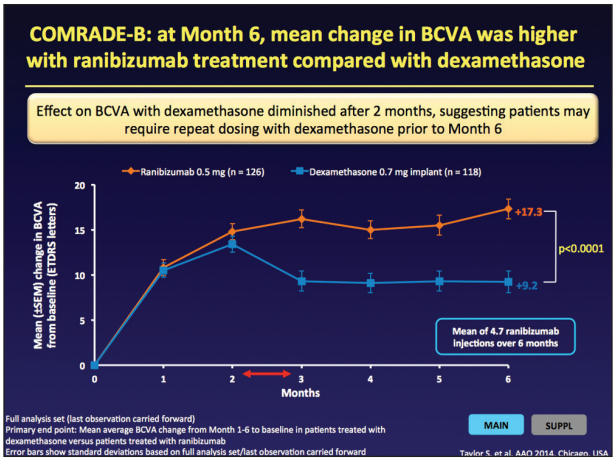

Figure 1. The effect on BCVA in patients treated with the 0.7-mg dexamethasone implant diminished after 2 months, suggesting patients may require repeat dosing with dexamethasone as soon as 3 months after the injection.

retinal implant (Ozurdex, Allergan).[9] This study also involved patients with a long duration of disease, which differs from previous studies. Ranibizumab patients received 3 initial doses, followed by PRN injections until month 6 of treatment, and the dexamethasone patients received initial injection of the dexamethasone implant followed by sham injections. The study showed that ranibizumab 0.5 mg was significantly more efficacious than the implant over 6 months for treatment of BRVO.

BCVA at baseline was 57.2 and 58.1 letters for the ranibizumab group and dexamethasone groups, respectively. The mean change at month 6 was +17.3 letters for the ranibizumab group versus +9.2. letters for the dexamethasone group. The mean average change at 6 months was +14.15 letters for the ranibizumab group and +9.66 letters for the dexamethasone group. Quality-of-life improvement assessed by National Eye Institute 25-Item Visual Function Questionnaire (NEI VFQ-25) from baseline to month 6 was significantly higher with ranibizumab than with dexamethasone, and no significant safety differences were noted except for a more frequent intraocular pressure increase seen with dexamethasone. BCVA improved steadily from baseline to month 2 in both groups. Ultimately, the study found that ranibizumab dosed PRN resulted in significantly higher BCVA gains compared with the 0.7-mg intravitreal dexamethasone implant. Although initial gains were comparable, these were not maintained with dexamethasone after month 2 (Figure 1). By 3 months, there was a clinically significant difference in efficacy between ranibizumab and dexamethasone.

The difference in visual outcome by the end of the study was statistically significant, but what was most

The results of COMRADE-B suggest that early treatment of BRVO offers the most benefit.

noteworthy was the finding that this difference was apparent after a relatively short period of time. By month 3, the difference in outcome was already clinically significant. Essentially, after the peak of dexamethasone intravitreal activity, there appeared to be a diminution of the drug's effect. The ocular pharmacological activity of the steroid implant waned after 3 months, as witnessed both by efficacy and side effects. Effect on BCVA with dexamethasone diminished after 2 months, suggesting that patients may require repeat dosing with dexamethasone as early as month 4, ie, exactly after the time period when peak drug activity of intravitreal dexamethasone occurs. This is also reflected by central retinal thickness and is witnessed by an important side effect of dexamethasone, which is increased intraocular pressure that peaks after 2 months and then returns to normal.

The safety profile of ranibizumab in the COMRADE-B study corresponded to the safety profile of previous studies.

CASE STUDIES

Data are important to gain perspective on trends in treatment choices, but for clinicians it is crucial to consider individual cases as well. For example, a 58-year-old male patient enrolled in the COMRADE-B study with arterial hypertension and baseline ischemia greater than 10 disc areas was treated with ranibizumab. After 1 month, there was a rapid improvement that remained consistent up to the end of the 6-month study, with an overall 20-letters gain in BCVA.

