Role of Ranibizumab in the Treatment of nAMD, DME, RVO, and mCNV
This supplement features summaries of three Novartis-supported symposia held in conjunction with the 2015 Euretina Meeting in Nice, France. The speakers for each symposium represent retina experts from around the globe discussing diabetic macular edema, neovascular age-related macular degeneration, retinal vein occlusion, and myopic choroidal neovascularization.
Ranibizumab Evidence in DME: From Clinical Trials to Clinical Practice

“A wealth of phase 3 evidence supports the efficacy of anti-VEGF therapies for diabetic macular edema (DME), from the as-needed (PRN) studies, RESTORE and Protocol I, to the monthly RIDE and RISE, the treat-and-extend RETAIN, and additional PRN studies REVEAL and RESPOND, and most recently, the monthly to bimonthly aflibercept studies VIVID and VISTA,” said Prof. Paul Mitchell, Sydney, Australia. Prof. Mitchell noted these studies provide data for at least 2 years and up to 5 years of anti-VEGF therapy. They have compared anti-VEGF monotherapy to sham and laser, as well as anti-VEGF therapy combined with laser. They have addressed various dosing parameters and have studied outcomes in various ethnic populations (Table 1).

“It is interesting that peak visual acuity scores were relatively similar in all of the studies that used 0.5 mg of ranibizumab (Lucentis; Novartis Pharma AG) or 2 mg of aflibercept (Eylea; Regeneron) (Figure 1),” Prof. Mitchell said. “These studies found that when patients have better starting vision, the gain with anti-VEGF therapy will be more limited compared with those with worse starting vision. When you add the baseline mean visual acuity to the gain with ranibizumab or aflibercept, the peak gain is about the same.”

KEY STUDIES

The study of DME management with ranibizumab has evolved progressively, starting with the RESOLVE dose-finding study (Figure 2). At the time of ranibizumab’s approval in 2011, the RESTORE data were presented, and subsequently, the RETAIN PRN versus treat-and-extend model was examined,” Prof. Mitchell said. “To date, eight trials support the use of ranibizumab 0.5 mg to treat DME. These trials studied a total of 1,800 patients and included sham and laser as controls and monthly PRN or treat-and-extend regimens for up to 5 years.”

Prof. Mitchell noted the pattern of treatment response was similar in all studies. “In RESTORE, for example, in the first year, there was progressive improvement in visual acuity gain over the entire 12-month period (Figure 3),” he said. “This is unlike what we see in age-related macular degeneration, where a response occurs in the first 3 months and is then maintained.”

Prof. Mitchell also noted patients in the RESTORE study required progressively fewer injections over time. “The number of injections decreased from 7.4 in year 1, to 3.9 in year 2, and 2.9 in year 3, for
a total of 14 over the first 3 years,” he said. “These are just averages, however, as many patients stopped needing treatment altogether in year 2. Indeed, some patients stopped needing treatment after the first 3 months. Similarly, in year 3, many patients did not need treatment after the first or second year.”

In RESTORE, patients initially treated with laser were offered the opportunity to be treated with ranibizumab at the end of 12 months. “Visual acuity in those patients who switched to ranibizumab improved to about three-fourths of the gain with ranibizumab monotherapy, but not to the full extent of patients who started with ranibizumab,” Prof. Mitchell said. “So the message is that monotherapy with ranibizumab is the appropriate initial therapy.”

The Diabetic Retinopathy Clinical Research Network’s Protocol I study found better visual acuity outcomes with ranibizumab and deferred laser compared with prompt laser over 5 years (Figure 4). Table 2 shows the number of injections required for each arm over 5 years.

**TABLE 2**

<table>
<thead>
<tr>
<th>Median number of injections</th>
<th>Ranibizumab + prompt laser</th>
<th>Ranibizumab + deferred laser</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year 1</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>Year 2</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Year 3</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Year 4</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Year 5</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**QUALITY OF LIFE**

In addition to measuring clinical outcomes, researchers for the RESTORE study also measured quality of life outcomes, using the National Eye Institute Visual Function Questionnaire-25. “Health-related quality of life improved significantly from baseline with ranibizumab alone and combined with laser versus laser monotherapy,” Prof. Mitchell said. “One important point is that quality of life gains were major and marked for the patients who had better starting vision and were able to improve to normal vision. Patients who started with much poorer vision, even though they gained more in letters, did not gain as much in quality of life. So the message is: Treat early for the most effective gains in quality of life and functional outcomes.”

**CONCLUSIONS: RANIBIZUMAB IN DME**

Ranibizumab’s long-term efficacy has been well established in randomized controlled trials utilizing monthly, PRN, or treat-and-extend regimens. Early visual acuity gains are sustained up to 5 years in randomized trials.
Prof. Mitchell also noted ranibizumab has a consistent and well-documented long-term safety profile across the five indications, based on experience with almost 20,000 patients, 3.7 million patient-years of exposure, and almost 20 million injections.


What is the Preferred First-Line Treatment Option in Patients With Mild DME?

Panel: Patricio Schlottmann, MD; Nicole Eter, MD; and Pascale Massin, MD, PhD, MBA

Patricio Schlottmann, MD, Buenos Aires, Argentina, presented the case of a 50-year-old man who is responding well to anti-VEGF therapy in one eye, but had prior focal laser treatment to his fellow eye. As shown by OCT in 2011 (Figure 1), numerous scars are visible in the macula, some of them quite close to the fovea. Four years later, OCT shows that the laser scars have enlarged significantly, particularly near the fovea (Figure 2).

"This is only 4 years of progression, and this patient is just 50 years of age," Prof. Schlottmann said. "What will happen to him in 10 years? I am sure when the laser was applied to this eye, it was beautiful. But even when treatment is outside the fovea, it is just a matter of time before scars develop and merge, and eventually they will affect vision. I am sure this patient’s visual field is already affected. In some countries, his ability to drive a car would be impaired."

Prof. Schlottmann noted the ETDRS trial showed that an increased proportion of patients lose 15 letters or more of visual acuity, and this proportion increases over time.1,2 “So every year, patients lose 15 letters or more after laser photocoagulation (Figure 3),” Prof. Schlottmann said. “If you look at any trial that has used a control arm with laser, you will see that patients usually do not gain more than 1 or 2 letters at most.”3-5

Prof. Schlottmann also pointed out that in the RESTORE trial,6

![Figure 1. Clinical case 1: Scars are visible on this retina previously treated with macular laser.](image1)

![Figure 2. Clinical case 1: The laser scars have enlarged over time.](image2)
Personalized Management of DME: An Expert Panel Discussion

you treat them with laser,” Prof. Schlottmann said.

Referring to the earlier question—What is your preferred first-line option for treating patients with mild diabetic macular edema (DME)—Prof. Schlottmann addressed the choice of a steroid.

“We have interesting data comparing visual acuity gains adjusted for baseline vision (Figure 5),” he said. “Studies of ranibizumab in patients with DME have demonstrated a similar mean best-corrected visual acuity of about 70 letters at 12 months. Patients treated with the dexamethasone intravitreal implant (Ozurdex; Allergan) achieved a lower mean gain in vision at the end of year 1 than patients treated with ranibizumab. Even pseudophakic patients starting with a baseline of 55 letters, patients gained only 5 letters with dexamethasone.”