Another noteworthy example from the COMRADE-B study was a 73-year-old female patient, also with arterial hypertension and pronounced macular edema, who was treated with the 0.7-mg dexamethasone implant. This patient also experienced improvement, but she had a recurrence of macular edema after 3 months. After an initial improvement in macular edema, the patient experienced an overall loss of 3 lines of BCVA.

With study data supporting early intervention, PRN dosing, and ranibizumab monotherapy, increasing numbers of vitreoretinal specialists may consider this the new standard treatment paradigm for BRVO treatment. ■

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CRYSTAL and COMRADE-C Help Inform CRVO Treatment Decisions

Evidence suggests treatment with an anti-VEGF inhibitor should not be delayed in patients with CRVO.

BY MICHAEL LARSEN, MD

Central retinal vein occlusion (CRVO) occurs when there is an occlusion of the central retinal vein at or near the lamina cribrosa.[1] If the CRVO is nonperfused, accompanied by macular edema, and left untreated, the visual prognosis for the patient is poor.[1] CRVO rarely resolves spontaneously, and prior to anti-VEGF therapy, there was no treatment that could improve vision.[1,2]

EARLY TRIAL DATA REVIEW

Several randomized, controlled, intervention trials have assessed ranibizumab (Lucentis, Novartis and Roche/Genentech) in CRVO. The phase 3 CRUISE trial[3,4] of ranibizumab 0.5 mg in patients with macular edema secondary to CRVO showed rapid and sustained increases in BCVA as early as 7 days after the initial injection. Improvement was sustained over the 12-month study with a mean change of 13.9 letters from baseline BCVA letter score. The study demonstrated that 50.8% of patients treated with 0.5 mg of ranibizumab gained 15 letters of more by month 12.

The CRUISE trial also demonstrated that patients treated late with ranibizumab gained some BCVA, but only about 50% of what would be gained with early ranibizumab treatment over 12 months.

A recent post hoc analysis[5] of the CRUISE trial by Thach and colleagues showed the mean average time to gain 15 letters was 5.9 months and 66% of patients achieved a cumulative incidence of more than 15 letters in the first year of treatment.

Among the questions that remain unanswered by the CRUISE trial is how intense the PRN follow-up phase should be to maintain visual acuity gains in patients with CRVO.

The extension studies, HORIZON[6] and RETAIN,[7] showed that these BCVA improvements were sustained with a flexible, PRN dosing regimen with a mean increase in BCVA from baseline of 14.0 letters 4 years after initial treatment. Additionally, the mean number of injections decreased from 8.7 in the first year, including mandated monthly injections during the first 6 months of CRUISE, to 2.1 injections in the fourth year. These results indicate that ranibizumab treatment provides rapid gains in BCVA that are sustained long term, with a low frequency of injections depending upon patient need.

Results from the HORIZON and RETAIN studies indicate that ranibizumab treatment provides rapid gains in BCVA that are sustained long term, with a low frequency of injections depending upon patient need.

The SHORE study[8] added further information to the already rich CRVO data pool; this time PRN versus a fixed regimen of ranibizumab was evaluated. PRN and monthly dosing of ranibizumab produced similar gains in BCVA at month 15. At the start of the trial, all patients were on a fixed dosage. If stability was achieved at 7 months, those patients were randomized to receive either fixed monthly dosing or PRN treatment; patients who had not reached stability remained on monthly treatment.

The CRYSTAL[9] and COMRADE-C[10] studies included a broader patient population. This culminated in findings

that will help make treatment decisions for a diverse patient base. The aim of these studies is to determine the optimal first-line therapy; the optimal dosing regimen; and the most effective treatment strategy for patients with ischemia or a long-term disease.

NEW STUDY OUTCOMES: CRYSTAL

The CRYSTAL study[9] enrolled patients with ischemic retinal vein occlusion and patients with a relatively long duration of disease. The enrollment criteria were designed to be inclusive so as to represent a broad CRVO population.