Prof. Schlottmann advised caution when performing cross-trial comparisons. He noted that MAGGIORE is a head-to-head trial comparing dexamethasone intravitreal implant with ranibizumab. “Patients treated with ranibizumab, even though they had similar baseline vision, had a much larger increase in visual acuity than those treated with dexamethasone.”

DISCUSSION

Prof. Schlottmann: Prof. Mitchell, how would you start your treatment?

Prof. Mitchell: First, I would explain to the patient that we are about to embark on a journey. In the first year, he or she will need at least seven and as many as nine treatments. This is not a small undertaking, and we should not underestimate the number of treatments patients will need. I reassure patients that we will make this journey as easy as we can for them. We will expedite their appointments for the times they want, and we will treat both eyes at the same time, if that is needed, to try to reduce the treatment burden. Patients will need a fair amount of treatment in that first year, starting monthly, but maybe with the ability to extend after the first few months.

I would start with three loading doses, but I expect we would be doing almost monthly treatments for up to the first 5 or 6 months to try to dry the retina maximally. So I would treat this patient aggressively during the first 12 months, assuming that in the second year, the patient would not need so many treatments. Hopefully, treatment could be stopped during the second or third year.

Prof. Schlottmann: You would definitely not use laser?

Prof. Mitchell: I definitely would not add laser from the beginning, because we have seen from the DRCR.net Protocol I and the RESTORE study that adding laser in the beginning produced inferior results to ranibizumab monotherapy.

Prof. Massin: Prof. Mitchell, when visual acuity is normal, what would you do?

Prof. Mitchell: Right now, we are restricted in terms of reimbursement by many authorities requiring visual acuity levels, but also, I am somewhat reluctant to treat people who have perfectly good vision,
“Patients treated with ranibizumab, even though they had similar baseline vision, had a much larger increase in visual acuity than those treated with dexamethasone.” —Patricio Schlottmann, MD

particularly if they are not symptomatic. We could recommend laser if there is non-center–involving edema, but we know that laser photocoagulation anywhere near the fovea will create laser burns that will expand. Definitely, I would not do laser any closer than 1 disc diameter from the center of the fovea.


Nicole Eter, MD
professor and chair University of Munster, Munster, Germany

Pascale Massin, MD, PhD, MBA
professor of ophthalmology at Paris VII University, Paris, France

Patricio Schlottmann, MD
consultant ophthalmologist, Organizacion Medica de Investigacion, Buenos Aires, Argentina

When is Switching Treatments an Option?

Panel: Patricio Schlottmann, MD; Nicole Eter, MD; and Pascale Massin, MD, PhD, MBA

Nicole Eter, MD, Munster, Germany, presented the case of a 69-year-old man who has had diabetes for more than 15 years. His best corrected visual acuity was 20/30 in each eye. He has macular edema involving the inner and outer retinal layers (Figure 1). Both eyes were treated with ranibizumab (Lucentis; Novartis Pharma AG) on the same day.

Four weeks later, visual acuity in the left eye had improved by 1 line, while visual acuity in the right eye remained the same (Figure 2). Both eyes were treated again with ranibizumab on the same day. Eight weeks later, the macular edema was worse in the right eye.

Figure 1. This patient presented with macular edema involving the inner and the outer retinal layers.

Figure 2. Visual acuity OD (A) remained the same, while visual OS (B) improved by 1 line. A second injection was administered to both eyes.

Figure 3. At this visit, ranibizumab was administered a third time in both eyes on the same day.

Figure 4. After continued treatment with ranibizumab, the macular edema had resolved and visual acuity had improved to 20/25.
Personalized Management of DME: An Expert Panel Discussion

(Figure 3); however, visual acuity stayed the same. “At this visit, we asked the patient about his diabetic control,” Prof. Eter said. “He told us he was trying to gain better control of his diabetes, and he had had some episodes of very low blood glucose levels, which might explain why his right eye had worsened. We administered ranibizumab a third time, again treating both eyes on the same day.”

By week 12, the macular edema had resolved in both eyes and visual acuity improved to 20/25 (Figure 4).

“This outcome leads me to another point,” Prof. Eter said. “Not only is the progression of this disease highly variable, because it is a systemic disease, but some patients are delayed responders.”

A pooled analysis from the RESTORE extension study, looked at refractory DME patients who had lost 4 or more letters from baseline to months 1 and 2 with as-needed ranibizumab with or without laser.1 “The question is: would you change the treatment or continue with the current treatment,” Prof. Eter said. “In this pooled analysis, those patients continued with the current treatment and gained 11 letters after 3 years (Figure 5). So changing treatment would not have produced the optimal outcomes.”

Prof. Eter also noted that more than 25% of patients in the RESTORE study did not require injections at months 3 and 4 (Table). “Compared with the overall results, patients who received no injection at month 3 had better visual acuity at month 12,” she said. “They gained 8.8 letters compared to 7.5 letters in the overall group, and they needed fewer injections: 4.9 compared to 7.2. In addition, the patients who needed no injection at months 3 and 4 had even better visual acuity at month 12 with 9 letters of improvement after only 4.3 injections. So there is huge variability in the number of injections needed in the first year.”

“When you compare the results of the RESTORE and RETAIN studies and the DRCR.net Protocol I (Figure 6),”1-3 she continued, “you see a huge variability, so each individual patient seems to need a specific number of injections.”

DISCUSSION

Prof. Mitchell: My impression is that clinicians’ opinions vary widely on the topic of switching therapies. Prof. Schlottmann, what are your thoughts?

Prof. Schlottmann: There does seem to be a trend toward switching to another anti-VEGF agent. In my opinion, however, whenever you switch from one agent to another, the second drug will take all the glory, because it will be injection number 4, 5, and 6. In other words, regardless of which drug you are switching from or to, injections number 1, 2, and 3 will lay the groundwork and 4, 5, and 6 will show the effect. Most clinicians will likely look at the patient subjectively and say, “This good outcome is because I switched,” but it is actually probably not so. Again, in a trial where switching is not permitted, the effect will be exactly the same.

Prof. Mitchell: Indeed, as shown in RESTORE1 and Protocol I, there was a progressive improvement in vision over the first 12 months. For some people, progress may be slow, while others progress more rapidly. I think we cannot expect everyone to improve as rapidly or as uniformly as others. Some people will improve after a delay.

Prof. Schlottmann: The ideal scenario would be to identify which patients will respond rapidly and which patients will need more time. Perhaps some patients have a plaque of lipids under the fovea.
Prof. Mitchell: Is there a number of injections after which you would consider switching?

Prof. Schlottmann: I think if you are switching within the same class of drug, you are not likely to get anything extra, because we know the three anti-VEGF drugs work more or less the same. So, basically, when switching within the class, you will see the effect of the third, fourth, fifth, and sixth injection.

Prof. Mitchell: Prof. Eter, do you have any comments on this topic?

Prof. Eter: Especially in diabetic cases, I believe it is not advisable to switch too early. We are currently updating the German guidelines, and our recommendation is to give at least five injections. Unlike age-related macular degeneration or retinal vein occlusion, diabetic macular edema is a systemic disease that definitely needs more time to resolve.

Prof. Mitchell: Prof. Massin, your comments?

Prof. Massin: I believe we switch too early. We must look at visual acuity but we must also look at OCT, and if we see an improvement on OCT, we must continue with anti-VEGF therapy.

Pascale Massin, MD, PhD, MBA, from Paris, France, presented details of a patient who had center-involving diabetic macular edema caused mainly by leakage from microaneurysms (Figure 1). His visual acuity was 20/50. The patient had been treated with ranibizumab (Lucentis; Novartis Pharma AG), and he responded well initially, but the edema recurred rapidly about 2 to 3 months after the third injection, and his visual acuity decreased to 20/63.

After three additional ranibizumab injections, the macular thickness decreased, but the patient’s visual acuity did not improve (Figure 2). “We considered this patient a late responder,” Prof. Massin said. “Because the retinal thickness had decreased, we continued monthly injections. After two additional injections, his visual acuity remained the same, but the retinal thickness decreased somewhat (Figure 3). After the second of the two injections, we felt the eye had stabilized, so we decided to go to a treat-and-extend strategy of one injection every 2 months.

“Surprisingly, after 6 months, the patient’s visual acuity improved from 20/50 to 20/32, indicating he was a very late responder,” Prof. Massin continued. “His macular thickness continued to decrease, but visual acuity did not improve.

Which DME Patients Can Be Managed With a Treat-and-Extend Regimen?

Panel: Patricio Schlottmann, MD; Nicole Eter, MD; and Pascale Massin, MD, PhD, MBA

Pascale Massin, MD, PhD, MBA, from Paris, France, presented details of a patient who had center-involving diabetic macular edema caused mainly by leakage from microaneurysms (Figure 1). His visual acuity was 20/50. The patient had been treated with ranibizumab (Lucentis; Novartis Pharma AG), and he responded well initially, but the edema recurred rapidly about 2 to 3 months after the third injection, and his visual acuity decreased to 20/63.

After three additional ranibizumab injections, the macular thickness decreased, but the patient’s visual acuity did not improve (Figure 2). “We considered this patient a late responder,” Prof. Massin said. “Because the retinal thickness had decreased, we continued monthly injections. After two additional injections, his visual acuity remained the same, but the retinal thickness decreased somewhat (Figure 3). After the second of the two injections, we felt the eye had stabilized, so we decided to go to a treat-and-extend strategy of one injection every 2 months.

“Surprisingly, after 6 months, the patient’s visual acuity improved from 20/50 to 20/32, indicating he was a very late responder,” Prof. Massin continued. “His macular thickness continued to decrease, but visual acuity did not improve.

Figure 1. This patient had center-involving diabetic macular edema caused mainly by leakage from microaneurysms.

Figure 2. After three additional treatments, macular thickness decreased, but visual acuity did not improve.
so we administered two injections every 2 months, and thereafter one injection every 6 months. After 1 year, the patient’s visual acuity was 20/32, and the macula was almost dry (Figure 4). We stopped treating the eye at this stage, and 9 months later (5 months without treatment) (Figure 5), the macula was completely dry, and the patient’s visual acuity was 20/25."

Prof. Massin noted that this case illustrates the value of a treat-and-extend regimen, as demonstrated by the RETAIN study.1 Patients in the RETAIN study were randomly assigned to one of three arms: a treat-and-extend regimen of either ranibizumab monotherapy or ranibizumab plus laser photocoagulation, or prn ranibizumab alone. “After 2 years, we found no significant differences among the three groups (Figure 6),” Prof. Massin said. “The RETAIN study was the first study to demonstrate the noninferiority of the treat-and-extend regimen to PRN dosing in DME.”

Prof. Massin also noted that patients in the treat-and-extend arms of the RETAIN study had significantly fewer visits than those in the PRN arm. “There was a 40% reduction in patient visits in the treat-and-extend arms,” Prof. Massin said, “and more than 70% of patients in those arms had a treatment interval of more than 2 months.”

DISCUSSION

Prof. Massin: Prof. Eter, do you think there is still a place for a fixed regimen for treating patients with diabetic macular edema?

Prof. Eter: I think treat-and-extend is a wonderful way to individualize the number of injections and the number of visits for patients.

“Diabetes is the largest epidemic the world is facing today (Figure 1),” said David Strain, MD, a diabetologist from Exeter, UK. “If every person with diabetes gathered in one place, it would be the third largest country in the world, with the second largest GDP just caring for those people. In addition, with so many working-age people affected with diabetes, lost earnings are significant.”

Prof. Strain went on to point out that a person is diagnosed with diabetes every 5 seconds, and someone dies of complications from diabetes every 10 seconds. “Diabetes is the main cause of heart disease and stroke in the world,” Prof. Strain said. “In fact, just about any vascular event you can name is tied to diabetes and dysglycemia. Diabetes affects the whole body. We tend to think about diabetic retinopathy and diabetic neuropathy as individual entities, but these diseases are all occurring in the same people at the same time. More than half of these patients are between 40 and 60 years old. This is a population of working people who are being afflicted by systemic vascular disease. As retina specialists, when you see patients with macular edema, the process that you are seeing in the eye is occurring in the whole body.”

According to Prof. Strain, the International Diabetes Federation surveyed people with diabetes to uncover the reasons for clinical inertia and the difficulties associated with integrating patients with physicians. “When we asked people with diabetes how they felt about having this life-changing disease, the majority of them did not see it as a problem (Figure 2),” Prof. Strain said. “If you consider that diabetes carries exactly the same prognosis as myocardial infarction, this was a surprise to us. Then we asked them which element of diabetes upset them the most. I am sure retina specialists are not

Figure 1. Diabetes has reached epidemic proportions worldwide.

Figure 3. Cardiovascular disease is the most common cause of death among people with diabetes.

Figure 2. This survey found that patients with diabetes most fear going blind.

Figure 4. Although VEGF in the eye is associated with retinopathy, in the rest of the body, VEGF is beneficial.
surprised to learn that they most feared going blind, even more than heart attack, stroke, or renal failure. This means that when patients first see a retina specialist, that is often the time when they first take their disease seriously. That is the reason we have become so involved with the retinologists in managing this disease.”

Cardiovascular disease is the most common cause of death among people with diabetes (Figure 3), and according to Prof. Strain, retinal disease is the first sign that the heart is affected. “We know that patients with macular edema are approximately four times more likely to develop ischemic heart disease,” he said.

Prof. Strain dispelled what he believes is a misperception among some physicians that vascular endothelial growth factor (VEGF) does harm in the body. “Although VEGF in the eye is thought to be pathogenic in retinopathy, in the rest of the body, VEGF is beneficial (Figure 4),” he said. “We know, for example, that if you upregulate VEGF in the canine model, it will hasten the recovery of myocardial infarction. We know that mouse models with diabetic cardiomyopathy do much better if you can induce VEGF over-expression. In humans, researchers are exploring the possibility that increased VEGF stimulation within the myocardium will produce a benefit in diabetic cardiomyopathy.

“We have gained a wealth of experience from studies of systemic VEGF treatment in oncology,” Prof. Strain continued. “Clearly, when you are treating a cancer with anti-VEGF therapy, you are not overly concerned about the vascular issues because, at the end of the day, this patient is dying from cancer, but by monitoring cancer treatments, we are able to see much of the effect of blocking systemic VEGF (Figure 5).”

Prof. Strain concluded his talk by presenting a typical case from his service. This 58-year-old man has had diabetes for approximately 5 years,” he said (Figure 6). “His HbA1c control is poor. His blood pressure is not optimal but is being treated. He has the typical diabetic adverse lipid profile, and he has had a stroke. We were informed by the retina service that this patient needs some retinal care.”