The 24-month, phase 3b, open-label, single arm, multicenter study was designed to evaluate the long-term efficacy and safety of ranibizumab using a flexible visual acuity stabilization-driven PRN dosing regimen, in patients with visual impairment due to macular edema secondary to CRVO.

The primary endpoint of the study was to evaluate the change in BCVA from baseline to month 12. Exploratory secondary endpoints included the evaluation of the efficacy of ranibizumab in relation to patients' baseline characteristics, including retinal ischemia and how the ischemia responded to treatment.

Patients were treated with monthly ranibizumab injections until stability was achieved over 3 consecutive visits. This was followed by PRN injections with monthly monitoring for the first 12 months. In the PRN portion of the trial, ranibizumab was administered only if monitoring indicated a loss of visual acuity due to macular edema secondary to RVO. In the second year of the trial, there was an option of less frequent monitoring. This was a single-arm study because it would have been unethical to have an untreated or a laser-treated control arm in this study.

Patients with any duration of CRVO were included; the mean disease duration was 8.9 months at baseline. Patients had a mean of 53 ETDRS letters at baseline and they gained a mean of 12.3 ETDRS letters. The CRYSTAL study findings demonstrated that even when including an expanded study population with a high proportion of patients with disease duration of greater than 12 months, ranibizumab 0.5 mg was effective as a flexible stabilization-driven PRN dosing regimen. Ranibizumab treatment improved visual acuity significantly in all patients; for patients with disease duration of 9 months or longer, the visual outcome resulted in lower mean BCVA letter gains, however these gains were still greater than 10 letters.

Another key finding from the CRYSTAL trial was the existence of a ceiling effect; patients with higher baseline visual acuity had lower gains. Additionally, it was also shown that the longer the delay to treatment, the less the patient had to gain. There is a lesson to be learned here: We cannot wait forever to treat CRVO patients with an anti-VEGF inhibitor.

> COMRADE-C was the first study to compare the efficacy and safety of ranibizumab 0.5 mg with intravitreal dexamethasone implant 0.7 mg therapy for treatment of visual impairment due to macular edema secondary to CRVO.

Another finding reported along with the CRYSTAL data was that the National Institute of Clinical Excellence found no statistically significant difference between ranibizumab and aflibercept (Eylea, Bayer and Regeneron) in the mean change in BCVA from baseline to 24 weeks.[9]

NEW STUDY OUTCOMES: COMRADE-C

COMRADE-C[10] was the first study to compare the efficacy and safety of ranibizumab 0.5 mg with intravitreal dexamethasone implant 0.7 mg (Ozurdex, Allergan) therapy, for treatment of visual impairment due to macular edema secondary to CRVO. The primary endpoints were differences in BCVA gain, anatomical improvement, and the safety profile.

Ranibizumab was administered PRN until the study eye was stable. The dexamethasone implant 0.7 mg was administered once at baseline and then sham implant injections were made PRN. Patients were monitored for 6 months. Mean change in BCVA from baseline to month 1 through month 6 was superior with ranibizumab compared with the dexamethasone implant, and the change in BCVA was statistically significant at month 6. In addition, the efficacy of the dexamethasone implant started to diminish after 2 months.

Patients treated with ranibizumab achieved a gain of 16.9 letters at month 6 versus -0.7 letters for the implant. Consistent with the COMRADE-B study, by 3 months there was a clinically significant difference in efficacy between ranibizumab and the dexamethasone implant. No new safety signals emerged for either of the 2 drugs.