CASE DISCUSSION

Retina specialist Christian Prüente, MD, PhD, of Basel, Switzerland, related his impressions of the patient described by Prof. Strain. “This patient came to us with numerous comorbidities and systemic risk factors,” he said. “His visual acuity was 20/200 OU, and he had clear lenses. He had undergone incomplete panretinal photocoagulation in both eyes. Fluorescein angiography and OCT showed typical diabetic macular edema with some ischemia in the central retina (Figure 7).

“Considering the patient’s comorbidities and risk factors, we held intensive discussions with the patient, his diabetologist, and his neurologist about first-line therapy—whether it should be intravitreal anti-VEGF, intravitreal steroid, or laser—as well as the treatment strategy—fixed regimen, PRN, or treat-and-extend,” Prof. Prüente said. “The patient wanted to have the best efficacy treatment with minimal visits in the clinic, so we decided that he would receive bilateral injections of ranibizumab (Lucentis; Novartis Pharma AG) on a treat-and-extend regimen.”

The edema in both eyes responded well to four monthly bilateral
injections of ranibizumab (Figure 8). His visual acuity improved slightly in the right eye (from 20/400 to 20/200), while visual acuity in the left eye improved to 20/50. “The treatment interval was extended to 6 weeks, which is our regimen for treat-and-extend,” Prof. Prüente said. “The situation further improved morphologically, visual acuity was stable, and the treatment interval was extended to 8 weeks. At the next visit, however, the DME had recurred, and the patient’s visual acuity had decreased to 20/100 (Figure 9). The treatment interval was reduced by 4 weeks, which is our standard, and the patient improved again. He was continued at 4 weeks, which is our usual regimen when there is a change, even if it is an improvement.”

When the patient returned, his visual acuity had improved to 20/50, but he had a stroke 2 weeks before the visit, and this situation prompted further consultation among the specialists to determine next steps.

“We decided to extend the bilateral injections of ranibizumab to 8 weeks (Figure 10), mainly because the neurologist felt the patient’s vision was so important,” Prof. Prüente said. “We continued treatment, and we discussed with the patient the possibility to have bilateral. Eight weeks later, the DME had recurred, so the treatment interval was reduced by 2 weeks (not by our standard 4 weeks), because of the patient’s history of stroke. He improved under this treatment regimen, which was continued to 6 weeks. His visual acuity further improved from 20/60 to 20/50. Another 6 weeks later, the patient’s visual acuity had improved to 20/40, so we tried to extend the regimen again. The patient developed slightly more fluid in the central retina, so we reduced the treatment interval to 6 weeks again and continued with this regimen, because the patient’s condition appeared stable.”

The patient continued with treatments at 6-week intervals for approximately 6 months, when we attempted again to extend the treatment interval to 8 weeks. Once again, the edema recurred, and the visual acuity decreased (Figure 11). “We reduced the treatment interval again to 6 weeks,” Prof. Prüente said, “and we will definitely not try again to extend to 8 weeks, because that is not the optimal treatment regimen for this particular patient.”

CONCLUSION

According to Prof. Prüente, this patient’s comorbidities and systemic risks were important considerations when choosing his therapy. “We chose ranibizumab for this patient,” he said. “We have a great deal of data from studies as well as our own clinical experience to support this choice. In addition, we considered that the half-life of ranibizumab delivered intravitreally is 9 days, which is good for efficacy over time, but the systemic elimination half-life is only 2 hours. Therefore, the systemic risk exists for a short time, and this was another reason to choose ranibizumab.”


Christian Prüente, MD, PhD
head of the department of ophthalmology, Kantonsspital Baselland, Liestal, Switzerland

David Strain, MD
senior clinical lecturer, University of Exeter, Exeter, UK
Visudyne photodynamic therapy (verteporfin for injection; Novartis) was considered a game-changer for its time, as it slowed the inevitable decline of visual acuity in patients with neovascular age-related macular degeneration (nAMD). It did not, however, lead to the recovery of visual acuity for the average patient, which led to difficult discussions with those individuals.

“A massive transformation occurred in 2006 with the publication of the ANCHOR and MARINA trial results,” said Prof. Adnan Tufail, MBBS, MD, FRCOphth, of London. “These pivotal trials demonstrated that monthly intravitreal injections with ranibizumab (Lucentis; Novartis Pharma AG) produced marked visual acuity gains in patients with nAMD. Further data from the HARBOR study showed that we could achieve a meaningful recovery of vision for the average patient and sustained benefit with a personalized treatment regimen.”

Since the introduction of ranibizumab for nAMD, a number of other indications have been approved, including central retinal vein occlusion, diabetic macular edema, and myopic choroidal neovascularization (Figure 1), and we now have a unified posology that can help us tailor therapy for individual patients.

“Of course, the long-term clinical trials are not always a reflection of the real world. Patients in these studies are typically much healthier than in our regular practice, so they may recover more quickly. We now have the ability to monitor treatment outcomes in the real world,” said Prof. Tufail.

VALUE OF REAL-WORLD DATA
Prof. Tufail pointed out several key differences between patients in clinical trials and patients who are seen every day in retina clinics. “Patients enrolled in trials are generally fit and healthy and can sustain the length and intensity of tests required for a clinical trial,” he noted.

“With clinical trial data, the assumption is made that the patient will not have any comorbidities. However, in the real world, 90% of patients have comorbidities,” Prof. Tufail continued. “In the real world, the patient’s health status and ability to control the disease are very important factors that we must consider.”

MINING EMR DATA
Electronic medical records (EMR), which are akin to electronic case reports in clinical trials, feature prominently in a study initiated in 2012 that involves EMR users who are treating nAMD with ranibizumab. “In the initial study, we asked 16 centers for permission to mine their data, pseudo-anonymize it, and analyze it in our research institute,” Prof. Tufail said. “Within 2 months, we had data on 11,000 patients, representing more than 90,000 ranibizumab injection episodes, 330,000 outpatient visits, and 2.8 million data items. We now have about three times this amount of data.”

In randomized controlled trials, researchers traditionally look at changes in visual acuity from baseline. “We all were slaves to
the concept that visual improvement is a marker of an effective therapy,” Prof. Tufail said. “If we were to look at the data in a more patient-meaningful way, we would be looking at absolute visual acuity. The patients who are losing visual acuity are those with very good starting visual acuity. Although they lose a slight degree of vision, they remain in a state of good visual acuity. In contrast, the patients with excellent visual acuity gains are those with poor starting visual acuity. What is important to patients is visual acuity status, not visual acuity gain.”

In the second report of the UK AMD EMR Users Group, researchers found that eyes treated second with ranibizumab did not show as much visual acuity gain as eyes treated first, because they start with better visual acuity (Figure 2).\(^3\) “Compared with first treated eyes, however, their benefit is maintained over time,” Prof. Tufail said. “We also found that 50% of eyes treated second become involved within 3 years, if the visual acuity of the second eye is good before the onset of nAMD (Figure 3).”

Researchers next examined what happens when patients have good vision in both eyes initially and are treated with ranibizumab in both eyes. “We found that the edema can resolve and recur intermittently, and good starting vision increases the chance of good vision at the end of 1 year of treatment,” Prof. Tufail said. “These data support the notion that we need to get patients into our clinics early for screening, so we can start treating them early.”

—Prof. Adnan Tufail

not respond well to ranibizumab, with the hope that our findings will lead to more personalized and targeted therapies and will influence clinical trial design.”

POTENTIAL ETDRS BIAS

According to Prof. Tufail, researchers studying “big data” from the UK AMD EMR Users Group detected some biases associated with ETDRS visual acuity that were not noticeable in cohorts of a few hundred patients.

“As the number of patients increases to more than a few thousand, we see some characteristic peaks at 5-letter increments. So there was a bias in ETDRS visual acuity that absolutely stabilized at about 10,000 eyes,” Prof. Tufail said. “The bias is that, when patients read to the end of a line, they tend to want to stop. Whether that is a patient factor or a tester factor needs to be explored, but this finding has implications in how we interpret data, how we perform clinical trials, and how a 5-, 10- or 15-letter gain may be biased.”
“The result will be better outcomes for our patients and better designs of clinical trials.”
—Prof. Adnan Tufail

CONCLUSION

“Big data visualization can inform personalized medicine and give us novel insights,” Prof. Tufail said. “The result will be better outcomes for our patients and better designs of clinical trials.”

Clinical Decision-Making Based on Evidence

With expanding treatment options for neovascular age-related macular degeneration (nAMD), clinicians closely examine outcomes from randomized, controlled clinical trials and subsequent meta-analyses when deciding on initial therapy, and also when they consider switching therapies. Frank G. Holz, MD, from Bonn, Germany, addressed this topic during the symposium.

“When comparing outcomes from large-scale randomized clinical trials of anti-VEGF therapies, we can see that the performance of ranibizumab (Lucentis; Novartis Pharma AG) and aflibercept (Eylea; Regeneron), in terms of their ability to increase visual acuity from baseline, is comparable and maintained over time (Figure 1),” Prof. Holz said.1-5 “The ocular and systemic safety profiles of both agents are also comparable (Figure 2), which is reassuring when we educate our patients before initiating and maintaining treatment.1-8

“With choice, however, comes additional considerations,” Prof. Holz continued. “Some patients do not have an adequate response to the initial anti-VEGF agent, and this raises the issue of how to best manage these patients.”

PED IN HARBOR

According to Prof. Holz, a particularly challenging subgroup of patients includes those with vascularized pigment epithelial detachments (PEDs). “We have learned that the variability of responses—both functional and morphological—is simply enormous,” he said,

Figure 1. In terms of visual acuity gains, ranibizumab and aflibercept have produced comparable outcomes in major clinical trials.
Do Not Lose Sight: The Evolution of nAMD Management With Ranibizumab

**Figure 2.** Duration of safety data available. Both ranibizumab and aflibercept have comparable safety profiles.

**Figure 3.** A post-hoc analysis of the HARBOR study found functional and anatomic responses were quite variable among patients with PEDs.

**Figure 4.** HARBOR: Vision improvements with ranibizumab regardless of PED status at baseline. Visual acuity outcomes with ranibizumab treatment were similar, regardless of PED status at baseline.

**Figure 5.** Real-world evidence showed that the presence or absence of PED did not impact the visual acuity outcomes over 12 months.

Prof. Holz also noted there were no statistically significant differences in visual acuity outcomes in patients treated with ranibizumab, regardless of PED status at baseline, in the HARBOR study (Figure 4). “They behaved quite the same,” he said. “I believe we all have had experience with some patients whose PEDs persist and enlarge, regardless of what we do, so it is reassuring to know that, overall, patients fare well when treated with ranibizumab.”

**PED IN LUMINOUS**

LUMINOUS is a global, 5-year, multicenter, observational study across all approved indications to evaluate the long-term safety, effectiveness, treatment patterns, and health-related quality-of-life outcomes in patients treated with ranibizumab in routine clinical practice.

“So far, LUMINOUS has enrolled more than 30,000 patients—many more than in prospective, randomized clinical trials—and absent a long laundry list of exclusion and inclusion criteria,” Prof. Holz said. “Basically, the findings from the prospective studies were reproduced, in that the presence or absence of PED did not impact the visual outcomes over 12 months (Figure 5). LUMINOUS will examine a much longer follow-up period, but from these early data, we can surmise that presence of PED does not necessarily mean a poorer response. We can tell our patients they may expect improvement, and there does not seem to be a difference between the approved and licensed drugs in this regard.”

**SWITCHING DRUGS**

When a patient is not responding to initial anti-VEGF therapy, clinicians have the option to switch to another approved and licensed agent. However, criteria have not been established to predict which patients will not respond well to initial therapy. “In Prof. Tufail’s ‘big data’ analysis, (see page 14), he highlighted the huge variability between responses,” Prof. Holz said. “When we look at average curves, the outcomes appear to be stable, but as a matter of fact, behind those average values, responses from one patient to another...”
Do Not Lose Sight: The Evolution of nAMD Management With Ranibizumab

therapy is a confounding factor in treatment decisions. Figure 6. The potential for a delayed response to initial anti-VEGF treatment interval by 2 weeks (Figure 2).

Figure 6. The potential for a delayed response to initial anti-VEGF therapy is a confounding factor in treatment decisions.

CONCLUSION

“Overall, we have good visual outcomes in the vast majority of our patients, particularly those with pigment epithelial detachments, regardless of anti-VEGF choice,” Prof. Holz said. “To date, however, current data on switching therapies originate chiefly from small, uncontrolled case reports/series that report varying visual and anatomical outcomes. I am looking forward to ongoing prospective studies to further inform us about switching therapies.”


Prof. Frank G. Holz, MD
chairman, department of ophthalmology, University of Bonn, Germany

Treat and Extend: Trials and Experience

According to the 2015 Preferences and Trends Survey by the American Society of Retina Specialists,1 most US retina specialists prefer—by a wide margin—to use a treat-and-extend regimen for neovascular age-related macular degeneration (nAMD) with active choroidal neovascularization (CNV). In Europe, however, according to the same survey, most retina specialists prefer an as-needed (PRN) regimen (Figure 1).

Katja Hatz, MD, of Basel, Switzerland, noted the European label for ranibizumab (Lucentis; Novartis Pharma AG) includes guidelines for treat-and-extend, specifying a loading dose and then extending the treatment interval by 2 weeks (Figure 2).

Figure 6. The potential for a delayed response to initial anti-VEGF therapy is a confounding factor in treatment decisions.

CONCLUSION

“Overall, we have good visual outcomes in the vast majority of our patients, particularly those with pigment epithelial detachments, regardless of anti-VEGF choice,” Prof. Holz said. “To date, however, current data on switching therapies originate chiefly from small, uncontrolled case reports/series that report varying visual and anatomical outcomes. I am looking forward to ongoing prospective studies to further inform us about switching therapies.”


Prof. Frank G. Holz, MD
chairman, department of ophthalmology, University of Bonn, Germany

Treat and Extend: Trials and Experience

According to the 2015 Preferences and Trends Survey by the American Society of Retina Specialists,1 most US retina specialists prefer—by a wide margin—to use a treat-and-extend regimen for neovascular age-related macular degeneration (nAMD) with active choroidal neovascularization (CNV). In Europe, however, according to the same survey, most retina specialists prefer an as-needed (PRN) regimen (Figure 1).

Katja Hatz, MD, of Basel, Switzerland, noted the European label for ranibizumab (Lucentis; Novartis Pharma AG) includes guidelines for treat-and-extend, specifying a loading dose and then extending the treatment interval by 2 weeks (Figure 2).