At month 1 and month 2, the visual acuity curves were almost identical for ranibizumab and the dexamethasone

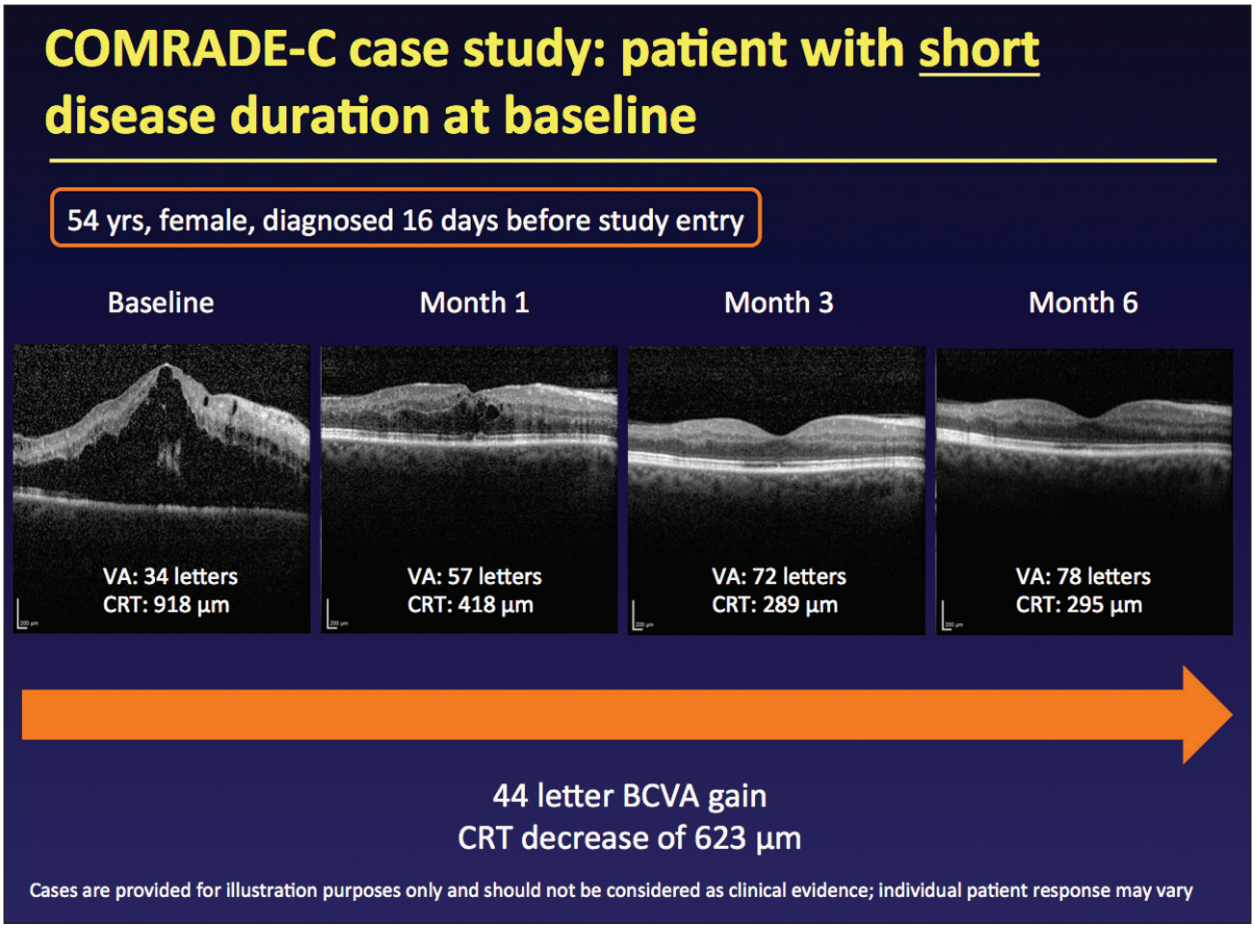

Figure 1. Optical coherence tomograms showing a very prominent macular edema diagnosed only 16 days before study entry (baseline). Three months after initiation of ranibizumab therapy, the anatomy of the macula was nearly normal and after 6 months BCVA had improved by 44 ETDRS letters.

implant. At month 3, there was a drop off in the effect of the dexamethasone implant. In this study, where early retreatment with the implant was not allowed, the visual acuity gain achieved at months 1 and 2 had disappeared by month 6. Conversely, a nearly 17-letter gain at 6 months was seen in the ranibizumab arm.

Anatomic outcomes in terms of change in foveal thickness were consistent with changes in visual acuity among patients in COMRADE-C. As well, intraocular pressure (IOP) changes were as expected: an insignificant change in IOP was seen in the ranibizumab group compared with a brief rise in IOP that returned to baseline by month 6 in the dexamethasone implant group.

Adverse events in the COMRADE-C study were minor, and not of clinical significance; however, visual acuity loss and macular edema were recorded at every time point. Some patients who received the dexamethasone implant had a recurrence of macular edema, and that was chronicled in the study outcomes.

An insignificant change in intraocular pressure was seen in the ranibizumab group compared with a brief rise in IOP that returned to baseline by month 6 in the dexamethasone implant group.

In summary, COMRADE-C demonstrated an impressive visual acuity gain among patients treated with ranibizumab for CRVO, further confirming its efficacy.

COMRADE-C CASE STUDIES

Individual COMRADE-C cases reflect the trial's cumulative outcomes. A 54-year-old woman, who was diagnosed with CRVO 16 days prior to enrollment, and

who had a baseline visual acuity of 54 ETDRS letters and significant thickening of the fovea responded to ranibizumab therapy and was stable from month 1 to month 3 with considerable gains in visual acuity. By month 6, she had achieved a 44-letter gain in BCVA (Figure 1). ■

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Question & Answer Session

EXPANDING HORIZONS IN RETINAL VEIN OCCLUSION MANAGEMENT

Jordi Monés, MD, PhD: The new data from the BRIGHTER, COMRADE-B, and COMRADE-C studies significantly enhance the body of evidence supporting ranibizumab as a first-line therapy for retinal vein occlusion (RVO). The new European Union label for ranibizumab (Lucentis, Novartis and Roche/Genentech) supports personalized as-needed (PRN) dosing in combination with consistent monitoring and appropriate treatment criteria. Did the COMRADE-C results surprise you, and how will they affect treatment decisions in the future?

Lars-Olof Hattenbach, MD: The COMRADE study outcomes will definitely affect treatment decisions because they confirm that the dexamethasone implant requires repeated injections after a relatively short time. The trial design was complicated by the fact that the retreatment interval with the dexamethasone intravitreal implant 0.7 mg (Ozurdex, Allergan) is not known. In COMRADE, we observed that retreatment was needed after 2 to 3 months. This was considered during the planning of the study; however, myself and the other monitors of the study were surprised just how early the treatment effect with the dexamethasone implant wore off. The difference was clinically significant after just 3 months. Ultimately, this means that the initial advantage of the dexamethasone implant is diminished because we have to reinject earlier than expected.

Michael Larsen, MD: I agree that getting the pharmacokinetic results from the COMRADE studies will be helpful for making treatment decisions regarding RVO treatment. In clinical practice, we do not usually have the time to evaluate patients as frequently as we do in controlled clinical trials. In clinical practice, it is more likely that we may bring in the patient very early in the treatment process to find out whether a new therapy is working, and then we titrate and retreat based on what we find. The COMRADE studies confirm that there is much to be learned from frequent monitoring, and it should be done in the first few months of RVO treatment to find the relevant retreatment interval.

OPTIMAL TIME FOR TREATMENT

Dr. Monés: What do the results from the BRIGHTER and CRYSTAL trials add to our knowledge about the treatment for RVO?