“According to the 2015 Preferences and Trends Survey by the American Society of Retina Specialists,1 most US retina specialists prefer—by a wide margin—to use a treat-and-extend regimen for neovascular age-related macular degeneration (nAMD) with active choroidal neovascularization (CNV). In Europe, however, according to the same survey, most retina specialists prefer an as-needed (PRN) regimen (Figure 1).

Katja Hatz, MD, of Basel, Switzerland, noted the European label for ranibizumab (Lucentis; Novartis Pharma AG) includes guidelines for treat-and-extend, specifying a loading dose and then extending the treatment interval by 2 weeks (Figure 2).

“According to the 2015 Preferences and Trends Survey by the American Society of Retina Specialists,1 most US retina specialists prefer—by a wide margin—to use a treat-and-extend regimen for neovascular age-related macular degeneration (nAMD) with active choroidal neovascularization (CNV). In Europe, however, according to the same survey, most retina specialists prefer an as-needed (PRN) regimen (Figure 1).

Katja Hatz, MD, of Basel, Switzerland, noted the European label for ranibizumab (Lucentis; Novartis Pharma AG) includes guidelines for treat-and-extend, specifying a loading dose and then extending the treatment interval by 2 weeks (Figure 2).

“According to the 2015 Preferences and Trends Survey by the American Society of Retina Specialists,1 most US retina specialists prefer—by a wide margin—to use a treat-and-extend regimen for neovascular age-related macular degeneration (nAMD) with active choroidal neovascularization (CNV). In Europe, however, according to the same survey, most retina specialists prefer an as-needed (PRN) regimen (Figure 1).

Katja Hatz, MD, of Basel, Switzerland, noted the European label for ranibizumab (Lucentis; Novartis Pharma AG) includes guidelines for treat-and-extend, specifying a loading dose and then extending the treatment interval by 2 weeks (Figure 2).

“We now have a wealth of evidence supporting the efficacy of treat-and-extend as a really good treatment regimen, starting with a retrospective analysis in 2009 and leading up to the recent LUCAS study2,3 in 2015 (Figure 3),” Dr. Hatz said. In addition, visual acuity outcomes from numerous PRN and treat-and-extend regimens are similar to those in the LUCAS trial and other retrospective trials (Figure 4). In addition, data from my clinic falls within the same range.4

REAL-WORLD DATA FROM VISTA KLINIK

Dr. Hatz presented 12-month results from two analyses performed at Vista Klinik in Switzerland.4,5 In one analysis, patients who had
been treated using a PRN regimen were switched to a treat-and-extend regimen, and outcomes from both regimens were compared. In the second analysis, 70 treatment-naïve lesions were treated PRN, and 70 treatment-naïve lesions were treated in a treat-and-extend regimen, and outcomes were then compared.

“Let us first look at the switch-over lesions (Figure 5), because that is what we have in everyday practice when we want to change our treatment regimen,” Dr. Hatz said. “One hundred and forty-six eyes received a PRN loading dose and were maintained PRN for a mean of 17 months. Visual acuity increased at the beginning but declined over the time, despite the strict PRN regimen. You will also notice a delta visual acuity of 0.31, which is the difference between the maximum and minimum visual acuity a patient reached within this main maintenance phase. This is quite large, and it reflects a drawback of a PRN regimen, where we are always awaiting recurrence with visual acuity loss. In the end, this adds to a visual acuity loss over time.”

When patients were switched from a PRN regimen to a treat-and-extend regimen, their visual acuity increased slightly and was maintained over 12 months. “We found much less oscillation between the maximum and minimum visual acuity in the treat-and-extend phase versus the PRN phase,” Dr. Hatz said. “The mean maximum recurrence-free interval was 7.8 weeks.”

In the second analysis, which assessed the effects of both regimens on treatment-naïve lesions, researchers found a significant difference in mean BCVA at 12 months (Figure 6). “Both groups had a baseline visual acuity of 0.39, and patients in the treat-and-extend group improved to 0.57, while those in the PRN group reached 0.46,” Dr. Hatz said. “Again, the oscillation, the difference between maximum and minimum visual acuity, was much lower in the treat-and-extend group, which was also significant.”

Researchers also measured central retinal thickness in both treatment groups with similar results (Figure 7). “At 12 months, the mean central retinal thickness in the treat-and-extend group was 311 µm, while in the PRN group it was 357 µm, and this is significant,” Dr. Hatz said. “After the loading phase, both groups were at exactly the same point, but then central retinal thickness increased in the PRN group, while it remained stable in the treat-and-extend group.”

Dr. Hatz noted the mean number of injections was 8.6 in the treat-and-extend group and 6.0 in the PRN group, reflecting a real-world PRN scenario. “The number of visits in the PRN group was 11.9; in a trial, it would have been 13, including baseline and exit visits,” she
said. “This also reflects a real-life PRN scheme, and both values are significantly different.”

See Figure 8 for a summary of these data.

INTEGRATING TREAT-AND-EXTEND

For clinicians wishing to incorporate a treat-and-extend regimen into their practices, Dr. Hatz offered the following advice: “Most importantly, plan ahead and take your time. Also, discuss this change with your staff, and be sure to include everyone who is involved in patient visits, nurses, photographers, technicians, and, of course, all of the doctors. You must explain the differences between the two schemes and the advantages of treat-and-extend. If you have two-step scheduling, so that you are not administering injections the same day as examinations, you must transform your daily practice, because in the treat-and-extend scheme, every time the patient comes in, you give an injection.”

Dr. Hatz also stressed the importance of preparing patients for this change, and she recommended reinforcing the information you provide in person with printed material. “When switching patients to treat-and-extend, we have found information leaflets to be useful,” she said. “Explain the regimen in simple terms and include an example that the patient will understand.”

Dr. Hatz has found that patients who have been switched to treat-and-extend have been accepting of this change. “When patients have been treated in the treat-and-extend scheme two or three times, they really love it, because it is a pre-planned regimen and they know what to expect,” she said. “These are elderly people. They love it if they know what is happening beforehand and can plan for it.”


Katja Hatz, MD

Head of Medical Retina and Research Department, Vista Klinik Binningen, Basel, Switzerland
Anti-VEGF therapy has helped to transform the lives of many patients with a range of retinal diseases, and ranibizumab (Lucentis; Novartis Pharma AG) has been at the forefront of these transformations, with indications for neovascular age-related macular degeneration (nAMD), diabetic macular edema (DME), macular edema secondary to branch (BRVO) and central retinal vein occlusion (CRVO), and choroidal neovascularization (mCNV) secondary to pathologic myopia.1

More than 8 years of clinical data from more than 460 clinical trials, as well as 3.7 million patient-treatment years worldwide, and more than 2,000 publications provide a preponderance of evidence of ranibizumab’s efficacy and safety. During this time, the focus of monitoring and diagnostic criteria has shifted from visual acuity to visual acuity plus optical coherence tomography (OCT) data. Since 2014, the new ranibizumab European label supports personalized treatment with monthly injections until maximum stable visual acuity is reached or there are no signs of disease activity. When applying a treat-and-extend regimen, the treatment interval should be extended by 2 weeks at a time for nAMD and CRVO, or by 1 month at a time for diabetic macular edema and BRVO.

“Medical decisions are based on the totality of evidence, beginning with small case reports and case-controlled studies, but the maximum evidence comes from prospective, controlled, randomized trials and meta-analyses,” said Prof. Lars-Olof Hattenbach, of Ludwigshafen am Rhein, Germany. He noted that pivotal trials, such as RADIANCE,2 BRAVO,3 and CRUISE,4 demonstrate the superiority of ranibizumab treatment for its various indications.

“One typical feature observed again and again in all of these studies is that patients who received the sham treatment in the control groups, even after being switched to ranibizumab, never really caught up with patients who started in the treatment groups,” Prof. Hattenbach said. “These outcomes underscore the importance of early treatment.”

Prof. Hattenbach also cited data from the HORIZON extension trial,5 in which patients who had completed the BRAVO and CRUISE studies were monitored and treated as needed (PRN) for an additional year. “The HORIZON trial showed that improved visual acuity can be maintained in both branch and central RVO with a PRN approach over a period of at least 24 months (Figure),” he said. “I think this trial also demonstrates the importance of continuing with intensified treatment in patients with CRVO, perhaps more than in those with BRVO, in order to reach or maintain improvement in visual acuity.”

Prof. Hattenbach noted the outcomes from the HORIZON trial were also borne out in the RETAIN study,6 which showed improved visual acuity was maintained over 54 months with PRN treatment. In another study of BRVO, the COMRADE B study,7 Prof. Hattenbach and colleagues compared visual acuity outcomes in patients who received three loading doses of ranibizumab followed...
Preserving Sight in RVO and mCNV: A Noble Aim or a Clinical Reality?

by PRN treatment against outcomes in patients who received a single injection of a dexamethasone implant 0.7 mg (Ozurdex; Allergan). “At month 6, the mean change in BCVA was higher in patients treated with ranibizumab compared with those treated with dexamethasone,” Prof. Hattenbach said. “We found a final visual acuity increase of 16.9 letters in the ranibizumab group, and a loss of 0.7 letters in the dexamethasone group. The mean average change was 14.5 and 4.8 letters, respectively. The mean number of ranibizumab injections was 4.63. We all expected a difference at month 6, but we were surprised that the effect of dexamethasone diminished after 2 months. The significant difference was maintained over 12 months.”

CONCLUSION

“Overall, there is a great wealth of randomized controlled trial evidence in support of ranibizumab for treating retinal vein occlusion and myopic choroidal neovascularization,” Prof. Hattenbach said. “I believe we are entering a new era of larger data sets from global trials that will provide us with additional evidence from the real-world use of ranibizumab.”

7. Hattenbach LO, Eter N, Hans I, et al. Efficacy and safety of 0.5 mg ranibizumab compared with intravitreal implant containing 0.7 mg dexamethasone in patients with branch retinal vein occlusion over 6 months. Presented at: 14th Euretina Congress; September 11, 2014; London, UK.

New Evidence Emerges in Retinal Vein Occlusion

Treatment options for retinal vein occlusion (RVO) address the causes of vision impairment (ie, edema, ischemia, and neovascularization). Anti-VEGF agents and steroids are typically used to treat both branch (BRVO) and central RVO (CRVO), while grid-pattern laser photocoagulation is generally employed only for BRVO.1-3 Ramin Tadayoni, MD, PhD, presented new 24-month data from the BRIGHTER and CRYSTAL studies,4 showing the long-term benefits of an as-needed (PRN) regimen of anti-VEGF therapy for BRVO and CRVO.

BRIGHTER

BRIGHTER4 was a phase 3b, randomized, open label, active-controlled, multicenter study of BRVO. Patients (n=455) were randomly assigned to ranibizumab 0.5 mg (Lucentis; Novartis Pharma AG), ranibizumab plus laser, or laser alone. The primary endpoints were superiority at month 6 and noninferiority at month 24. Among the baseline characteristics (Figure 1), visual acuity and disease duration are of particular interest, according to Prof. Tadayoni.

“Patients were treated until they achieved their best-corrected visual acuity, which means they received three anti-VEGF injections and then were treated PRN based on visual acuity,” Prof. Tadayoni said. “At 6 months, the laser was inferior to ranibizumab plus laser and ranibizumab monotherapy (Figure 2).

After 6 months, patients in the laser arm were permitted to switch to anti-VEGF therapy. Although their visual acuity increased, their...
Preserving Sight in RVO and mCNV: A Noble Aim or a Clinical Reality?

Gains at 24 months remained inferior to those of patients who received anti-VEGF therapy from the beginning of the study (Figure 3). “Patients who had early anti-VEGF therapy had very good results, gaining about 16 letters,” Prof. Tadayoni said.

In BRIGHTER, ranibizumab treatment increased visual acuity regardless of baseline visual acuity. “It is interesting to see how the visual acuity evolved, depending on the baseline visual acuity (Figure 4),” Prof. Tadayoni said. “Patients who had visual acuity of 39 letters or fewer had an impressive increase, whereas patients who had better visual acuity at the beginning gained fewer letters. At the end of 24 months, those who started with better visual acuity had better visual acuity than those who started with lower visual acuity.”

CRYSTAL

CRYSTAL was a phase 3b, open-label, single-arm study of macular edema secondary to CRVO. “Similar to the BRIGHTER trial, many patients in the CRYSTAL trial had a long duration of disease,” Prof. Tadayoni said. “Almost 20% of patients had CRVO for more than 12 months, with a mean of 9 months. Visual acuity with anti-VEGF therapy increased rapidly and was maintained at 24 months (Figure 5). Again, with a PRN regimen based on the European label in 2014, patients received only 13 injections over 2 years.”

In terms of baseline visual acuity, CRYSTAL results were similar to those achieved in the BRIGHTER study. “Patients with good visual acuity gained fewer letters, but they had the best prognosis,” Prof. Tadayoni said. “Those who had low visual acuity when they started treatment still gained vision, but not as much as those who started with better visual acuity.”

“Concerning duration of disease, there was a trend toward better results in patients who had the disease for fewer than 3 months, but the difference was not significant,” Prof. Tadayoni continued. “All patients gained visual acuity quickly, and they gained more than 10 letters after anti-VEGF injection.”

24-MONTH EFFICACY

Based on results from the BRIGHTER and CRYSTAL studies, Prof. Tadayoni noted the following:

• anti-VEGF PRN regimens based on visual acuity mainly result in rapid vision gains in CRVO and BRVO;
• BRVO and CRVO patients treated early with ranibizumab achieve better visual acuity than those treated later;
• compared with laser, ranibizumab improved and sustained gains over 24 months in patients with BRVO.
Preserving Sight in RVO and mCNV: A Noble Aim or a Clinical Reality?

IMPACT OF ISCHEMIA

According to Prof. Tadayoni, a question persists: Does the presence of some macular ischemia further complicate RVO? He noted that cross-trial comparisons are difficult, because considerable heterogeneity exists in classifying and grading retinal ischemia in RVO studies (Figure 6). For example, the aflibercept CRVO studies used CVOS classification, which does not consider macular ischemia, while the ranibizumab studies, including CRYSVAL, did focus on central macular ischemia.5-7

In the BRIGHTER study, the presence of macular ischemia did not affect outcomes in patients treated with ranibizumab or ranibizumab plus laser (Figure 7). In the laser arm, however, patients who had some ischemia in the macula did better than those who had no ischemia. In the CRYSTAL study, macular ischemia did not affect visual acuity gains over 24 months (Figure 8).

Based on outcomes in these two studies, researchers concluded that ranibizumab is effective in treating RVO, regardless of baseline macular ischemia status.