Dr. Larsen: First, they tell us that Lucentis improves visual outcome also in patients with ischemia. Second, they also tell us that it is best to treat patients early. I think the take-home message is that patients with central retinal vein occlusion (CRVO) should be treated within a week or so of presentation. For patients with wet AMD, I would say that a good clinical guideline would be to have patients treated within 2 work days from the day of presentation. Finally, the new RVO studies demonstrate that it is not hopeless to start treating patients after about 6 months of undiagnosed CRVO. However, I hope that we will never see a patient who has a documented untreated period of 120 days with CRVO. The earlier we treat, the better the outcome for the patient. But even patients who are not diagnosed until quite late in the disease process can improve once treatment is initiated. As the studies show, patients will not improve as much as if treatment was initated early, but they can expect some improvement. This is particularly important when the patient's last eye is concerned.

Dr. Hattenbach: We also have to keep in mind that some issues remain unaddressed, such as VEGF inhibition and its potential ability to save the patient from developing neovascular glaucoma. Even when patients are seen late in the disease process, with a limited potential for gaining visual acuity, we can still check the anterior segment and determine if there are additional reasons to treat. If the patient's intraocular pressure is normal, the patient may benefit from VEGF treatment and avoid neovascular glaucoma.

FACTORS TO CONSIDER WHEN CHOOSING TREATMENT

Dr. Monés: Do you have any comments about your decisions when starting treatment or for retreatment?

Dr. Hattenbach: One important point is that we only take into account the ophthalmic factors, especially because anti-VEGF treatment with ranibizumab has become the reference. In the initial phase, when anti-VEGF therapies first emerged on the scene, there was a discussion about systemic side effects. One of the striking findings with Ranibizumab treatment during the past several years has been that this is not really an issue. Ischemia, at least at the initial onset of disease, is not an issue either, nor is the existence of systemic diseases, as we have seen from the BRIGHTER study.

Dr. Larsen: There are young patients who come in with severe CRVO, have visual acuity loss and respond very well to ranibizumab. For those patients, especially young women who want to become pregnant, it is desirable for them not to be on a permanent therapy because there would be concerns regarding the safety of the fetus. In those patients, we have tried switching between treatment alternatives. Then we identify the longest possible reinjection interval by waiting until the patient begins to have disease recurrence. So far, we have found that it is safe to allow approximately a 50 µm relapse of foveal thickness, at which point we will reinject.

We have seen successful retreatment intervals as long as 8 to 12 weeks, and some patients end up no longer needing treatment. When monitoring patients, we are hoping to see signs that some vessels on the optic disc will expand and develop into collaterals that can solve the venous congestion problem by draining the venous blood from the retinal vessels down into the choroid. This does occasionally happen, but not very often, unfortunately. Often, one sees what looks like collaterals that turn out not to allow patients to stop the injections. Have you had the same experience?

Dr. Hattenbach: There are many patients for whom we can extend treatment, and sometimes BRVO may fade away and not reach the point of being irreversible or chronic. But we have helped them in the acute phase.

Another factor we have to take into account is the duration of the disease. We have seen results from studies that indicate the longer the duration of the disease, the less favorable the results. Still, we know from our clinic that it makes sense to treat even those patients who have had disease for years. For instance, we have a patient who has had recurrent macular edema secondary to CRVO for 13 years, and the ranibizumab treatment still works. Ultimately, although the studies show that early treatment is important, we all should be aware that it still makes sense to treat these patients whose disease is longstanding.

Dr. Monés: The 2 main factors that influence my choice of ranibizumab as a first-line therapy for RVO are that it is an effective and easy treatment. Sometimes I use the dexamethasone implant 0.7 mg as my first-line treatment, especially in patients with high-risk cardiovascular disease, because it has proven to be beneficial. Another factor that influences my choice is if patients are not willing to get monthly injections, especially if they are pseudophakic. In this situation, I may also consider dexamethasone implant 0.7 mg as my first choice. In general, however, since the implant does not last more than 3 months in many cases, I usually rely on ranibizumab as my first-line therapy because of its efficacy, duration, ease of use, and risk profile. ■

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