SUMMARY

In summary, Prof. Tadayoni said, “We have a wealth of data supporting anti-VEGF therapy as an effective treatment for retinal vein occlusion, and studies have found that the early initiation of anti-VEGF results in superior visual acuity gains over laser in BRVO. In addition, ranibizumab provides visual acuity gains regardless of baseline macular ischemia status. BRIGHTER and CRYSTAL definitely support a personalized ranibizumab regimen in a broad patient population.”


Figure 7. The presence of ischemia did not have a significant impact on patients treated with ranibizumab in the BRIGHTER study (A and B). In the laser arm, patients who had some ischemia demonstrated better outcomes than those who had no ischemia (C).

Ramin Tadayoni, MD, PhD
professor at Chirurgien des Hôpitaux, Paris, France
Pathologic myopia is a major cause of blindness worldwide. Studies have ranked pathologic myopia as a leading cause of blindness in Asian populations, as well as the third to the fifth most common cause of blindness in Caucasian populations. Also, prevalence of pathologic myopia has been found to be higher in Asian populations compared with Caucasian populations. For example, the Blue Mountain Eye Study found pathologic myopia occurred in 1% of the general population of Australia. In Asian adults in Japan and China, the prevalence has been estimated to be about 3%. High myopia is generally defined as 6.00 D or higher and is a risk factor for pathologic myopia. Eyes with pathologic myopia have progressive, abnormal elongation of the eye together with some degenerative abnormal fundus changes. In individuals with pathologic myopia, choroidal neovascularization (CNV) will develop in approximately 5% of eyes in Caucasians and approximately 11% of eyes in Asians. If left untreated, most patients with pathologic myopia will become blind within 5 to 10 years.

RADIANCE

Timothy Y.Y. Lai, MD, FRCPhth, from Hong Kong, discussed at a recent symposium new findings and new guidance related to myopic CNV, but first discussed the first available treatment for myopic CNV, verteporfin PDT, based on findings from the VIP study. In general, verteporfin PDT stabilizes but does not improve vision.

“We have very good data from the RADIANCE study that ranibizumab (Lucentis; Novartis Pharma AG) is effective and superior to verteporfin PDT,” Prof. Lai said. In RADIANCE, more than 250 patients were randomly assigned to one of three groups: 0.5 mg ranibizumab based on visual stabilization criteria; 0.5 mg ranibizumab based on disease activity criteria; and verteporfin PDT. At 12 months, both ranibizumab groups had significantly improved visual acuity (Figure 1). In addition, the mean number of injections was quite low, about 3.5 for patients in the disease activity group and 4.6 for patients in the visual stabilization group.

“The number of injections was higher in the visual stabilization group, because these patients required mandatory two initial injections to achieve stable visual acuity,” Prof. Lai explained. “The primary endpoint was measured at 3 months. Patients treated with verteporfin PDT gained only 1 letter of visual acuity, and the differences between the PDT group and the ranibizumab groups are highly significant. In addition, patients who were switched to ranibizumab at 3 months never caught up to those who were treated with ranibizumab initially. The RADIANCE study shows that there was clear superiority in terms of visual acuity gained compared with PDT, and also the visual acuity gain was sustained over 12 months with a low number of injections.”

Prof. Lai also reported on subgroup analyses of RADIANCE data.
had gained a mean of 14.3 letters from baseline, and this was maintained throughout this period,” Prof. Lai said, noting that some patients were treated with additional anti-VEGF therapy, while others had no treatment during this period. “At the end of the study, the improvement in visual acuity was maintained, with a total gain of about 16 letters.”

Patients in the post-RADIANCE study were divided into two cohorts, depending on whether they needed additional anti-VEGF therapy. “Regardless of whether they had treatment or not, these patients had improvement in vision,” Prof. Lai said. “Duration of follow-up was quite long for these patients—a mean of 3 years for patients requiring additional anti-VEGF and 2.3 years for patients with no further treatment—and shown in Figure 3, both groups maintained visual acuity compared with baseline at the post-RADIANCE visit. Patients who had some recurrences were offered additional therapy, and they regained the visual acuity they had lost initially.”

Prof. Lai went on to explain: “In this study, we defined myopic CNV recurrence as any signs of leakage or fluid as assessed by fluorescein angiography and optical coherence tomography (OCT) after a period of at least 3 months without signs of disease activity. The seven patients requiring additional anti-VEGF therapy had a total of 10 episodes of CNV recurrence, most of which were reactivations of previously regressed CNV owing to new CNV formation. For patients who did not have any further treatment, there was one reactivation of a previously regressed CNV.”

**MYRROR**

The MYRROR study evaluated aflibercept (Eylea; Regeneron) for the treatment of myopic CNV in East Asian patients (n = 121). “With aflibercept, the mean gains at 24 weeks were about 12 letters compared with minus 2 letters for the sham group,” Prof. Lai said. “Some patients in the sham arm were switched to aflibercept, so at week 48, the mean improvement was about 4 letters. For the aflibercept group, the mean gain was 13 letters. The mean number of injections was about 4.2 over this period.”

“This study showed that the BCVA achieved with aflibercept (Figure 4) was similar to results with ranibizumab in the RADIANCE study at 12 months with a similar number of injections,” Prof. Lai said.

**SEEKING CONSENSUS**

Based on new evidence from clinical trials, Prof. Lai noted that consensus is needed to determine the optimal clinical management of patients with myopic CNV. “We brought together a group of clinicians to critically appraise and summarize the latest myopic CNV literature findings,” he said. “Our goal was to clarify some terminology used in the literature and to provide ophthalmologists with evidence-based treatment algorithms for myopic CNV.”

The researchers first identified the stages of myopic CNV. In the active phase, there is direct damage to the photoreceptors, causing central visual acuity loss. With treatment, the CNV regresses, causing fibrous pigmented scar formation. In the late stage, atrophy forms around the regressed CNV. Early diagnosis and treatment are essential to prevent poor long-term outcomes. The treatment algorithm resulting from the consensus study is summarized in Figure 5.

“A patient who presents to his or her general ophthalmologist or...
optometrist with blurred vision or metamorphopsia or symptoms of CNV should be referred to a retina specialist within the first week of presentation,” Prof. Lai explained. “After confirming the diagnosis using fluorescein angiography and OCT, the retina specialist can then offer the patient first-line therapy, which should be an anti-VEGF agent that is licensed for treatment of myopic CNV. After initial treatment, the patient should be monitored monthly for the first 2 months to detect any disease activity, and then he or she should be monitored at least quarterly in the first year. For patients with any disease activity or loss of visual acuity, additional treatment with anti-VEGF agent should be employed.”

CONCLUSION

Prof. Lai concluded his presentation with the following key take-away points:

• Severe vision loss owing to the progression of myopic CNV should be prevented by prompt diagnosis and early treatment.
• The RADIANCE study confirmed that the treatment of myopic CNV with ranibizumab results in rapid and sustained gains in visual acuity, with a limited number of injections over 12 months.
• Similar BCVA gains were observed across all RADIANCE subgroups. East Asian patients had a higher numerical gain in BCVA and fewer injections compared to Caucasians.
• Long-term post-RADIANCE data showed that visual acuity gains were maintained over 4 years, with a low recurrence of myopic CNV.
• Expert consensus guidelines recommend first-line licensed intravitreal anti-VEGF therapy for the treatment of myopic CNV.

---
